

Hormonal, anthropometric and lipid factors associated with idiopathic pubertal gynecomastia

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BACKGROUND AND OBJECTIVES: To determine factors associated with pubertal gynecomastia.

DESIGN AND SETTINGS: A cross-sectional study among healthy male school children and adolescents in Riyadh, Saudi Arabia.

METHODS: Subjects were selected from diverse socioeconomic backgrounds. Tanner stage, height, weight, blood hormonal levels (leutilizing hormone [LH], follicle-stimulating hormone [FSH], total testosterone, and estradiol), and anthropometric and lipid parameters (body mass index [BMI], triglycerides, high-density lipoprotein [HDL], and low-density lipoprotein [LDL]), were collected and compared in children with and without gynecomastia.

RESULTS: The study included 542 children and adolescents. Median (interquartile range) age in the whole group was 11(8-13) years. The prevalence of gynecomastia was 185/542 (34%), with a peak at age 14. The 2 groups compared had nonsignificant difference in cholesterol ($P=.331$), LH ($P=.215$) and FSH ($P=.571$) levels. Those with gynecomastia were significantly older, had lower gonad stage, had higher anthropometric (height, weight, and BMI), and lipid (triglycerides, HDL, and LDL) values. In multivariate regression analysis, factors significantly associated with gynecomastia were BMI (odds ratio [OR]=1.05; 95%CI 1.00-1.10; $P=.013$), HDL (OR=0.42; 95%CI 0.19-0.92; $P=.03$), and gonad (Stage II OR=2.23; 95%CI 1.27-3.92; $P=.005$, Stage III OR=6.40; 95%CI 2.70-15.0; $P<.0001$, Stage IV OR=3.24; 95%CI 1.32-7.95; $P=.01$, Stage V OR=1.37; 95%CI 0.52-3.56; $P=.53$, compared with stage I).

CONCLUSION: Pubertal gynecomastia tends to increase in mid-puberty. In our setting, BMI, HDL, and gonad stage were the major factors associated with the development of pubertal gynecomastia.

Gynecomastia is a proliferation of glandular elements, resulting in concentric enlargement of one or both breasts in males. It is not an uncommon phenomenon and is prevalent in 40% to 65% of pubertal males.¹ However, prepubertal gynecomastia is rare and is considered to be pathological. It is characterized by the presence of breast tissue without other secondary sexual characteristics in male children less than 9 years.²

Gynecomastia can present as a unilateral, bilateral, and/or asymmetrical enlargement of breasts or as a painless or tender mass from the acute, nonspecific stretching of tissues. Gynecomastia is frequently seen

in normal males in the neonatal period, during puberty, and with increasing age. Gynecomastia appears at least 6 months after the onset of male secondary sex characteristics, and it positively correlated with age ranging from 10 to 13 years and negatively associated with age ranging from 14 to 19 years.¹ Neonatal gynecomastia is due to placental transfer of maternal estrogens, while pubertal gynecomastia is believed to be the result of an imbalance within the breast tissue between estrogens and androgens since estrogens stimulate the proliferation of breast tissue and androgens antagonize this effect.³⁻⁵ With aging, the production of testosterone decreases, and the peripheral conversion of androgens

to estrogen often rises because of an age-associated increase in adipose tissues.²

Published studies evaluating causes of gynecomastia were conducted as early as 1970s.⁶ However, the conflict in the etiology still seen in many of the reported studies. Evidence suggest that gynecomastia is more common in pubertal males with high body mass index (BMI), and the breasts are often greater in size and more persistent than the usual pubertal gynecomastia.⁷ It is a well-known fact that most of the circulating estradiol in man is derived from the aromatization of precursors, mostly testosterone, in extragonadal tissues, mainly adipose tissue. Thus the increase of adipose tissue mass may be a direct cause of increased aromatization leading to an imbalance between estradiol and testosterone levels.⁷

Pubertal gynecomastia has a negative impact on the self-esteem of adolescent boys. It can lead to depression as well as decreased participation in various social activities.⁸ We studied the prevalence of gynecomastia and hormonal changes in healthy male children in relation to puberty.

METHODS

Population and sampling technique to construct the sampling frame.

This is a cross-sectional study carried out among school children and adolescents in Riyadh, Saudi Arabia. Participates were selected using a cluster sampling strategy. Clusters (schools) were sampled from the Riyadh region using information from the Ministry of Education and Ministry of Planning. Schools were selected from affluent areas of Riyadh (north and east) as well as areas of a low socioeconomic status (west and south). The sampling frame included a representative number of private and public schools from the four regions. The sampling protocol was as follows: from each area, a K-12 school was randomly selected and all students in the class were invited to participate in the study. Data was collected from each school by a team of Pediatric Endocrinology Consultants and Fellows.

Blood samples were collected for hormonal levels, including testosterone (Architect system, 2002, Abbott Laboratories, USA), estradiol (Architect system, 1998, 2004, Abbott Laboratories, USA), FSH (Architect system, 2002, Abbott Laboratories, USA), and LH (Architect system, 2004, Abbott Laboratories, USA). One week prior to data collection, each student received an envelope containing an informational brochure about the study, an informed assent and con-

sent form, and a self-administered child's health and other demographic information to be completed by the student's parent or guardian, with a focus on drug history, systemic illness, or endocrine illness. Only students with signed consent forms were allowed to participate in the study. The study protocol was approved by the Research and Ethics Subcommittee at King Abdullah International Medical Research Centre in Riyadh.

Data collection

The study was conducted between January and June 2006. Each boy was examined by the data collection team in his school clinic or a specifically designated area. A systematic data collection protocol was followed to collect data on the following variables:

Systematic examination

Careful general and systematic examination was performed, including height and weight, paying particular attention to the presence of abnormal physical or endocrinological finding to exclude secondary causes of gynecomastia.

Growth parameters

Height was measured using a wall-mounted stadiometer and measurement was recorded to the nearest 0.1 cm. Weight was measured to the nearest 0.1 kg with a beam-balance scale. All measurements were collected by a nursing member of the data collection team in the child's school clinic.

Breast examination

Student was asked to lie supine with hands above the head. The examination was performed by compressing the breast area between the thumb and forefinger, which enabled the distinction of the presence of breast from adipose tissue in children with suspected gynecomastia. For the purpose of this study, gynecomastia diagnosis was confirmed as the presence of a palpable fibroglandular mass that measures at least 0.5 cm in diameter and is located concentrically beneath the nipple-areolar complex.

Maturation

The boys' sexual maturity stages were assessed using Tanner criteria. In addition, the gonadal stage was assessed by direct testes palpation; testicular volume was measured using a prader orchidometer.^{9,10} Orchidometry sizing was used, but data were entered as Tanner gonadal stages, with the equivalent of 1 to 3 mL as Stage 1, 4 to 8 mL as Stage 2, 8 to 12 mL as Stage 3, 12 to 15 mL as Stage 4, and 15 mL or above as Stage 5.^{11,12}

Statistical analyses

Categorical variables were reported as percentages or proportions, and continuous variables as means (standard deviation) or medians (interquartile range [IQR]). The analysis was stratified by gynecomastia status. Tanner stage, height, weight, blood hormonal levels (leutilizing hormone [LH]), follicularfollicle -stimulating hormone [FSH], total testosterone, and estradiol), and anthropometric and lipid parameters (BMI, triglycerides, high-density lipoprotein [HDL], and low-density lipoprotein [LDL]) were compared in children with gynecomastia (diffused or firm) and those without. χ^2 test or Mann-Whitney test were used as appropriate. Univariate logistic regression analysis was conducted to identify factors associated with gynecomastia. Statistically significant variables were included in a final multivariate logistic regression model. All tests were 2-sided and a *P* value <.05 was considered significant. Data analysis was carried out using SPSS, version 15 SPSS (IBM SPSS Vers. 20, Chicago, USA).

RESULTS

Of the 650 students invited to participate, 542 were included in the study. Thus, the overall response rate was 83%. Gynecomastia was found in 185/542 (34%) of the children and adolescents studied. Median (IQR) age in the whole group was 11 years.⁸⁻¹³ Participants with gynecomastia were significantly older, had lower gonad stage, had higher anthropometric (height, weight, and BMI), and lipid (triglycerides, HDL and LDL) values than those without (Table 1). Of the blood hormonal parameters studied, testosterone and estradiol were significantly higher in individuals with gynecomastia. FSH and LH levels were also higher in individuals with gynecomastia, but the difference was not statistically significant; Table 1.

The prevalence of gynecomastia was 43/136(32%), 44/175(25%), 65/145(45%), and 33/86(38%) among individuals aged 6 to 8, 9 to 11, 12 to 14, 15, and older (Figure 1).

In a univariate logistic regression analysis, age, BMI, Estradiol, triglycerides, LDL, HDL, and gonad stage were the factors significantly associated with gynecomastia. However, in the final multivariate logistic regression model, only BMI (Odds ratio [OR]=1.05; 95%CI 1.00-1.10; *P*=.013), HDL (OR=0.42; 95%CI 0.19-0.92; *P*=.03), and gonad (Stage II OR= 2.23; 95%CI 1.27-3.92; *P*=.005, Stage III OR=6.40; 95%CI 2.70-15.0; *P*<.0001, Stage IV OR=3.24; 95%CI 1.32-7.95; *P*=.01, Stage V OR =1.37; 95%CI 0.52-3.56; *P*=0.53, compared with stage I) were the factors independently associated with gynecomastia (Table 2).

Table 1. Baseline characteristics of study participants with (n=185) and without gynecomastia (n=357).

Characteristic	Gynecomastia	No-Gynecomastia	<i>P</i> value ^a
Age (y)	12 (9-14)	11 (8-14)	.009
Gonad stage (%)			
Stage I	68 (36.8)	203 (56.9)	
Stage II	46 (24.9)	68 (19)	
Stage III	28 (15.1)	17 (4.8)	<.0001
Stage IV	23 (12.4)	25 (7)	
Stage V	20 (10.8)	44 (12.3)	
Height (cm)	150 (135-160)	142 (131-159)	.001
Weight (kg)	47 (31-63)	38 (28-52)	<.0001
Body mass index (kg/m ²)	21 (16-26)	19 (16-23)	<.0001
Testosterone (ng/dL)	1.1 (0.5-7.2)	0.9 (0.4-7.7)	.007
Estradiol (pg/mL)	74 (57-95)	68 (47-92)	.001
Follicular stimulating hormone (mIU/mL)	1.7 (0.7-2.3)	1.4 (0.8-2.3)	.53
Leutilizing hormone (mIU/mL)	0.5 (0.07-1.4)	0.3 (0.07-1.6)	.08
Cholesterol (mg/dL)	4.2 (3.6-4.8)	4.1 (3.7-4.8)	.42
Triglycerides (mg/dL)	1.3 (0.88-1.8)	1.1 (0.8-1.7)	<.0001
High-density lipoprotein (mg/dL)	1.2 (1.05-1.4)	1.3 (1.1-1.5)	.002
Low-density lipoprotein (mg/dL)	2.3 (1.9-2.9)	2.2 (1.9-2.6)	.09

^aUnless specified otherwise, all numbers are median (inter-quartile range).

^a*P* value: Chi-square test for categorical variables and Mann-Whitney test for continuous variables.

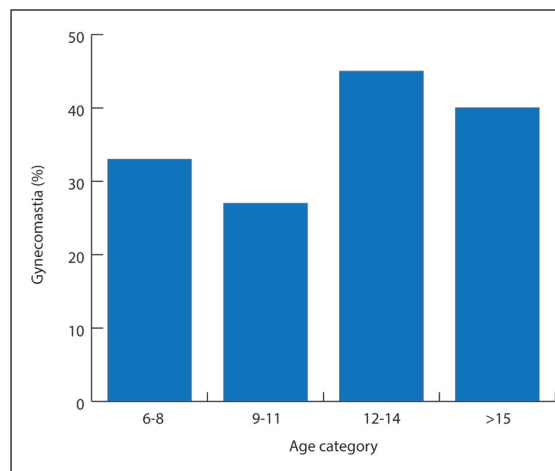


Figure 1. Prevalence of gynecomastia by age category.

DISCUSSION

This is the first study reporting the frequency of gynecomastia in healthy children and adolescents in the Middle East. We found that the prevalence of pubertal gynecomastia among healthy, Saudi male children is 34.5%. This is close to worldwide prevalence range that was reported from other populations to be 40% to 64%.^{1,13,14} It was not surprising that the prevalence of pubertal gynecomastia varies significantly according to Tanner stage of maturation, which peaks at Stage 3 of gonadal development and regresses with further pubertal maturation. This is in keeping with the benign nature of pubertal gynecomastia and reassuring finding to health profession. If gynecomastia did not regress with time, then pathological conditions should be excluded.¹⁵

In our study, gynecomastia was observed more frequently in children and adolescent with higher BMI, which is similar to a report by Rivera et al. In his study, a sample of 109 cases was selected from the Adolescent Outpatient Health Unit, with males aged between 11 and 19 years. It demonstrated that pubertal gynecomastia is associated with a higher BMI.¹⁶ A similar finding was reported by Ersöz et al, who found a significant increase in body weight and BMI in the gynecomastia group compared with healthy controls.¹⁴

The relationship between gynecomastia and higher BMI may be explained by the presence of extra adipose tissue, which is a major site for aromatization of testosterone to estradiol. There has been a number of conflicting studies against this theory. Kumanov et al

reported in a large cross-sectional study that adolescent boys with low BMI were more likely to develop gynecomastia.⁸ This finding was not clearly explained in that study. However, the same observation was reported by Biro et al who found that boys with pubertal gynecomastia are shorter, leaner, and have lower BMI.¹⁷ This conflicting finding may be explained by the causes of gynecomastia other than obesity such as certain drugs ingestion, environmental exposure, and chronic or endocrine illness.^{18,19}

The result of this study indicates a protective effect for HDL cholesterol against gynecomastia development even after adjusting for BMI and pubertal stage. This relationship has not been addressed directly in the published reports as a cause and effect. However, high HDL cholesterol was linked to the high testosterone concentration but not to the gynecomastia development.²⁰ Dai et al could not explain the observed positive correlation between HDL and testosterone level in healthy men.²¹

We found no significant difference in gonadotropic hormone levels (FSH and LH) between 2 groups. This could be explained by the fact that these are random, nonstimulated hormone values. Another hormone that has been evaluated in other studies in relation to gynecomastia is leptin. Dundar et al found significantly higher serum leptin levels in gynecomastia group compared with controls (without gynecomastia). This study demonstrated that the role of circulating leptin in pubertal gynecomastia is prob-

Table 2. Univariate and multivariate logistic regression analyses of factors associated with gynecomastia.

Factor	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	P value ^a	Odds ratio (95%CI)	P value
Age	1.08 (1.01-1.14)	.016	0.91 (0.82-1.02)	.10
Body mass index	1.07 (1.04-1.10)	<.0001	1.05 (1.01-1.08)	.013
Estradiol	1.001 (1.00-1.01)	.049	1.00 (0.99-1.01)	.31
Triglycerides	1.42 (1.12-1.80)	.003	1.04 (0.79-1.37)	.77
Low-density lipoprotein	1.40 (1.03-1.91)	.34	1.35 (0.95-1.91)	.09
High-density lipoprotein gonad	0.36 (0.18-0.72)	.004	0.41 (0.19-0.92)	.03
Stage II	2.02 (1.27-3.21)		2.23 (1.27-3.92)	
Stage III	4.92 (2.54-9.54)		6.40 (2.70-15.0)	
Stage IV	2.75 (1.46-5.15)	<.0001	3.24 (1.32-7.95)	<.0001
Stage V	1.36 (0.75-2.46)		1.37 (0.52-3.56)	
Stage I	1		1	

^aP value: Wald test.

ably related to increase in estrogen and/or estrogen/androgen ratio due to the stimulating effect of leptin on aromatase enzyme activity in both adipose and breast tissues. In addition, leptin has a direct growth stimulating effect on mammary epithelial cells, and it might increase the sensitivity of breast epithelial cells to estrogen.²²

The prevalence of prepubertal gynecomastia among male children in our study was 5.4%. These children were otherwise healthy. This is similar to findings of a large cohort study by Einav-Bachar et al on boys with prepubertal gynecomastia in which the prevalence was calculated at 5%. Of 29 boys with prepubertal gynecomastia, only 2 were found to have an

underlying pathology, namely, hyperaromatase syndrome. The other 27 had idiopathic gynecomastia.²

We acknowledge the limitations of the cross-sectional design of our study. Moreover, although this study was based on a relatively large sample size that contained both prepubertal and pubertal students from different socioeconomic status, it was conducted in one region in Saudi Arabia; Riyadh. However, our findings were similar to those of other studies that selected and compared individuals affiliated with different urban and rural regions.¹²

In conclusion, pubertal stage, HDL, and BMI are the factors contributing to the pubertal gynecomastia development in our setting.

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