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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

Relationship of Sex Hormones with Obesity and Non-alcoholic Fatty Liver Disease in Boys with Gynecomastia

Jinekomastili Erkek Çocuklarda Seks Hormonlarının Obezite ve Alkolsüz Yağlı Karaciğer Hastalığı ile İlişkisi

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Abstract

Objective: We aimed to investigate the relationship between sex hormone levels [estradiol (E2), total testosterone (TTest)] and lipid profiles, body fat distributions, and non-alcoholic fatty liver disease (NAFLD) in obese boys with gynecomastia.

Methods: This prospective study included 79 obese boys with idiopathic pubertal gynecomastia between 10 and 18 years. The cases were divided into two groups as with (n=48) or without (n=31) NAFLD determined by ultrasonography.

Results: E2 levels had a significant positive correlation with age, body mass index, and fat mass of the patients and had a negative correlation with high-density lipoprotein-cholesterol (HDL-C) ($p<0.05$). TTest levels had a significant positive correlation with age of the patients and a negative correlation with HDL-C, percent of body fat (PBF) (%), and percent of trunk fat (PTF) ($p<0.05$). There was no significant difference in terms of sex hormone levels between the two groups with and without NAFLD ($p>0.05$).

Conclusion: The results of this study reveal that as the PBF and PTF increase, the TTest levels of the patients decrease and as the fat mass increases, the E2 levels increase significantly. We could not find a significant relationship between sex hormones and the presence of NAFLD.

Keywords: Obesity, gynecomastia, children, testosterone, estradiol, non-alcoholic fatty liver disease

Öz

Amaç: Jinekomastili obez erkek çocuklarda seks hormonu [estradiol (E2), total testosteron (TTest)] ile lipid profilleri, vücut yağ dağılımları ve alkolsüz yağlı karaciğer hastalığı (AYKC) arasındaki ilişkiyi araştırmayı amaçladık.

Yöntem: Bu prospektif çalışmaya, 10-18 yaşları arasında idiyopatik pubertal jinekomastili 79 obez erkek çocuk dahil edildi. Olgular ultrasonografi ile AYKC saptanan (n=48) ve saptanmayan (n=31) olarak iki gruba ayrıldı.

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Öz

Bulgular: E2 düzeyleri hastaların yaşı, vücut kitle indeksi ve yağ kitlesi ile anlamlı pozitif, yüksek yoğunluklu lipoprotein-kolesterol (HDL-K) ile negatif korelasyon gösterdi (p<0,05). TTest düzeyleri hastaların yaşı ile anlamlı pozitif, HDL-K, vücut yağ yüzdesi (PBF) (%) ve gövde yağ yüzdesi (PTF) ile negatif korelasyon gösterdi (p<0,05). AYKC olan ve olmayan iki grup arasında cinsiyet hormonu düzeyleri açısından anlamlı fark yoktu (p>0,05).

Sonuç: Bu çalışmanın sonuçları, PBF ve PTF arttıkça hastaların TTest düzeylerinin düştüğünü ve yağ kütlesi arttıkça E2 düzeylerinin önemli ölçüde arttığını ortaya koymaktadır. Seks hormonları ile NAYKH varlığı arasında anlamlı bir ilişki bulunamadı.

Anahtar Kelimeler: Obezite, jinekomasti, çocuklar, testosteron, östradiol, alkolsüz yağlı karaciğer hastalığı

Introduction

Gynecomastia is defined as the development of fibroepithelial structures in the male breast and its appearance similar to the female breast. Gynecomastia is physiologically seen in infancy, advanced ages and most frequently in adolescents. The majority of gynecomastia cases in adolescence are idiopathic. The main causes of idiopathic pubertal gynecomastia are increased aromatization of androgen precursors in the breast tissue, low testosterone (T) secretion remaining all day at the beginning of puberty, and genetically estrogen-sensitive breast tissue[1].

An imbalance between estradiol (E2) and T levels is associated with the increased peripheral aromatase activity in adolescents with obesity[2]. Because of this, a relationship between obesity and gynecomastia in adolescents has been define [3]. Although obesity plays a role in the growth of male breast tissue[4], the relationship between obesity related clinical and laboratory variables and sex hormones (E2 and T) is not fully known. Non-alcoholic fatty liver disease (NAFLD) refers to fat accumulation in the liver that is not due to excessive alcohol use[5]. NAFLD is strongly linked to central obesity, insulin resistance (IR) and metabolic syndrome[6]. Additionally, the effects of sex hormones on NAFLD have been identified in various studies[7,8]. The human liver has low levels of estrogen and androgen receptors[9], and physiological changes during puberty are known to affect NAFLD status[10].

In the literature, studies investigating the relationship between sex hormone levels and obesity in boys with gynecomastia are limited. However, no study investigating its relationship with NAFLD was found. In our study, we aimed to investigate the relationship between sex hormone levels (E2 and T) and lipid profiles, body fat distributions, and NAFLD in boys evaluated for idiopathic pubertal gynecomastia and obesity.

Materials and Methods

Participants and Research Design

This prospectively planned study included 79 pubertal boys with obesity aged between 10 and 8 years who were presented to the Çiğli Training and Research Hospital, Pediatric Endocrinology Outpatient Clinic between January 2019 and July 2019 with the complaint of breast tissue growth and diagnosed with pubertal idiopathic gynecomastia. Patients with known systemic or metabolic disease, malignancy, a liver disease that may cause NAFLD (hepatitis, autoimmune disease, etc.), another liver disease (such as hemochromatosis, Wilson's disease), genetic syndrome, abnormal thyroid function tests, drug use, and alcohol consumption history and patients having gynecomastia due to pathological causes such as adrenal or testicular tumors, human chorionic gonadotropin (hCG) secreting tumors, primary or secondary hypogonadism, androgen insensitivity syndromes, prolactinoma, and extraglandular aromatase activity and prepubertal patients were excluded from the study.

The relationship between sex hormone levels (E2-T) and clinical and laboratory features of all patients included in the study was evaluated. In addition, the cases were separated into two groups with or without NAFLD determined by abdominal ultrasonography (USG), and the clinical and laboratory characteristics and body fat distribution of the groups were compared.

Statement of Ethics

For the study, approval was obtained from the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Researches Ethics Committee (decision no: 2018/18-09, date: 06.12.2018). The study protocol was carried out in accordance with the Helsinki criteria. Informed consent was obtained from the families of the patients included in the study.

Physical Examination and Anthropometric Measurements

The evaluation of the patients was done by a pediatric endocrinologist. To distinguish between gynecomastia and lipomastia, the patients were examined carefully while lying on their back, gently rubbing the breast tissue between the thumb and index finger at the level of the nipple and in the areolar region. Gynecomastia was defined as the detection of glandular tissue with the thumb and index finger as previously described[11].

Anthropometric measurements of the child were made in the morning on an empty stomach and with the shoes and upper clothes removed. The heights of the patients were measured with the Harpenden stadiometer (Holtain Limited, Crymych, Dyfed, UK), which has a sensitivity of 0.1 centimeters (cm), and patients' body weights (BW) were measured with the SECA (name and no expansion), which measures BW with an accuracy of 0.1 kg (kg) (GMBH & CO KG Hamburg, Germany). Body mass index (BMI) and BMI standard deviation scores (SDS)/percentiles (P) of the patients were calculated according to national references by child metrics[12]. Patients with BMI ≥85th P were considered overweight, and those ≥95th P were considered obese.

The pubertal status of the cases was evaluated according to the Tanner Marshall puberty staging system[13]. The puberty stages of all patients were 2 (testicular size >4 mL) and therefore all patients were considered pubertal. Fat mass (kg), percent of body fat (PBF) (%), and percent of trunk fat (PTF) (%) of the patients were measured in the morning after 12 h of fasting using bioelectric impedance analysis (TANITA MC 780 P).

Hormonal and Biochemical Measurements

Blood samples of the patients were taken between 8 and 9 am after 12 h of fasting. Fasting serum lipids [triglyceride (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C)], aspartate aminotransferase (AST), alanine amino transferase (ALT), follicle stimulating hormone (FSH), luteinizing hormone (LH), E2, total testosterone (TTest) and prolactin (PRL) levels of all patients were recorded. Renal function tests, thyroid hormones, hCG, and alpha fetoprotein levels were evaluated to exclude patients with abnormalities.

Imaging

In our study, abdominal USG was performed for the diagnosis of NAFLD in all patients during fasting by a single radiologist who was blind to clinical and laboratory results. Results were recorded as no fatty liver or stage 1-2-3. Breast USG was performed by the same radiologist to distinguish between gynecomastia and lipomastia.

Statistical Analysis

The categorical variables were analyzed with frequency tables, and descriptive statistics were used for continuous variables. The Shapiro-Wilk normality test was used to examine whether the numeric variables had a normal distribution in groups. Since the numeric values were not normally distributed, the Mann-Whitney U test was used to compare the median values of two independent groups. The Spearman correlation coefficient was used to examine the correlation between continuous variables. The level of significance was taken as 0.05 in all hypothesis tests. IBM SPSS Version 25.0 statistical package was used for the statistical analyzes.

Results

A total of 79 boys, 15 overweight and 64 obese, who were diagnosed with idiopathic gynecomastia and met the inclusion criteria were included in the study. The mean age of the patients was 13.5±1.8 standard deviation (SD) (minimum-maximum: 10.0-17.9). When the puberty stages of the cases were evaluated, 30 (38%) patients were compatible with stage 2, 10 (12.7%) were compatible with stage 3, 11 (13.9%) were compatible with stage 4, and 28 (34.4%) were compatible with stage 5 puberty. Gynecomastia stages evaluated by physical examination were compatible with stage 1 in 30 (38%) cases, stage 2 in 21 (26.6%) cases, stage 3 in 26 (32.9%) cases, and stage 4 in 2 (2.5%) cases.

The correlation of the sex hormone levels (E2-TTest) of the cases with clinical and laboratory findings is shown in Table 1. While E2 levels showed a statistically significant positive correlation with age (r=0.564, p<0.001), BMI (r=0.284, p=0.011) and fat mass (r=0.329, p=0.041) of the patients, E2 levels had a negative correlation with HDL-C levels (r=-0.326, p=0.004). While T-Test levels showed a statistically significant positive correlation with age of the patients (r=0.651, p=<0.001), T-Test levels had a statistically negative correlation with HDL-C levels (r=-0.286, p=0.011), PBF (r=-0.492, p=0.001) and PTF (r=-0.372, p=0.021).

Non-alcoholic fatty liver disease, evaluated by whole abdomen USG, was detected in 48 of the patients (stage 1 fatty liver was observed in 36 patients, stage 2 fatty liver was observed in 12 patients and stage 3 fatty liver was not

detected) and there was not fatty liver in 31 of the patients. The cases were divided into two groups with NAFLD (n=48) and without NAFLD (n=31). In the NAFLD group, 42 (87.5%) patients were obese and 6 (12.5%) were overweight. In the group without NAFLD, 22 (71%) patients were obese and 9 (29%) patients were overweight. There was no significant difference between the groups in this respect (p=0.067). There was no statistically significant difference between the two groups in terms of age distribution, puberty, and gynecomastia stages. BMI, BMI SDS, AST, and ALT levels were significantly higher in the group with NAFLD than in the group without NAFLD (p values; 0.004, 0.028, 0.030, <0.001 respectively). There was no significant difference between the two groups in terms of fasting lipid and sex hormone (E2-TTest) levels. In the comparison of the body fat analysis of the cases, the fat mass of the patients with NAFLD was found to be significantly higher, but no statistically significant difference was found between the two groups in terms of PBF and PTF (p values; 0.01, 0.15, 0.08, respectively). A comparison of the characteristics of the two groups (with and without NAFLD) is presented in Table 2 in detail.

Discussion

The pathogenesis of idiopathic pubertal gynecomastia is explained by the relative excess of serum estrogen levels compared with androgens. The relationship between gynecomastia and increased BMI has been demonstrated in some studies[14,15]. It has been shown that males with obesity present with lower serum T-Test and higher E2 levels compared with a healthy control population[16]. These low T-Test levels are largely explained by lower sex hormone binding globulin (SHBG) levels. In addition, the increase in aromatase activity due to obesity and the inhibitory effects of leptin on T production may explain the gynecomastia observed in males with obesity[17]. Testosterone is an important anabolic hormone involved in the regulation of visceral fat accumulation. It has been shown that T increases lipid mobilization from visceral fat by inhibiting the uptake of TG. T-Test levels are inversely proportional to visceral fat mass and significantly decreased in cases with obesity[18]. Higher E2 levels can be produced by aromatization of T in adipose tissue in men with obesity[19]. In our study, we did not find a significant relationship between obesity degree (BMI, BMI SDS, BMI P) and T-Test level. However, as an important outcome, we found that T-Test levels were decreasing while the PBF and PTF increased in our study group. Estradiol levels tended to increase significantly as BMI and fat mass increased. In line with these results, it can be thought that the increased aromatase activity is related to fat mass and PBF rather than obesity degree. These results supported the increase in the peripheral conversion of T-Test to E2 as the PBF increased in patients with obesity.

We found no significant relationship between sex hormones and TG, LDL-C, and TC levels. We found a negative correlation

Table 1. Correlation of sex hormone levels (estradiol, total testosterone) with clinical and laboratory findings

Variables	Estradiol		Total testosterone	
	r	P*	r	P*
Age (year)	0.564	<0.001	0.651	<0.001
BMI (kg/m^2)	0.284	0.011	0.160	0.158
BMI SDS	0.097	0.393	-0.092	0.422
BMI P	0.087	0.445	-0.094	0.409
TC (mg/dL)	0.096	0.402	-0.009	0.936
TG (mg/dL)	0.129	0.261	0.123	0.283
HDL-C (mg/dL)	-0.326	0.004	-0.286	0.011
LDL-C (mg/dL)	0.166	0.146	0.122	0.286
AST (IU/L)	-0.070	0.539	-0.156	0.171
ALT (IU/L)	0.014	0.900	-0.047	0.684
Fat mass (kg)	0.329	0.041	0.075	0.650
PBF (%)	0.065	0.696	-0.492	0.001
PTF (%)	0.022	0.894	-0.372	0.021

*Spearman correlation analysis

BMI: Body mass index, SDS: Standard deviation score, P: Percentile, TC: Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, AST: Aspartate aminotransferase, ALT: Alanine amino transferase, PBF: Percent of body fat, PTF: Percent of trunk fat

Table 2. Comparison of clinical and laboratory characteristics of the two groups with and without NAFLD

Variables	With NAFLD median (min-max) n=48	Without NAFLD median (min-max) n=31	P*
Age (year)	13.6 (11.1-17.9)	13.2 (10-17.1)	0.327
BMI (kg/m^2)	31.1 (22.8-37.2)	27.9 (23.8-36.1)	0.004
BMI SDS	2.18 (1.1-3.1)	1.94 (1.08-3.13)	0.028
BMI P	98.3 (86.4-99.8)	97.4 (85-99.9)	0.075
TC (mg/dL)	146 (97-211)	148 (114-200)	0.727
TG (mg/dL)	105.9 (59-250)	91 (61-335)	0.342
HDL-C (mg/dL)	42 (27-56)	43 (30-65)	0.196
LDL-C (mg/dL)	82.2 (36.7-126.6)	82.6 (36.7-130)	0.551
AST (IU/L)	22.5 (13-45)	22 (13-31)	0.030
ALT (IU/L)	28.5 (11-73)	19 (8-53)	<0.001
FSH (mIU/mL)	2.8 (0.6-9.71)	2.59 (0.34-7.7)	0.139
LH (mIU/mL)	3.13 (0.0-6.87)	1.87 (0.01-8.4)	0.068
E2 (pg/mL)	30.2 (5-52)	25 (5-51)	0.107
T-Test (ng/mL)	1.53 (0.06-5.17)	0.61 (0.03-5.7)	0.182
PRL (ng/mL)	10 (1.58-47.7)	9.5 (4.2-26.4)	0.846
E2/T-Test	20.5 (1.6-161.1)	38 (2.3-475)	0.405
Fat mass (kg)	27.6 (17.7-40.3)	22.3 (13.3-37.1)	0.010
PBF (%)	33.7 (24.8-48)	29.1 (21.8-43.3)	0.149
PTF (%)	28.7 (19.4-41.7)	23.5 (16.9-41.6)	0.081

*Mann-Whitney U test's

NAFLD: Non-alcoholic fatty liver disease, BMI: Body mass index, SDS: Standard deviation score, P: Percentile, TC: Total cholesterol, TG: Triglyceride, HDL-C: High density lipoprotein-cholesterol, LDL-C: Low density lipoprotein-cholesterol, AST: Aspartate aminotransferase, ALT: Alanine amino transferase, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, E2: Estradiol, TTest: Total testosterone, PRL: Prolactin, PBF: Percent of body fat, PTF: Percent of trunk fat

between both TTest and E2 levels with HDL-C. HDL-C is an anti-atherosclerosis factor. In Laskarzewski et al.[20], HDL-C level was negatively correlated with T level and positively associated with E2 level. This suggested the detrimental effect of T on vascular functions and the protective role of E2. If all the patients in our study group were at the same stage of puberty, it would be expected that the HDL-C level would have a positive correlation with E2 and a negative correlation with T-Test, considering that it is antiatherogenic. However, the fact that the cases in our study group are at different stages of puberty may have prevented us from understanding the relationship between E2 and T-Test with HDL-C.

Obesity often leads to NAFLD. Clinical series and population-based studies show that NAFLD is more common in males than in females[21,22]. Differences in the prevalence of NAFLD according to gender strongly suggest that the observed changes in sex hormone levels in males with obesity play a role in the etiopathogenesis of NAFLD. In childhood, studies on the relationship between sex hormones and NAFLD are very limited[23]. It can be thought that changes in sex hormone metabolism and physiological IR during the progression of cancer.

Pubertal development may play a role in susceptibility to NAFLD in children with obesity. In this study, we investigated the relationship between NAFLD and serum sex hormone levels in boys with obesity and gynecomastia. Consistent with the literature, although we found that PBF increased significantly in boys with low T levels, we could not reveal a significant effect of T-Test level on the presence of NAFLD. We did not find a significant difference between E2 and T levels between boys with and without NAFLD. Similar to our findings, in the study by Birzniece et al.[24], it was found that T only stimulates extrahepatic fat oxidation, increases whole body fat oxidation by affecting extrahepatic tissues, and the effect of T level on NAFLD could not be shown. On

the other hand, body fat distribution and regional lipolysis may have an important effect on the pathogenesis of NAFLD. Perhaps if we increase the number of study cases, we may have the opportunity to show lower T-Test levels in the group with NAFLD because of the relationship between low T-Test levels and increased PTF. In the study of Kurku et al.[25], T concentrations in boys with NAFLD were found to be significantly lower than in other groups (non-NAFLD and controls). It has been suggested that higher aromatase activity may induce a decrease in T levels in boys with obesity and NAFLD[25]. In Mueller et al.[26], a lower degree of steatosis and fibrosis was found in boys with higher T. The results of studies investigating the relationship between estrogen levels and NAFLD in childhood are also inconsistent. In the study by Mueller et al.[26], they found that E2 levels decreased in children with severer portal inflammation and fibrosis. Lazo et al.[27] reported that higher E2 was associated with higher levels of liver fat measured by imaging in both adult males and females, and inconsistent effects of E2 on different histological features of NAFLD require further evaluation in pediatric populations.

Study Limitations

This study had some limitations. First, due to cost and risk, the diagnosis of NAFLD was not made from liver biopsy results. NAFLD diagnosis was made by ultrasonographic imaging because of its sensitivity to fat accumulation. USG is the most widely used imaging technique to scan patients with suspected steatosis. Advantages of USG include its excellent security profile, portability, widespread use, and relatively low cost compared with other modalities. However, USG has several important limitations; it is operator- and machine-dependent, and its interpretation is subjective. USG can be useful in detecting severe stratosis, but if the degree of stratosis detected by biopsy is less than 30%, its sensitivity is significantly reduced[28]. Second, circulating androgen levels other than TTest such as SHBG, dehydroepiandrosterone, and androstenedione were not evaluated in our study. Third, the difference in puberty stages of the patients included in the study and the small number of cases may be considered as an important limitation of the study in terms of detecting statistically significant relationships.

Conclusion

Consequently, it is still unclear whether body composition affects sex hormone concentrations or not and conversely, whether sex hormone concentrations alter the body composition or not. However, the relationship between body composition and sex hormones is probably bidirectional. The results reveal that as the PBF and PTF increases, the T-Test levels of the patients decrease and as the fat mass increases, the E2 levels increase significantly. Although we could not find a significant relationship between sex hormones and NAFLD in our study, when animal and human data obtained from previous studies are evaluated, it is clearly understood that sex hormones play a critical role in hepatic lipid homeostasis. However, the results of studies that deal with the effect of sex hormones on the human liver are inconsistent, and all studies, including this study, do not contain gold standard methods for identifying NAFLD and are far from determining causation. The knowledge to be gained from extensive studies in this area will create unique opportunities to develop new therapies to beat NAFLD. Considering the scarcity of available treatments for NAFLD and its long-term harmful consequences, it is necessary to understand the etiopathogenesis of NAFLD to alleviate the course of the disease and to determine appropriate treatment approaches.

Ethics

Ethics Committee Approval: For the study, approval was obtained from the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Researches Ethics Committee (decision no: 2018/18-09, date: 06.12.2018).

Informed Consent: The study protocol was carried out in accordance with the Helsinki criteria. Informed consent was obtained from the families of the patients included in the study.

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Authorship Contributions

Surgical and Medical Practices: D.Ö.K., E.İ., Concept: D.Ö.K., E.İ., Design: D.Ö.K., H.T., E.İ., Data Collection or Processing: D.Ö.K., H.T., Ş.A., Analysis or Interpretation: D.Ö.K., H.T., A.S., Literature Search: D.Ö.K., H.T., Ş.A., A.S., Writing: D.Ö.K., H.T., Ş.A., A.S.

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