

Research Article

DOI: <http://dx.doi.org/10.22192/ijamr.2019.06.08.003>

Alterations of the pubertal development in Mexican children with obesity

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Abstract

Background: Puberty is a key moment in the maturity process whose main characteristic is represented by the development of secondary sexual characters. Precocious puberty has been associated with the risk of developing psychosocial problems, breast cancer in women, hepatocellular carcinoma, as well as cardiovascular diseases. The increase in adiposity in pediatric age has received special attention as a potential etiological factor of secular changes related to the early onset of puberty.

Objective: Describe the behavior of the onset of pubertal development in obese patients of (from) the Obesity Clinic of (for) Children and Adolescents of the General Hospital of Mexico.

Material and Methods: 89 girls between 6 and 7 years old and 128 boys between 7 and 8 years old of (from) the Obesity Clinic of (for) Children and Adolescents of the General Hospital of Mexico with a body mass index above the 95th percentile were included in the study. of the General Hospital of Mexico with a body mass index above the 95th percentile. The degree of pubertal development was determined through the Tanner scale and the perimeters of neck, waist and hip. *Student's t* test was performed to assess the difference between means (median) in groups with premature thelarche or premature gonadarche; In addition, binary logistic regression models were carried out in order to find associations between anthropometric variables and premature thelarche or premature gonadarche. A ROC curve was performed to evaluate the behavior of the hip measurement as a diagnostic marker of premature gonadarche in children.

Results: In the boys' group, 9.4% (n = 12) presented Tanner stage II in genitals volume and in the girls' group, 11.2% (n = 10) presented Tanner stage II of breast development. The variables that had a significant association with premature gonadarche were hip circumference and waist measurement by the WHO method.

Conclusions: We found a higher prevalence of premature thelarche and premature gonadarche in children with obesity compared to that reported in eutrophic children. Males with a gynecoid distribution of adiposity are more likely to develop this disorder.

Keywords

Precocious puberty;
Hip circumference;
Obesity.

Introduction

Obesity and overweight represent one of the main public health problems among the pediatric population in Mexico. According to the information obtained through the Health and Nutrition National Survey (ENSANUT – Encuesta Nacional de Salud y Nutricion) in 2012 and from the halfway report (ENSANUT MC – ENSANUT Medio Camino) in 2016, the prevalence of obesity in school-age children is greater than (over) 33.2%, while for adolescents is 36.3%^{1,2}.

Obesity is associated to a great number of comorbidities. It is most often recognized as a cardiometabolic risk factor, however, when representing a disease of importance in childhood it is relevant to know its impact on the growth and development of children^{3,4}.

Puberty is a key moment in the maturity process whose main characteristic is represented by the development of secondary sexual characters.⁵ Clinically the beginning of puberty is marked in girls by the onset of breast development and in boys by the increase in testicular volume, usually assessed through the pubertal development scale suggested by Tanner^{6,7}. In girls, puberty normally begins between 8 and 13 years old and in boys between 9 and 14 years old. In Mexico, girls begin their pubertal development at an average age of 9.6 years old and present their menarche at 12.3 years old. In Mexican boys, the pubertal onset occurs at an average age of 12 years old.

The increase in adiposity in pediatric age has received special attention as a potential etiological factor of secular changes related to the early beginning of puberty⁸. A relationship has been found between the presence of obesity and alterations in the onset and progression of puberty, so that interest arises to investigate what is the behavior of these comorbidities in the Mexican population⁹. Precocious puberty is defined as the development of sexual characteristics before the age of nine in boys and eight in girls¹⁰.

In girls, precocious puberty is idiopathic in most cases and although there are multiple genetic and environmental factors that contribute to the early onset of puberty¹¹⁻¹⁴, it is also be proven an early start of pubertal development in women with obesity. In men with obesity, studies are controversial¹⁵⁻¹⁷. Currently, anthropometric parameters have not been determined

in children and adolescents who are overweight and obese, unable to predict early pubertal development. Precocious puberty has been associated with the risk of developing psychosocial problems, breast cancer in women^{18,19}, hepatocellular carcinoma²⁰, as well as cardiovascular risk factors, with a negative association between early pubertal moment and cardiovascular mortality, hypertension, metabolic syndrome and abnormal fasting blood glucose^{21,22}.

It is very important to know the behavior of the pubertal onset of patients of (from) the Obesity Clinic of (for) Children and Adolescents of the General Hospital of Mexico “Eduardo Liceaga”, identifying precocious puberty o delayed puberty according to the gender and other anthropometrics parameters in order to offer attention to those pathologies associated with obesity. Once patients with pubertal disorders have been identified, relevant management can be provided, and long-term complications can be avoided.

Objectives

- 1.- Describe the behavior of the onset of pubertal development in obese patients of (from) the Obesity Clinic of (for) Children and Adolescents of the General Hospital of Mexico.
- 2.- Compare the differences in the behavior of the onset of puberty between male and female patients and their association with anthropometric variables.

Methods

Patients of (from) the Obesity Clinic of (for) Children and Adolescents of the General Hospital of Mexico who attended a first-time consultation, who had body mass index for the age above the 95th percentile were included. They were divided into two groups, by gender and age; women between 6 to 7 years 11 months old and men between 7 to 8 years 11 months old. Breast development was assessed in the case of women and testicular size in the case of men, determining the degree of pubertal development through the Tanner scale, considering clinically the beginning of puberty from stage II, characterized by the onset of breast development or thelarche (breast button) in women and by increased testicular volume (which we call gonadarche) greater than 4cc using a Prader orchidometer.

We decided to classify inclusion groups based on age given the prevalence of early puberty (between 6-8 years old in women (girls) and 7-9 years old in men (boys) that has been suggested as normal for some ethnic groups. We also analyzed the presence of puberty data in children under 6 years old and older than 15 years old. The physical examination was performed by experienced pediatricians and pediatric endocrinologists, appropriately differentiating the development of the mammary gland from the adipomastia. For the purpose of our study, the degree of pubarche was not considered, as this may be due to a process of physiological adrenarche. In the same way, anthropometric measurements of neck, waist according to WHO, waist according to NHANES and hip were evaluated, in order to assess whether these parameters could predict the presence of precocious puberty in the patients studied. Weight and height measurements were made by pediatricians and pediatric endocrinologists trained for it, according to international techniques²³; blood pressure was measured at rest using sphygmomanometer and stethoscope. Neck circumference was measured at the most prominent point of the cricoid cartilage. Waist circumference by NHANES method was determined with the subject standing in front of the examiner, with the arms at the sides, the feet together and the bare torso; the edge of the iliac crest and the last rib was located and the midpoint of the distance between these two points was marked. The measurement was made there, using a 0.6 mm wide metal tape. To determine the waist circumference by the WHO method, the measurement was made at the height of the iliac crests.

Statistic Analysis

Descriptive statistics were performed reporting measures of central tendency and dispersion for numerical variables and percentage for categorical

variables. For inferential statistics, student t was used to assess difference in means between groups with early thelarche or gonadarche; In addition, CHAID (Chi Squared Automatic Interaction Detection) type decision trees and binary logistic regression models were performed in order to find associations between anthropometric variables and early thelarche or gonadarche. The independent variables chosen for these models were neck circumference, abdomen circumference, BMI, waist circumference by WHO and hip circumference. The analyzes were performed with the SPSS statistical package (Armonk, NY, USA) version 24. An alpha error probability of less than 5% was considered statistically significant.

Results

Descriptive statistics

89 girls between 6 and 7 years 11 months and 128 boys between 7 and 8 years 11 months were included, with body mass index above the 95th percentile of a total of. In the group of girls, 11.2% (n = 10) presented early loom determined by breast Tanner II. The average age reported was 6.5 (SD \pm 0.50) years, the average percentile of the Body Mass Index was 97.3 (DS \pm 3.0).

In the group of children, 9.4% (n = 12) presented testicular volume 4cc corresponding to a stage II genital Tanner. The average ages reported were 7.57 years (\pm 0.49), the average percentile of the body mass index was 97.63 (\pm 2.77). There was no presence of thelarche or gonadarche in girls under 6 years old and in boys under 7 years old. Which could have corresponded to cases of true precocious puberty.

The most relevant demographic and anthropometric characteristics of both groups are shown in Table 1.

Table 1.

Variable	Value	
	Masculine	Femenine
Gender	128	89
Age (Years)	7.57 (± 0.49)	6.5 (± 0.50)
Weight (kg)	41.6 (± 10.06)	36.7 (± 8.75)
Size (cm)	131.3 (± 6.82)	125.9 (± 8.4)
BMI (kg / m ²)	23.4 (± 2.99)	22.7 (± 3.32)
BMI Percentile	97.63 (± 2.77)	97.3 (± 3.0)
Neck (cm)	31.6 (± 2.66)	30.3 (± 2.49)
Waist * (cm)	76.3 (± 7.20)	72.8 (± 7.33)
Waist ** (cm)	78 (± 7.40)	74.7 (± 8.12)
Abdomen (cm)	79.8 (± 10.11)	76.9 (± 8.01)
Hip (cm)	79.7 (± 7.40)	76.8 (± 7.84)

* Waist by NHANES method; ** Waist by WHO method

Inferential statistics

Women

Differences in anthropometric measurements were evaluated between the precocious and the non-precocious puberty group by means of analysis of variance for neck circumference, waist circumference according to WHO and NHANES, hip circumference and BMI.

T test was performed for independent samples, using the parameters of body mass index, neck circumference, waist circumference according to WHO and according to NHANES, hip circumference and BMI among girls with and without precocious puberty. No significant differences found between the means of the parameters considered between both groups

Non-linear relationships with CHAID (Chi squared automatic interaction detection) decision trees were evaluated to assess whether the body mass index, neck circumference, waist circumference (according to WHO and according to NHANES) or circumference of hip could predict the development of precocious puberty in girls.

A logistic regression model was carried out using the body mass index, neck circumference, abdomen circumference, age in months, hip measurement and waist circumference according to WHO as predictive variables. These variables were chosen because they did not violate the assumption of multicollinearity of the logistic regression. The model had a small effect

size R² of Nagelkerke = 0.34 and correctly predicted 94.5% of the cases with telarche.

Men

T test was performed for independent samples, using the parameters of body mass index, neck circumference, waist circumference according to WHO and according to NHANES, hip circumference and BMI among children with and without precocious puberty without significant differences between the means of the parameters considered between both groups.

Variance analysis was performed to assess differences in body mass index, neck circumference, waist circumference according to WHO and according to NHANES or hip circumference and BMI among children with and without precocious puberty. Significant differences were not found.

A logistic regression model was carried out using the BMI, neck circumference, abdomen circumference, age in months, hip measurement and waist circumference according to WHO as predictive variables. These variables were chosen because they did not violate the assumption of multicollinearity of the logistic regression. The model had a small effect size R² of Nagelkerke = 0.19 and correctly predicted 88.2% of cases. The variables that had a significant association with early gonadarche were hip circumference and waist measurement by the WHO method. According to the beta coefficients of the regression, the greater the hip circumference increases the probability of having early gonadarche, $b = 0.338$, $p = 0.040$, OR = 1.4, 95% CI = 1.01-1.93.

On the other hand, by increasing the waist circumference according to WHO, the risk of presenting gonadarche is decreased, $b = -0.332$, $p = 0.034$, $OR = 0.71$, $95\% CI = 0.52-0.97$. This indicates that a greater hip circumference and a lower waist circumference have a higher risk of early gonadarche. Therefore, children with a gynecoid distribution are more likely to develop this disorder.

Finding that the greater the hip circumference, the greater the risk of early gonadarche, an ROC curve was performed to assess the behavior of the hip measurement as a diagnostic marker of early gonadarche in children. The area under the curve was 0.7 and the p of 0.06. A cut-off point was sought that would give us greater sensitivity even if specificity was a trade off, choosing a 76.9 cm hip perimeter as the cut-off point, which obtained a sensitivity of 91.7% and specificity of 37% to detect early gonadarche in children and a positive predictive value of 13.92% and a negative predictive value of 97.56%.

Discussion

Puberty is one of the crucial moments in the development of an individual and, like many other aspects, it undergoes significant modifications when obesity occurs concomitantly²⁴. One of the objectives proposed in our work group is the search for clinical tools that allow us to identify comorbidities associated with obesity in an accurate way. In Mexico we do not have prevalence of precocious puberty, however studies at an international level show prevalence of 0.2% for girls and less than 0.05% for eutrophic boys²⁵, so based on our results we find higher prevalence's in our study group as reported, so that obesity could be considered a risk factor for the development of this pathology in both sexes.

Among the findings of this study we find a behavior similar to that of other series in which an increased incidence of precocious puberty in obese girls is reported, which is most likely related to an increase in peripheral aromatization of androgens and therefore increased the production of estrogens of an increased adiposity^{26,27}. Likewise, the feedback mechanisms are regulated by the estrogen receptor (ER), which are found in the Kiss neurons of the arcuate nucleus and in the anteroventral periventricular area (AVPV) of the hypothalamus. At this level, the importance of RE is that estrogen increases the expression of Kiss1 in the AVPV via RE, activating the secretion of GnRh at the hypothalamic level²⁸.

On the other hand, the findings in the male group differs from that reported in most of the literature, since delay in the onset of pubertal development is usually described in male patients with obesity^{29,30}. Based on this, it has been suggested that although overweight and obese patients maintain increased circulating levels of leptin, it works ambivalently; since despite being a permissive factor for pubertal onset at the hypothalamic level, its peripheral inhibitory effect has also been demonstrated, acting directly on the gonads, decreasing testosterone secretion, in this case delaying pubertal development in men²⁹. However, it was possible to document an increased frequency of precocious puberty in male patients. When trying to delve into factors that could predict an advance in pubertal development, hip circumference was found as a predictor. This parameter has been significantly correlated with the rates of adiposity and BMI in children³¹, suggesting an increase in the secretion of sex steroids in patients with obesity, without the origin of early puberty in these patients being elucidated to date^{32,33}. It is worth noting that the hip circumference may be related to cardiometabolic alterations in patients with obesity, and that its advantages are easy to obtain and adequate reliability^{18,34}, so it could be used as a screening method and as a predictor of precocious pubertal development in men with obesity and overweight.

The greater hip circumference, which corresponds to an unexpected distribution of adiposity in men, makes us assume that the accumulation of "ectopic" fatty tissue could have a prominent hormonal activity or if the dysfunction of the adipose tissue typical of the obese patient could be related to alterations in the metabolic control of the onset of puberty, thus involving abnormalities such as hyperleptinemia. It is known that leptin, produced in adipose tissue and directly related to stored energy, acts through its receptor to stimulate the secretion of kisspeptin in the arched nucleus³⁵. This would explain that the body composition in childhood is involved in the onset of puberty, since it has been identified that at higher levels of adiposity, the higher frequency of precocious puberty. In our study the evaluation of body composition was not carried out, however, waist circumference is directly related to fatty tissue viscerally³⁶.

One of the main limitations of this study is the lack of determination of Stimulating Follicle Hormone (SFH), Luteinizing Hormone (LH), estradiol and testosterone that support or rule out clinical findings, however

there is evidence that baseline levels of LH and FSH of obese and non-obese patients with clinical data of pubertal onset, remain in prepubertal ranges at least until Tanner's pubertal stage III³⁷, but not testosterone and estradiol levels, which have been found in ranges higher than those of patients with normal weight³⁸.

Despite what was reported in our study in relation to precocious puberty and obesity, important questions remain to be answered:

- 1) the differential diagnosis between true precocious puberty or precocious pseudopuberty and the different normal variants of puberty, including the interpretation of results of the hormonal tests that support the diagnosis,
- 2) the respective role of the genetic and environmental factors and
- 3) the evolution of estrogen secretion and the indications of management with GnRH analogue in these patients³⁹.

In the assessment of these patients it will be worthwhile in the future to contemplate the possibility of exposure to substances such as bisphosphonols or other endocrine disruptors related to the early appearance of pubertal development data. One of the main concerns or adverse effects reported in pediatric patients managed with GnRH analogues is precisely the weight gain, which would be inconvenient in these cases. On the other hand, this treatment could improve the evolution only in the case of those patients with gonadotropin-dependent precocious puberty. In general, overweight management slows the progression of puberty in most patients, so the standard of care for the patient with obesity remains prevalent. Similarly, it is convenient to study other aspects that have been proposed as metabolic mechanisms for regulating the reactivation of hypothalamic secretion of GnRH^{41,42,43}.

Conclusion

The onset of puberty is an aspect influenced in an important way by adiposity, so it can often be modified by the presence of obesity, however despite its importance it is a little studied aspect with discordant opinions among various authors. In our population of children with obesity we managed to document an increased incidence of precocious puberty in both girls and boys. This phenomenon is contradictory, particularly in men, and the approach of other studies that allow us to elucidate the etiology of

this phenomenon becomes necessary. We hope that our findings will serve as a reference for future research that determines the mechanisms and causal effects of precocious puberty and obesity, leading to the development of new approaches to analyze precocious puberty in the clinical context of patients with obesity and overweight.

Conflict of interests

None of the editors authors of this article stated the existence of possible conflicts of interest that should be declared in relation to this article.

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	Website: www.ijarm.com
	Subject: Medical Sciences
Quick Response Code	
DOI: 10.22192/ijamr.2019.06.08.003	

How to cite this article:

Luis López-Rivera, Nayely Garibay-Nieto, Estibalitz Laresgoiti-Servitje, Eréndira Villanueva-Ortega. (2019). Alterations of the pubertal development in Mexican children with obesity. *Int. J. Adv. Multidiscip. Res.* 6(8): 24-31.

DOI: <http://dx.doi.org/10.22192/ijamr.2019.06.08.003>