Original Article

Adolescent gynecomastia is associated with a high incidence of obesity, dysglycemia, and family background of diabetes mellitus

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ABSTRACT

Background: Gynecomastia during adolescence is common though etiology is not clear. We studied the clinical and hormonal profile of adolescent patients with gynecomastia. **Methodology:** Patients who had onset of breast development between age 10 and 20 years were included in this study. Their clinical profile, biochemical, and hormonal parameters were studied. **Results:** Of 94 patients with gynecomastia, 4 had hypogonadotropic hypogonadism, 4 had hypergonadotropic hypogonadism, and 1 had fibroadenosis, but in majority (90.4%), no apparent cause for breast enlargement was evident. In the idiopathic group, majority were obese (63%). Fourteen (16%) patients had impaired fasting glucose or impaired glucose tolerance. Another twenty patients had subtle abnormalities (high 1 h glucose or glucose peak at 2 h). Twenty-nine percent of lean and 38% of obese patients had mild abnormalities in glucose profile. Sixty percent of patients had family background of diabetes. Obese patients had lower testosterone as compared to lean patients; however, estradiol, luteinizing hormone, and follicle-stimulating hormone levels were similar in the two groups. **Conclusion:** Gynecomastia during adolescence is associated with obesity, dysglycemia, and family background of diabetes mellitus.

Key words: Adolescent, diabetes mellitus, dysglycemia, gynecomastia, obesity

Introduction

Gynecomastia, a benign proliferation of the breast tissue, is common among peripubertal males. Although altered testosterone-estradiol ratios as a consequence of endocrine causes such as hypogonadism or hyperthyroidism or drugs could cause gynecomastia, in most cases, the disorder remains idiopathic.[1-3]

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Relative excess of serum levels of estrogens compared with androgens is implicated in the pathogenesis of pubertal gynecomastia, due to estradiol rising sooner than testosterone as puberty advances. Family background of gynecomastia may be a predisposing factor.[3,4] Some studies have also observed association of breast enlargement with increasing body mass index (BMI).[4-7] Aromatase activity known to be upregulated in obesity could explain gynecomastia in obese males.[8] However, the etiology of gynecomastia in lean males is unclear. In the present study, we plan to study the clinical and hormonal profile of patients who had onset of gynecomastia during adolescence.

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Methodology

Patients with gynecomastia who presented to the endocrine clinic during the period 2010–2014 were participants in this study. Patients who had onset of breast enlargement between ages 10 and 20 years were included in this study. Gynecomastia was defined as detection of the glandular tissue with thumb and forefinger as previously described.[1] Those with only lipomastia on clinical examination or ultrasound were excluded from this study. Patients were enquired about their presenting complaints and family history of gynecomastia or other chronic diseases among parents and grandparents. Files of these patients were retrospectively reviewed for presenting complaints, phenotype, and biochemical and laboratory parameters, and family history. Missing data were obtained from the patients or accompanying attendants during the clinic visit. This study was approved by the Institutional Ethics Committee.

The patients were classified as lean and overweight as per Coles criteria of the International Obesity Task Force.[9] Impaired fasting glucose (IFG) was defined as glucose levels between 100 and 125 mg%. Postglucose load levels were considered as abnormal if any of the three criteria was met: (i) 2 h glucose more than 140 mg%, (ii) 1 h glucose more than 155 mg%,[10] and (iii) 2 h value more than 1 h value.[11] All these parameters' postglucose load are known to be associated with a high risk of diabetes and poor beta-cell function.[12] Homeostatic model assessment-insulin resistance (HOMA-IR) levels more than 2.5 were considered abnormal as per cutoffs given by Singh *et al*. on adolescent Indian males.[13]

Hormonal parameters

Plasma glucose levels were determined by the glucose-oxidase technique. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, testosterone, thyroid function tests, and estradiol were performed by chemiluminescence (vitros ECIQ, Johnson and Johnson). Plasma insulin was performed by ELISA (on Biorad Evolis, Twin Plus).

Statistical analysis

The data were entered in Microsoft Excel and converted into SPSS version 11 (Chicago, Illinois, USA). The data are expressed as mean ± standard deviation (SD), percentage, and median where SD is high. Independent *t*-test was used to compare the parametric variables between lean and obese patients. Chi-square test was used for comparison of nonparametric variables.

Results

There were 102 patients who had onset of breast development between ages 10 and 20 years. Of these, eight with lipomastia on examination were excluded from this study. The average age and BMI of the 94 included patients were 16.5 ± 3.3 years and 25.2 ± 4.7 kg/m^2, respectively. Of 94 patients, 4 had hypogonadotropic hypogonadism, 4 had hypergonadotropic hypogonadism, and 1 had fibroadenosis. None of the patients had thyrotoxicosis, hyperprolactinemia, drug-induced gynecomastia, or human chorionic gonadotropin-secreting tumors. Thus, in majority 85 (90.4%), no apparent cause for breast enlargement was evident (idiopathic group). In this group, three patients had delayed puberty.

The mean age of onset of breast development and duration of gynecomastia in patients with idiopathic gynecomastia was 13.4 ± 2.7 and 3.1 ± 2.8 years, respectively. The mean BMI of these patients was 24.8 ± 5.0 kg/m^2. Fifty-four (63.5%) were obese and 31 (37.5%) were lean as per Coles criteria. Gynecomastia was supplemented by ultrasound in thirty (34.1%) patients. There were unilateral gynecomastia in 18% and bilateral in 82% of the patients. Tenderness in breast was reported in 42% of the patients. The average breast enlargement was right breast size – 5.2 ± 2.8 cm (longitudinal) and 4.9 ± 2.7 cm (transverse) and left breast 5.2 ± 2.8 cm (longitudinal) and 4.8 ± 2.6 cm (transverse). The mean testicular volume was 14.5 ± 6.6 ml (right) and 14.4 ± 6.6 ml (left), respectively.

The mean levels of biochemical parameters including hormones in lean and obese patients are given in Table 1. The mean basal LH, FSH, and testosterone levels were in the pubertal range. Luteinizing

Table 1: Clinical and biochemical parameters among lean and obese gynecomastia patients

Parameter	Lean (*n*=31)	Obese (*n*=54)	*P*
Age (years)	17.1±2.9	16.2±3.9	0.25
Age at onset (years)	14.9±2.6	12.5±2.3	0
BMI (kg/m^2)	19.9±2.3	27.8±3.5	0
Glucose (mg/dl)			
0 h	90.6±9.1	90.1±9.5	0.84
1 h	98.2±31.1	118.6±39.2	0.10
2 h	101.7±23.4	105.7±25.3	0.55
Insulin (μIU/ml)			
0 h	14.6±21.6	13.9±8.6	0.88
1 h	61.4±42.7	97.7±125.8	0.27
2 h	49.2±34.9	87.7±124.7	0.06
HOMA IR	2.8±3.5	3.3±1.9	0.73
LH (mIU/ml)	2.1±1.2	3.2±2.9	0.78
FSH (mIU/ml)	2.9±1.7	3.8±5.0	0.42
Testosterone (nmol/L)	10.4±7.8	6.1±5.6	0.008
Estradiol (pmol/L)	64.1±73.0	55.7±28.0	0.54
Right breast larger diameter (cm)	3.4±2.1	6.0±2.7	0
Left breast larger diameter (cm)	3.6±1.8	6.0±2.9	0.002
Testicular volume right (ml)	14.6±5.2	14.5±7.1	0.91
Testicular volume left (ml)	14.5±5.8	14.2±7.0	0.84

LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, BMI: Body mass index, HOMA: Homeostatic model assessment, IR: Insulin resistance

hormone-releasing hormone stimulation test available for 32 patients showed a LH-predominant response. The mean testosterone levels were lower in obese patients; however, there was no difference in LH, FSH, or estradiol levels in the two groups. The testicular volume at presentation to us was comparable in the two groups; however, testicular volume at initiation of gynecomastia was not available.

Fasting and postglucose insulin and glucose levels were available for 68 (80%) patients. The mean levels of glucose at 0, 1, and 2 h were 90.2 ± 9.3, 112.8 ± 37.9, and 104.4 ± 24.6 mg/dl, respectively. Corresponding median insulin values at same time points were 10.7 (14.1 ± 14.4 mU/L), 55.8 (85.8 ± 106.8 mU/L), and 57.7 (74.4 ± 104.2 mU/L), respectively. A high prevalence of abnormalities in glucose-insulin homeostasis was observed among patients with idiopathic gynecomastia. Eleven patients had IFG, and three had impaired glucose tolerance (IGT). Five patients had 1 h glucose value more than 155 mg% (of whom two had IGT and one had IFG). Fifteen patients had 2 h glucose levels more than 1 h glucose values of whom one had IGT. In all patients, 30 patients (35.2%) had mild abnormalities of glucose metabolism, 11 (12.1%) in fasting, and 19 (22.3%) in the postprandial state. 45.2% of patients had insulin resistance as defined by HOMA-IR values >2.5. Figure 1 gives the relative distribution of glucose abnormalities between lean and obese patients. In all patients, 29% of lean and 38% of obese patients had mild abnormalities in glucose profile.

A family background (affected parents or grandparents) of diabetes was observed in 62% of patients, hypertension in 61.1%, and coronary artery disease in 33%. Around 30% of patients with gynecomastia had parents with diabetes and 40% had affected parents with hypertension. The family background of diabetes mellitus (DM) was significantly higher in obese patients as compared to lean patients (62.0% vs. 38.7%, $P = 0.02$).

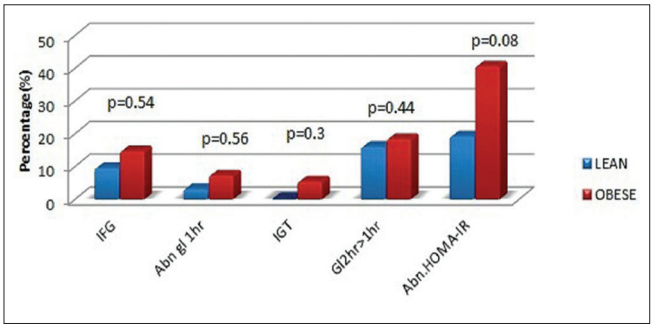

Figure 1: Frequency of glucose abnormalities among lean and obese gynecomastia patients

Discussion

In the present study, we observed that there was no clear etiology for breast enlargement in almost 90% of the patients with adolescent gynecomastia. Ersöz *et al*. also observed that the most common form of gynecomastia was idiopathic (58%) among young males.[5] Pathologic gynecomastia is rare in adolescents and prepubertal-aged males. It is believed that puberty, especially late, stages favor bioactive estrogen despite rise of androgens.[1] However, pubertal gynecomastia occurs in about 30%–60% of adolescents. The reasons as to why only a subset of patients develop breast enlargement during puberty are not clear. Apart from altered estrogen-androgen ratios, insulin-like growth factor 1 levels, leptin, and endocrine disruptors have also been implicated for pubertal gynecomastia.[1,14-16]

The average age at onset of breast enlargement in our patients was around 13.4 years. Previous studies have also observed the age at onset of gynecomastia between 13 and 15 years with a peak age at 14 years.[14,17] Most patients (64%) in the present study were obese as per Coles criteria, the average BMI being 25 kg/m^2. Obese patients had an early onset of breast enlargement as compared to lean patients (12.5 years vs. 14.9 years). Simon *et al*. also observed a relation between BMI and gynecomastia in their study.[18] Al Alwan *et al*. observed that BMI and gonad stage were the major factors associated with pubertal gynecomastia.[14] Another study by Rivera *et al*. also observed correlation of mammary diameters to higher BMI percentiles.[19] Aromatase activity increases with elevation of BMI, thereby causing increased peripheral conversion of androgens to estradiol.[2,20] Obese patients had a younger age at onset of gynecomastia as compared to lean patients. Obese patients had lower testosterone but comparable estradiol levels when compared to the lean subgroup, thereby suggesting increased peripheral conversion of testosterone to estradiol in obese patients. Decreased testosterone levels in obese patients could also reflect late onset of puberty; however, we did not have age at pubertal initiation in these patients.

We observed a high incidence of glucose abnormalities in our patients in the fasting as well as postprandial state. As many as 14 (16.4%) patients had IFG or IGT. We also observed glucose abnormalities at 1 h and a delay in glucose peak postglucose load. Both these parameters have been observed to be associated with a high risk of diabetes or altered beta-cell function. In all patients, 30 patients (35.2%) had mild abnormalities of glucose metabolism, 11 in fasting (12.1%), and 19 (22.3%) in the postprandial state. Ranjani *et al*. observed that 4.2% of urban South Indian adolescent males had glucose intolerance; however, these patients were

lean in comparison to our patients.[21] Anjana *et al*. reported IFG - 7.8%and IGT - 7.8% in overweight adolescents.[22] However, glucose at 1 h or glucose pattern was not reported in these studies. Tandon *et al*. reported 4.3% prevalence of metabolic syndrome among urban Delhi adolescents.[23] We observed insulin resistance in as many as 19% of lean and 40% of the obese patients. This is similar to a study by Tandon *et al*., where 19.7% of the lean and 50% of overweight patients were reported to have insulin resistance.

A high incidence of abnormalities in glucose homeostasis could be related to obesity since most our patients were obese. While around 38% of obese patients had glucose-related alterations, as many as 29% of the lean patients also had abnormalities in glucose profile. The reasons for abnormal glycemic profile in our lean patients are not clear. Puberty is a stage characterized by rising sex steroids that can adversely affect insulin resistance. However, we observed greater abnormalities in the postprandial state, thereby indicating anomalous insulin secretion. Pancreatic beta-cells compensate for the transient decrease in insulin sensitivity during adolescence by augmenting insulin secretion, leading to postprandial hyperinsulinemia.[24,25] *In vitro* studies suggest that insulin could cyclically upregulate aromatase activity in the fat and breast, thereby resulting in gynecomastia.[26]

We observed a high incidence of family background of diabetes among patients with gynecomastia. As many as 60% of patients had a family background of DM and hypertension. Offsprings of diabetic patients are known to have a high incidence of insulin resistance, beta secretory defects, altered glucose tolerance, and obesity.[27-30] All these were observed in the present cohort also. Around 40% of lean patients with gynecomastia had a family background of DM. Inheritance of insulin resistance and beta-cell dysfunction from diabetic parents may explain dysglycemia in our lean patients. The association of a family background of hypertension and gynecomastia, if any is unclear. We first reported that family background of hypertension and diabetes could affect obesity and first symptom of polycystic ovary syndrome (PCOS) patients.[31] Gynecomastia in males is believed to be a sine qua non of PCOS in females. Obese patients with gynecomastia had a significantly higher incidence of parental and family background of DM compared to lean patients though there was no difference in family background of hypertension among our lean and obese patients.

Conclusion

Adolescent gynecomastia is associated with a high incidence of obesity, dysglycemia, and family background of DM.

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Conflicts of interest
There are no conflicts of interest.

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