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The Diagnostic Value of Free Androgen Index in Obese Adolescent Females with Idiopathic Hirsutism and Polycystic Ovary Syndrome

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ABSTRACT

Objective: The free androgen index (FAI) is the ratio between total testosterone and sex hormone binding globulin (SHBG), and it has been proposed as a marker. FAI is increasingly used in the definitive diagnosis of patients with hyperandrogenism. Although the reference range of FAI in adult females has been identified, there are no adequate studies on the reference range for adolescent girls. We determined the diagnostic value of FAI in adolescent girls diagnosed with obesity, idiopathic hirsutism (IH) and polycystic ovary syndrome (PCOS).

Methods: Patients aged 12 to 21 years and diagnosed with obesity, IH and PCOS were included in the study. FAI was found by calculating the ratio of total testosterone to SHBG.

Results: According to receiver-operating characteristic (ROC) analysis results, FAI level under 3.45 indicated that the participants were healthy. ROC analysis was also used to determine the usefulness of FAI in distinguishingbetween healthy participants and those diagnosed withPCOS, obesity, IH. It was determined that patients with FAI above 6.15 should be evaluated for PCOS.

Conclusion: We concluded that FAI is a reliable marker to identify and followup patients with hyperandrogenism and the reference values we found in our study can be used in clinical practice.

Keywords: Free androgen index, obesity, idiopatic hirsutism, PCOS

INTRODUCTION

Androgen excess is one of the most common endocrine disorders of reproductive-aged women, affecting approximately 7% of this population (1-3). Androgen excess results in the development of androgenic features in the affected women with the development of hirsutism, androgenic alopecia, acne and ovulatory dysfunction, and if it is extreme and prolonged, it could even lead to virilisation and masculinisation (4). Androgen excess is the cardinal underlying phenomenon in various disorders in females, particularly polycystic ovary syndrome (PCOS), idiopathic

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hirsutism (IH), congenital adrenal hyperplasia and ovarian/adrenal neoplasms, as well as insulin resistance/obesity. Increased insulin in obese patients stimulates ovarian androgen production driven by increased luteinising hormone secretion and contributes to hyperandrogenism. Free or bioactive testosterone is responsible for the pathogenesis of androgen excess status. Nevertheless, it is difficult to identify hyperandrogenism in the laboratory in children and adolescents and associate it with clinical findings. However, there is no consensus regarding what serum level is significantly higher and when treatment should be started (5,6). Simple and practical criteria/methods, therefore, need to be developed.

The free androgen index (FAI) is the ratio between total testosterone and sex hormone binding globulin (SHBG), and it has been proposed as a marker. FAI is increasingly used in the definitive diagnosis of patients with hyperandrogenism (5). Although the reference range of the FAI in adult females has been identified, there are no adequate studies on the reference range for adolescent girls (7). In our study, we determined the diagnostic value of FAI in adolescent girls diagnosed with obesity, IH and PCOS.

METHODS

Patients aged 12 to 21 years and diagnosed with obesity, IH or PCOS in the pediatric endocrinology clinic of our hospital were included in the study.

Definition of the groups:

The obesity group consisted of patients with a body mass index (BMI) of >2 standard deviation score (SDS).

IH group consisted of patients with IH who had a Ferriman-Gallwey score 8 or more and no other reason for the hirsutism.

The PCOS group consisted ofpatients who met all of the PCOS Amsterdam 2013 diagnostic criteria for adolescents, which are as follows (8):

1- Oligomenorrhea or primary amenorrhea present 2 years after menarche,

2- At least one ovary of a volume >10 mL,

3- Presence of a clinical and biochemical hyperandrogenism (diagnosis criteria for clinical hyperandrogenism: Ferriman-Gallwey score of 8 or more; diagnostic criteria for biochemical hyperandrogenism: Total testosterone level >51 ng/dL).

The control group consisted of healthy adolescent females with a normal weight, without any clinical or laboratory signs of hyperandrogenism, and not using any medication affecting the androgen metabolism.

Laboratory studies:

Blood samples were drawn in the first week of the menstrual cycle. Total testosterone and SHBG were studied from the sera. All tests were performed at the biochemistry department of our hospital. Total testosterone was measured by solid-phase competitive chemiluminescent enzyme immunoassay, using the ADVIa Centaur-XP instrument (Siemens, Germany), and SHBG was measured by radioimmunoassay, using Beckman Coulter (USA).

FAI and homeostasis model assessment-estimated insulin resistance (HOMA-IR) calculation:

FAI was calculated according to the formula: [total testosterone (nmol/L)/SHBG (nmol/L)]×100 (5). Total testosterone was measured in ng/dL, so ng/dL was converted to nmol/L (ng/dL×0.03470: nmol/L). HOMA-IR was calculated according to the following formula: fasting blood glucose (mg/dL)×fasting blood insulin (IU/mL)/405 (9).

Statistical Analysis

Descriptive statistics for the study variables were presented as median, mean, standard deviation and minimum and maximum values. The Kruskal-Wallis test was used to compare the control and patient groups. The cut-off value for the hormone was determined by receiver-operating characteristic (ROC) analysis. Statistical significance levels were considered at 5%. The SPSS (ver. 13) statistical programme was used for all statistical computations.

The study was approved by the Ethical Committee of Dr. Zekai Tahir Burak Women's Health Training and Research Hospital, and conducted according to the principles of the Declaration of Helsinki. The approval number is 23/2014 (approval date: 15.04.2014). All parents/guardians of the children provided written informed consent before the children were included in the study.

RESULTS

The patients' ages, BMI, BMI-SDS, HOMA-IR, total testosterone, SHBG and FAI values are shown in Table 1. There were differences in ages between the four groups. The PCOS group consisted of patients older than those in the obesity and control groups. The ages of patients in IH group were similar to those in other groups. As expected, BMI and BMI-SDS were higher in the obesity group than the other groups. In addition, BMI and BMI-SDS were found to be higher in the PCOS and IH groups than the control group. While HOMA-IR was similar in obesity, IH and PCOS groups, it was higher in these groups than the control group. While serum total testosterone levels were the highest in the PCOS group (total testosterone: 84.3±22.9 ng/dL), serum total testosterone levels were 68.5±16.3, 60.5±10.6 and 37.1±12.6 ng/dL in IH, obesity and control groups, respectively. There was no difference in testosterone levels between IH and obesity groups. Testosterone levels were lower in the control group than the other groups. While serum SHBG levels were similar in obesity, IH and PCOS groups, it was higher in the control group.

ROC analysis was used to determine the usefulness of FAI in distinguishing healthy adolescents (control group) from other groups. According to ROC analysis, the area under the curve (AUC) was found to be 0.930±0.22. The sensitivity and specificity values for FAI, whose cut-off value was 3.45, were found to be 90% and 84%,respectively. Accordingly, FAI under 3.45 indicated that the participants were healthy (Figure 1).

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Table 1. Patients' clinical features, anthropometric measurements and laboratory values

	Obesity n=26	IH n=26	PCOS n=20	Control n=72	p
Age (years)	14.6±2.02[b] 12-18	15.6±1.56[ab] 12-18	16±1.58[a] 13.5-19	14.9±1.72[b] 12-18	0.040
BMI (kg/m²)	31.7±4.1[a] 26-40.68	24.5±3.88[b] 17.3-31.60	25.4±4.96[b] 18.2-34.9	21±2.82[c] 15.7-27.34	0.01
BMI-SDS	2.8±0.69[a] 2-4.33	1.1±1.1[b] -1.20-3.5	1.2±1.4[b] -1.60-3.98	-0.1±1.2[c] -1.80-1.91	0.01
HOMA-IR*	3.89±1.7[a] 1.44-8.48	3.06±2.2[a] 0.80-11.20	3.19±1.3[a] 1.16-6.60	1.7±0.56[b] 0.90-3.5	0.01
Total testosterone (ng/dL)	60.5±10.6[b] 51-89.10	68.5±16.3[b] 52.97-112.66	84.3±22.9[a] 53.10-142	37.1±12.6[c] 10-50	0.01
SHBG (nmol/L)	23.9±14.8[b] 6.71-66.71	34.8±16[b] 7.35-77.40	28.6±18.1[b] 9.54-75.68	56.1±22.6[a] 17.44-10.2	0.01
FAI (%)	9.9±6.4[a] 1.70-27.30	7.7±6[a] 1.80-29.70	14.4±9.6[a] 3.40-43.0	2.4±1.3[b] 0.20-6.40	0.01

*HOMA-IR was calculated according to the following formula: fasting blood glucose (mg/dL)×fasting blood insulin (IU/mL)/405 (9).
[a,b,c] Statistically different groups represented by different letters ($p<0.05$). IH: idiopathic hirsutism, PCOS: polycystic ovary syndrome, BMI: body mass index, SDS: standard deviation score, HOMA-IR: homeostasis model assessment-estimated insulin resistance, SHBG: sex hormone binding globulin, FAI: free androgen index

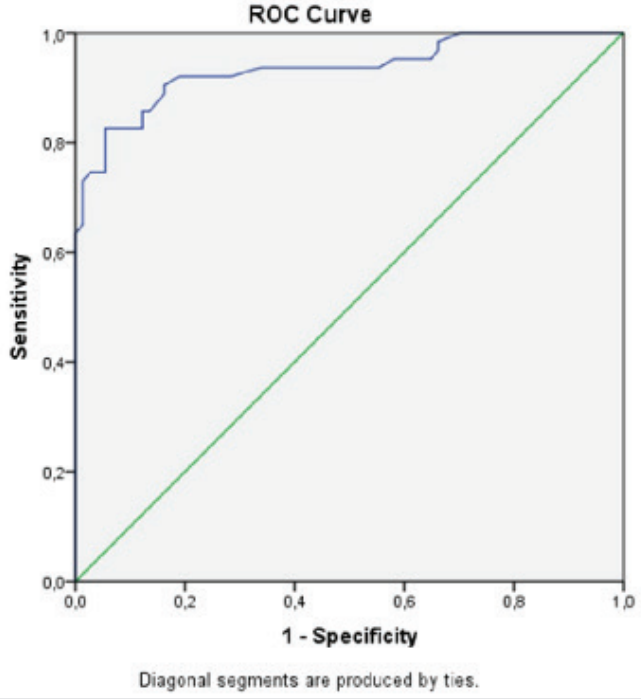

Figure 1. ROC analysis curve detecting the usefulness of free androgen index in distinguishing between the control group and other groups
ROC: receiver-operating characteristic

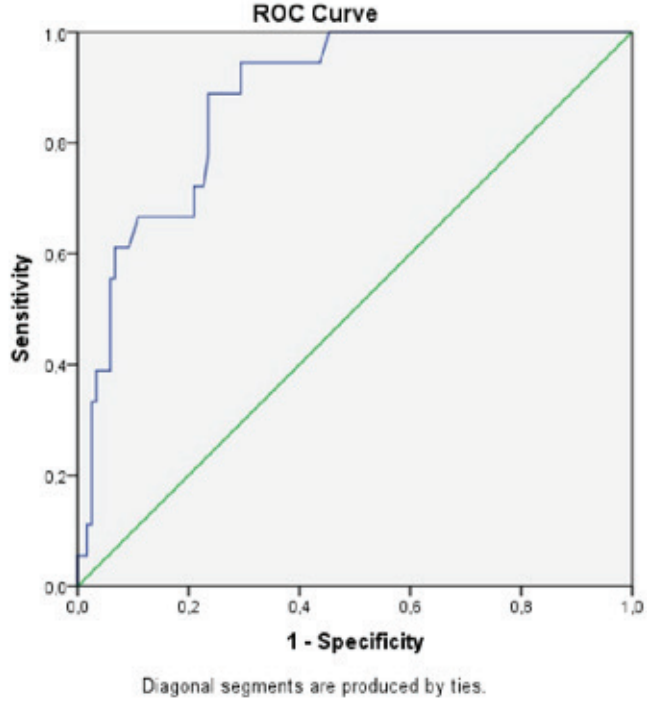

Figure 2. ROC analysis curve detecting the usefulness of free androgen index in distinguishing between polycystic ovary syndrome group and other groups
ROC: Receiver-operating characteristic

ROC analysis was also used to determine the usefulness of FAI in distinguishing between patients in PCOS group and those in obesity and IH groups. According to ROC analysis, AUC was found to be 0.88±0.35. Sensitivity and specificity values for FAI with a cut-off value under 6.15 were found to be 89% and 77%, respectively. Therefore, it was determined that patients whose FAI was above 6.15 should be evaluated for PCOS (Figure 2).

In the obesity group, there was a positive correlation between FAI and BMI (r=0.426; p=0.048) and HOMA-IR (r=0.530; p=0.011).

DISCUSSION

Androgen excess is the cardinal underlying phenomenon in various disorders in females. Free or bioactive testosterone is responsible for the pathogenesis of androgen excess status. It is

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difficult to identify hyperandrogenism in the laboratory in children and adolescents and associate it with clinical findings.

In literature, studies on FAI were commonly conducted on adult females. In a study, Pinola et al. (7) found that FAI was 2.1±1.3 in adult females, whereas it was 4.4±3.8 in females with PCOS. In females aged 18-24 years old, healthy females had an FAI of 1.9±1.1, while females diagnosed with PCOS had an FAI of 4.9±3.2. In addition, it was cited that FAI could be used as an important parameter to diagnose PCOS in all age groups. Our study evaluated adolescentsin the age range of 12-21 years, and it was found that FAI with a cut-off value <3.45 indicated that the participants were healthy and a cut-off value >6.15 indicated that participants should be evaluated for PCOS. These values had a high sensitivity and specificity.

A study from China reported FAI reference range of 0.7-6.4 in 444 patients aged 20-46 years selected from a group of 1,526 females after excluding disorders influencing the androgen level. The 5th percentile FAI value was 0.8 and the 95th percentile value was 6.7 for patients aged 20-28 years. The same study found FAI to be negatively correlated with age. They stated that FAI was higher in patients diagnosed with hirsutism and PCOS than in the healthy population, and BMI and FAI had a positive correlation (10). Moreover, FAI increased in insulin excess (11,12).

In our study, similar to previous studies, a positive correlation was found between FAI and HOMA-IR in the obesity group. In a previous study reported in Mexico, FAI of 83 healthy nonobese females was 5.3±3.8, while that of 238 obese females was 8.5±5.3 (13).

Few studies on FAI in adolescents are available. A study by Ibanez et al. (14) reported that normal FAI in healthy adolescents aged 14-18 years was <5. A Canadian study by Raizman and Quinn (15) investigated FAI in 66 females aged 9-14 years. The lowest value was 0.12 and the highest value was 2.63. In healthy females aged 14-19 years, the lowest and highest values were 0.59 and 6.5, respectively.

The age range of our control group was 12-18 years. The lowest and highest FAI values were 0.2 and 6.4, respectively. These values are close to the values found by Raizman and Quinn (15). In a study by Liimatta et al. (16), FAI was 0.38 (0.32-0.53) in 97 healthy females younger than eight years old and 2.93 (2.33-5.94) in 16 healthy adolescent females.

Few studies investigating FAI values in adolescents with PCOS are available. A study by Yetim et al. (17) reported that FAI was 6.75 (0.97-23.66) in the PCOS group consisting of 53 adolescent females and 3 (0.22-36.65) in the control group. These values are consistent with ours, with a cut-off value of 6.15, indicating a diagnosis of PCOS, and 3.45 in healthy adolescents.

Study Limitations

The limitation of this study is the small number of participants.

CONCLUSION

In our study, we determined that an FAI with a cut-off value of 6.15 indicated a diagnosis of PCOS and 3.45 in healthy adolescents and these valuescan be used in practice. We concluded that FAI is a reliable marker to identify and follow-up patients with hyperandrogenism in clinical situations with elevated androgen levels and that the reference values we found in our study can be used in clinical practice.

Ethics Committee Approval: The study was approved by the Ethical Committee of Dr. Zekai Tahir Burak Women's Health Training and Research Hospital (approval number: 23/2014, approval date: 15.04.2014).

Informed Consent: All parents/guardians of the children provided written informed consent before the children were included in the study.

Peer-review: Externally peer-reviewed.

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