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Clinical and Biochemical Phenotype of Adolescent Males with Gynecomastia

Short title/Running Head: Gynecomastia

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Abstract

Objective: Gynecomastia is defined as benign proliferation of male breast glandular tissue. Its prevalence during puberty stands at 50-60% and this condition is common also in neonatal and elderly males. It develops mainly due to the disequilibrium between estrogen and androgen activity in breast tissue, where estradiol binds to estrogen receptor and stimulates ductal and glandular cells.

The aim of this work was to find a relationship between the sex hormones alterations and the natural history (evolution) of gynecomastia. Furthermore, the work tries to indicate the importance of checking the E2/TTE ratio.

Materials and Methods: Participants in this study were 93 male patients aged 9 to 18 (mean age 13.8 ± 2.6) referred to an outpatient clinic between January 2011 and February 2016 with breast enlargement.

Results: In 63 of 93 boys the gynecomastia was confirmed and 28 of them were follow-up (median of 3 months). None of all observed boys have reduced the size of breast during the observation and there was no correlation between BMI Z-Score and size of breast ($p > 0.05$). Breast enlargement progressed in 9 boys (32.1%). We have observed a positive correlation between E2/TTE Ratio and Tanner B stage ($r = 0.47$; $p = 0.034$).

Conclusions: The E2/TTE ratio may be a helpful tool in diagnosing gynecomastia. Altered E2/TTE ratio might be responsible for part of cases described previously as idiopathic. Additionally, weight loss does not imply reduction of breast size in boys, nonetheless it should be the first step before further treatment of prolonged gynecomastia.

Key words: Pubertal, Gynecomastia, Estradiol, Testosterone, Ratio

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Introduction

Gynecomastia is defined as a benign, unilateral or bilateral proliferation of male breast glandular tissue. It is the most common breast alteration in males and has a trimodal age distribution, occurring in neonatal, pubertal, and elderly males. Gynecomastia is observed in 50% to 60% of boys during their puberty, usually bilaterally, although may be asymmetric in size [1–2]. Physiologically it should resolve within six months to two years after the onset. Otherwise, gynecomastia becomes pathological and then the further evaluation is indicated [3–6].

Increasing prevalence of gynecomastia raises the question of a factor which is associated with the pathophysiologic mechanism of gynecomastia. The imbalance between estrogen and androgen activity is considered to be responsible for gynecomastia [7–8]. Therefore, gynecomastia appears in response to increased estrogen production and/or activity and because of decreased production and/or activity of testosterone [9]. A rapid increase in E2 (estradiol), occurring before and delays similar increase in TTE (Testosterone), causes an elevated E2-to-TTE ratio at the start of puberty. E2 binds to estrogen receptor in the breast tissue and stimulates ductal and glandular cells proliferation causing gynecomastia. Oppositely, testosterone exerts a generalized inhibitory action on growth and differentiation, perhaps through a specific anti-estrogenic action [10].

The aromatase activity, which converts androstenedione and testosterone to estrone and estradiol, respectively, is the most important factor in the equilibrium [11]. Overexpression and increased activity of aromatase is a key factor of gynecomastia. This upregulation contributes to the excessive local production of estrogen, decreased estrogen degradation and changes in the levels or activity of estrogen or androgen receptors' sensitivity [12–13]. Gynecomastia is strongly associated with obesity [14–15]. Aromatization takes place in the adipose tissue and it is the main source of E2 in men. Subsequently, higher production and activity of aromatase are the key factors of gynecomastia in obese men [6, 16]. Furthermore, the elevated weight contributes to breast tissue proliferation by increased leptin level [12]. Due to an increasing prevalence of adolescent obesity, it is essential to identify patients with gynecomastia among all boys presenting with breast enlargement.

Testicular tumors, as well as adrenal tumors, may secrete estrogen causing disruption in the E2-to-TTE ratio [17–18]. On the other hand, all forms of male hypogonadism lead to testosterone deficiency interfering in sex hormones homeostasis [19].

In addition, puberty is accompanied by the fastest upward growth in children stature (peak height velocity – PHV) and at that time, insulin-like growth factor 1 (IGF-1) and growth hormone (GH) reach maximum levels. Both GH and IGF are responsible for linear growth, but besides that, they also stimulate breast tissue proliferation through their receptors located in breast tissue [20]. As PHV and gynecomastia occur in a similar period of young boy's life it may suggest that there is a relationship between them [21–22].

There are also other causes of gynecomastia that should not be disregarded as drug-induced gynecomastia, systemic illness, and familial disorders. Common drug contributors include antipsychotics, antiretrovirals, and prostate cancer therapies with long-term use [23–24]. Gynecomastia is also a common sign of chronic liver disease and human immunodeficiency viral (HIV) infection [25–26].

In some cases, the etiology remains uncertain and as we can not always easily determine a pathomechanism responsible for gynecomastia, the process of diagnosing every patient through reviewing past medical history and performing physical examination should be careful and precise.

What is known on this topic and what this study adds?

The aim of this work was to evaluate the clinical and hormonal profile of patients with gynecomastia in pubertal time. It is known how to diagnose and how to manage with this disease, however there are not many studies that actually calculated E2/TTE Ratio in gynecomastia patients. We aimed to find a relationship between the sex hormones alterations and the evolution of this condition. The work tries to indicate the importance of checking the E2/TTE ratio in gynecomastia patients. Altered E2/TTE ratio might be responsible for part of cases described previously as idiopathic.

Materials and methods

All study subjects were derived from Upper Silesian Child Health Centre in Katowice. 93 male patients in age 9 to 18 (mean age 13.8 ± 2.6) referred to an endocrine outpatient clinic because of breast enlargement and examined between January 2011 and February 2016 were participants in this study. Among all study subjects, 11 were excluded due to steatomastia and 19 due to the reduction of breast size at a time of consultation. Sixty-three of them were diagnosed with gynecomastia and enrolled in the study group. Follow-up visits were planned in every 3-6 months. Of these 63, two had a family history of gynecomastia and 3 boys had delayed puberty. There were also 4 cases of hyperprolactinemia and one patient had additionally a history of galactorrhoea and normal PRL level. In addition, one boy was followed-up for a longer time than 2 years. All mentioned patients (n=11) were additionally classified as pathological gynecomastia group and compared to the rest described as pubertal gynecomastia (n=52). None of the patients had diagnosed primary hypogonadism, drugs-induced gynecomastia, human chorionic gonadotropin-secreting tumors nor elevated aminotransferases.

The patients were divided into two groups with respect to the Tanner B stage (breast growth) at the start of observation:

group B2: 42/63 (66.7%) boys with Tanner stage 2 of breast development

group B>2: 21/63 (33.3%) boys with more than Tanner stage 2 of breast development

Clinical phenotype

The detailed anthropometrical analysis was based on the weight and height measurements along with body mass index (BMI) calculation, using the standard formula of weight (kg) divided by height (m) squared. Weight was measured with a precision of 100 g and height with stadiometer to 0.1 cm. hSDS (height standard deviation score) was calculated from population standards for healthy children using the following formula: $hSDS = \frac{\text{child's height} - \text{height for 50 pc}}{0.5 * (\text{height 50 pc} - \text{height 3 pc})}$. Short stature was defined as hSDS below -2.0 standard deviation (SD).

Given a child's age, sex, BMI, and the appropriate reference standard, the BMI Z-score was calculated using The Pediatric Z-Score Calculator. The tool is available at the website of The Children's Hospital of Philadelphia, Research Institute (<http://stokes.chop.edu/web/zscore/>) and is dedicated to patients aged between 2 and 20 years. A BMI Z-score over $+2.0$ SD was classified as obesity, between $+2.0$ and $+1.0$ SD as overweight, between -1.0 and -2.0 as weight deficiency, and under -2.0 SD as significant weight deficiency [27]. The boys' sexual maturity stages were assessed using Tanner scale [28].

Biochemical phenotype

Hormonal levels of estradiol (E2), testosterone (TTE), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL) were measured using chemiluminescent immunoassay by Immulite 2000 analyzer (DPC, USA). Concentrations of serum free thyroxine (fT4) and thyroid stimulating hormone (TSH) were measured with a chemiluminescent immunometric assay (Siemens, Immulite 2000 Free T4, Immulite 2000 Third Generation TSH, USA). Based on standardized E2 and TTE results, the E2/TTE ratio was calculated. To exclude other causes of breast enlargement such as cirrhosis and testicular tumors, alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), alanine transaminase (ALT) and aspartate transaminase activity (AST) were also measured in accordance with International Federation of Clinical Chemistry (Beckman Coulter, USA)

Statistical Analysis

All statistical analysis was made by the Statistica 13 PL software and P value <0.05 was considered as significant. Shapiro-Wilk test was utilized to verify the normality of E2 and TTE distribution. In order to calculate the E2/TTE ratio, raw results were compared by using Standard Score. The analysis was stratified by gynecomastia status. The comparisons between 2 parametric values were made by using Student's t-test or Mann-Whitney U test for non-parametric distributions. The correlation between quantitative values was analyzed by using Pearson's correlation and Spearman's rank correlation coefficient for ordinal variables. All results were reported as mean \pm standard deviation (SD).

All procedures in our study were performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki. Due to its retrospective design and non-experimental nature a formal consent as well as formal approval by a bioethics committee were not required.

Results

Clinical results

The mean age of all patients was 13.8 ± 2.6 years at the time of 1st consultation. At the start of observation 7 (11.1%) boys were obese, 24 (38.1%) were overweight, 29 (46.0%) had a normal weight and 3 (4.8%) boys had weight deficiency. Mean BMI was 22.9 ± 4.3 , BMI Z-score was 0.83 ± 1.0 , and the hSDS was 0.5 ± 1.3 . Among all 63 patients, only 28 (44.4%) turned up to scheduled visit in the outpatient endocrinological clinic and the longest follow-up lasted 7 visits (38 months). 14 (57.1%) boys were advised to lose weight and 8 (14.3%) children followed the recommendation. 2 (14.3%) of them achieved normal BMI Z-Score, but no one reduced the size of breast during the observation. There was no correlation between BMI Z-Score and size of breast ($p > 0.05$). Tanner B Stage of 16/28 (57.1%) patients did not change and breast enlargement progressed in 12/28 (42.9%) boys.

Gynecomastia was bilateral in 46/63 (73.0%) patients. The median B Tanner stage at present was B2 (n=42; 67.0%). B3 stage has been reported in 15 (23.8%) cases and 6 (9.5%) patients had B4 stage. Tanner stage 4 for pubic hair appeared most often (n=13, 20.6%), and testicular volume was 12.2 ± 5.5 ml when gynecomastia was observed for the first time.

The clinical characteristics of the patients with gynecomastia, divided into two groups (B2 or B>2), are displayed in Table 1. There were no statistically significant clinical differences between early and more advanced stage of the disease.

We could identify the cause of gynecomastia in 11 cases (17.4%) which were afterwards described as the pathological gynecomastia group (n=11), the mean age was 14.9 ± 3.0 years, hSDS was 0.3 ± 1.0 and Z-Standard BMI was 0.6 ± 0.8 during the start of observation. These results did not vary from the pubertal gynecomastia group ($p > 0.05$).

Hormonal results

Hormonal results of all patients are presented in Table 2. E2 level was elevated in 6 (12.5%) boys, from among one was obese and two were overweight. There were 5 (10.9%) patients with TTE results below the reference interval and two of them were also overweight. Both these with elevated E2 and decreased TTE had the Tanner B3 as a dominant stage. None of the patients had both E2 and TTE abnormal results. Figure 1 displays a flow chart of patients included in E2/TTE ratio evaluation. We have observed statistically significant positive correlation between E2/TTE ratio and Tanner B stage ($r = 0.47$; $p = 0.034$, Fig. 2). E2/TTE ratio did not correlate with BMI Z-Score ($p > 0.05$). The mean basal LH and FSH levels were in the pubertal ranges. TSH levels were elevated in 6 (12.8%) boys, although all of them had normal fT4 concentration. Four (11.1%) boys had hyperprolactinemia (617.2; 604.6; 567.4 and 381.6 mIU/L) and one patient had a history of galactorrhoea and normal PRL level. ALT, AST, hCG and AFP of all patients were within normal range.

The comparison of B2 and B>2 groups revealed that patients with >2 Tanner B Stage tend to have higher E2/TTE ratio (0.8 ± 1.8 versus -0.3 ± 1.5 ; $p = 0.057$; Fig. 3). There were no other differences between groups and all results are presented in Table 3.

Additionally, we investigated clinical profile of 6 boys (14.3% out of 42 boys who had calculated E2/TTE ratio) whose E2/TTE ratio was over +1SD (3.4 ± 1.1). They were in the middle of puberty (14.7 ± 2.1 years) with Z-Score BMI 1.0 ± 0.6 and hSDS -0.1 ± 1.5 . All of them were at Tanner stage B3 (n=2) or B4 (n=4). They had

TTE levels within the reference interval (242.3 ± 97.7 ng/dL). Mean E2 concentration among this group was 40.3 ± 7.6 pg/ml and there were three boys with elevated E2 level and three had normal E2 level.

Finally, we analysed hormonal results in pathological gynecomastia group, which were available for 9 patients. Mean E2 value was 26.8 ± 19.6 pmol/l, TTE was 260.6 ± 230.0 ng/L and E2/TTE Ratio was 0.2 ± 1.8 . Due to insufficient amount of hormonal results in this group, we could not compare it to pubertal gynecomastia group.

Discussion

Gynecomastia may be a cause of psychosocial discomfort, stress and worsening of boys' self-image, so it is important to understand patient's concerns in order to provide them proper management. The suggested diagnostic approach and treatment strategies for gynecomastia consist of expert opinion, case series, and observational studies. It implicates low quality of evidence and lack of unequivocal attitude.

This article reviews the validity of calculating E2/TTE ratio in diagnostic process of gynecomastia. Increased E2/TTE ratio is indicated as the main cause of gynecomastia [29-32], however according to literature, 25% cases of this condition are described as idiopathic. We have observed, that there was no clear etiology for breast enlargement in almost 65% patients, while sex hormones disturbances or noticeable cause were present in 35% study subjects.

According to latest recommendations, each patient suspected for gynecomastia in physical examination, without identified cause of it, should undergo hormonal tests such as LH, FSH, PRL, TTE, E2, B-hCG and TSH [3-4]. In the present study, we observed that only 2/3 gynecomastia patients had performed complete sex hormones diagnostics. Moreover, physicians should pay specific attention to "red flags" suggestive of non-physiologic gynecomastia [2, 8, 10]. We did not observe rapid growth of breasts, breast skin changes, firm breast mass, testicular mass nor other signs of malignancy. Only one boy was followed-up longer than 2 years. In this case, we were able to diagnose persistent gynecomastia (>2 years), which is also a "red flag". One boy had a history of galactorrhea, which also should draw attention, as nipple discharge may suggest pathologic etiology of gynecomastia as well.

The average age of our patients during the 1st visit (13.8 ± 2.6 years) and pubic hair development (stage 3 of Tanner scale) are consistent with previous studies [33-34]. Nevertheless, about 40% of study subjects were at more advanced Tanner stages for pubic hair and almost 35% had greater testicular volume (P4G4) than it is usually observed (P3G3) [22].

The fact, that most of our patients did not have any abnormalities in basal hormone levels, encouraged us to calculate E2/TTE ratio, which was possible for the group of 42 patients. We found that there was a weak correlation between the imbalance of estrogen and androgen expressed as E2/TTE ratio and the size of breast ($r=0.47$). It suggests that there may be possibility of sex hormones disturbances in gynecomastia patients, despite normal E2 and TTE results in serum. Nonetheless, lack of differences between B2 and B>2 groups in E2, TTE levels and E2/TTE ratio underlines that caution should be exercised while drawing conclusions.

To the best of our knowledge, there are no specific guidelines, how to calculate E2/TTE ratio and there is no cut off level for this coefficient. Group of +1 SD E2/TTE boys were distinguished by higher E2 results (40.3 vs 24.2 pg/ml) and breast tissue development, nonetheless we did not find any additional presumable causes and features of gynecomastia. The imbalance in estradiol to testosterone ratio may explain why some adolescents with normal hormonal results develop gynecomastia. We are proposing that cutoff point should be established for E2/TTE ratio in clinical practice.

A rapid increase of obesity among children and adolescents results in higher number of patients presenting with breast enlargement. Despite, that obesity causes pseudogynecomastia (a proliferation of adipose rather than glandular tissue), elevated weight is also associated with true gynecomastia. Rivera et. al indicated, that there is a correlation between pubertal gynecomastia and higher BMI percentiles [35]. Also Kulshreshtha et al. in their study observed, that most of the patients (64%) with breast enlargement were obese as per Coles criteria [34]. In our study patients had higher BMI than in the general population according to CDC growth charts, however we did not find a relationship between BMI Z-score and the size of breasts ($p>0.05$). Despite the fact, that 8 overweight children (57.1%) succeeded in weight loss on the following visits, none of them had reduced size of breast and weight changes did not affect sex hormones levels, as there was no correlation between BMI Z-Score and E2/TTE ratio ($p>0.05$). This observation is consistent with the other authors' attitude, that weight loss alone will not correct true glandular breast enlargement. [17, 36]

It should be also underlined that breasts of these patients did not enlarge as well, while in 19% of patients we noticed the progression of breasts' size. Adolescents with gynecomastia should be encouraged to weight loss because it is always a crucial part of the surgical treatment of long-standing gynecomastia. Handschin et al. report that in those adults, with gynecomastia who are overweight, more severe surgical complications are observed and larger resections are needed [37].

Further studies should be performed in order to measure whether the same conclusion could be derived according to active fractions of sex hormones - free testosterone and free estradiol as well as studies that take into account sex hormones binding globulin (SHBG). The implementation of this rate to the process of

diagnosing might be helpful to recognize true gynecomastia and differentiate it from lipomastia and pseudogynecomastia, especially in obese boys.

Study limitations

We are aware of the limitations of the retrospective design of our study. As a single-center investigation the number of study subjects was also constricted. Small study group in turn could result in overlooking the actual correlations. Moreover, the study was conducted in one region in Poland, Silesia. Despite these limitations, our study design provides also valuable estimates, as each patient underwent the same process of diagnosis and the hormonal results were established in the same laboratory.

Conclusions

In conclusion, according to our results, the E2/TTE ratio may be a helpful tool in diagnosing gynecomastia. Altered E2/TTE ratio might be responsible for part of cases described previously as idiopathic. Additionally, weight loss does not imply reduction of breast size in boys, nonetheless it should be the first step before further treatment of prolonged gynecomastia.

Conflict of interest - None to declare

Acknowledgments - None to declare

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Table 1. Clinical characteristics of adolescent boys with gynecomastia stratified by Tanner B Stage.

	B Stage = 2 (n=42)	B Stage >2 (n=21)	P value
Age (years)	13.6 ± 2.5	14.1 ± 2.2	0.25
Height (cm)	165.5 ± 13.7	168.1 ± 10.2	0.28
Weight (kg)	62.6 ± 17.1	66.3 ± 14.0	0.24
hSDS	0.46 ± 1.2	0.68 ± 1.4	0.54
BMI	22.4 ± 4.0	23.3 ± 4.0	0.43
BMI Z-score	0.72 ± 1.0	1.06 ± 0.9	0.20
Tanner G Stage	3 (2 - 4)	3 (2 - 4)	0.85
Tanner P Stage	3 (2 - 4)	3 (3 - 4)	0.30

Data are presented as mean ± SD or median (interquartile range). hSDS — height standard deviation score; BMI Z-score: body mass index standard deviation score; G — genitals; P — pubic hair (components of Tanner Scale);

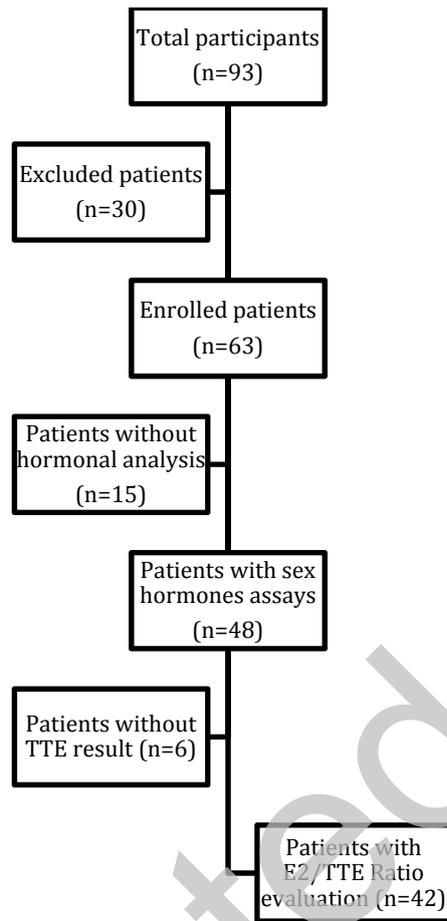


Figure 1. Flow chart of patients included in E2/TTE ratio evaluation

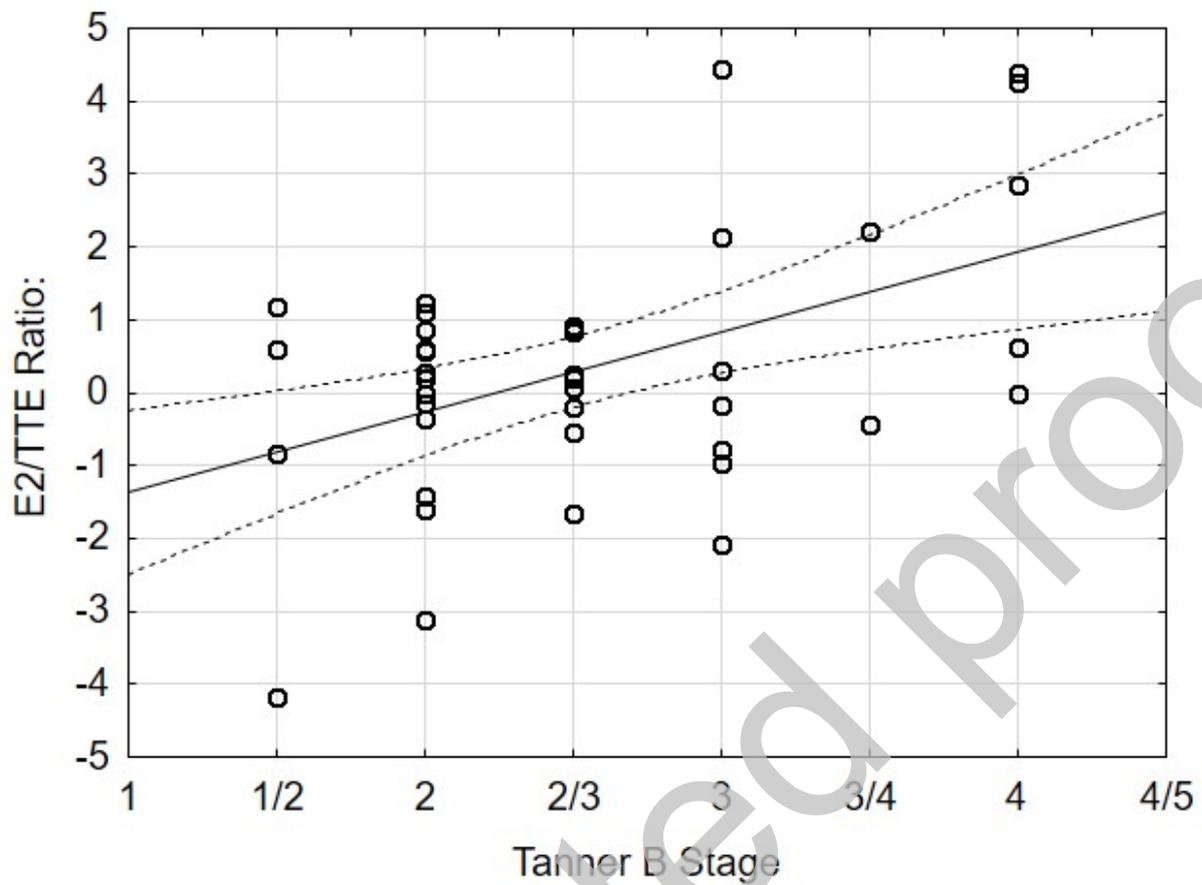


Figure 2. Correlation between E2/TTE ratio and the Tanner scale B stage.

Table 2. Hormone levels in all boys with gynecomastia

Hormone	n	Level	Hormone	n	Level
E2 [pmol/L]	48	25.0 ± 18.3	PRL [mIU/L]	36	150.3 ± 169.4
TTE [ng/L]	42	258.6 ± 215.9	ALT [IU/L]	24	18.4 ± 8.1
E2/TTE Ratio [SD]	42	0.3 ± 1.7	AST [IU/L]	23	23.0 ± 5.7
TSH [μU/mL]	47	2.9 ± 1.6	hCG [mIU/mL]	31	0.7 ± 0.7
LH [mIU/mL]	37	3.3 ± 1.9	AFP [IU/mL]	32	1.6 ± 0.9

Data presented as mean ± SD; E2 — estradiol; TTE — testosterone; PRL — prolactine; ALT — alanine transaminase; AST — aspartate transaminase; hCG — human chorionic gonadotropin; AFP — alpha-fetoprotein alanine transaminase.

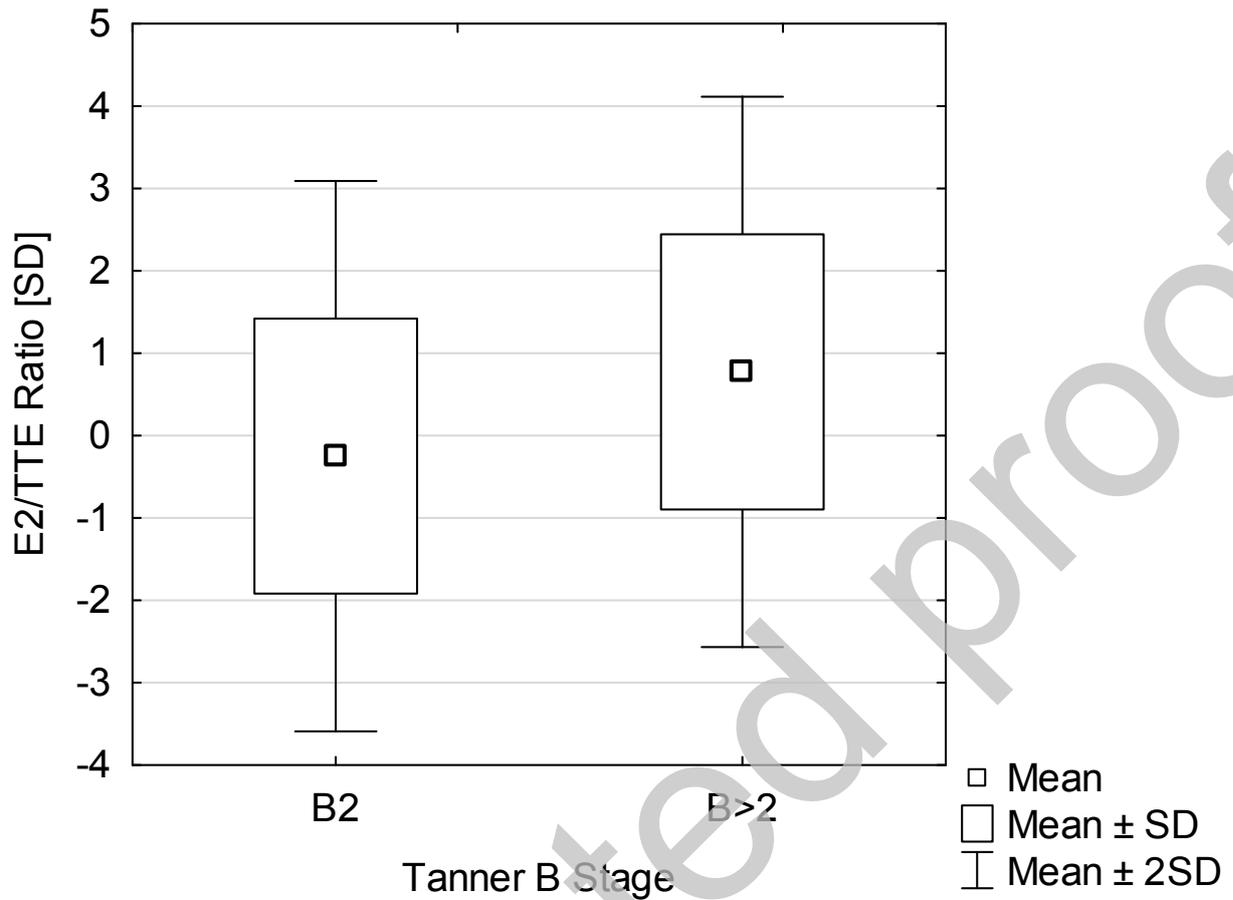


Figure 3. Comparison of E2/TTE Ratio stratified by gynecomastia status; $p=0.057$

Table 3. Biochemical characteristics of adolescent boys with gynecomastia stratified by Tanner B Stage.

	B Stage = 2 (n=42)	B Stage >2 (n=21)	P value
E2 [pmol/L]	23.7 ± 19.6	26.6 ± 17.6	0.55
TTE [ng/L]	278.8 ± 256.8	242.0 ± 178.3	0.58
E2/TTE Ratio	-0.5 ± 1.5	0.8 ± 1.8	0.057
TSH [μ U/mL]	2.9 ± 1.7	3.0 ± 1.3	0.82
LH [mIU/mL]	3.5 ± 2.2	3.2 ± 1.7	0.69
PRL [mIU/L]	145.7 ± 168.2	154.8 ± 175.0	0.88

Data are presented as mean \pm SD. E2 — estradiol; TTE — testosterone;