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ORIGINAL ARTICLE – OPEN ACCESS

Evaluation of Subclinical Inflammation in Children with Premature Adrenarche

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ABSTRACT

Objective: The objectives of this study were to compare the serum inflammatory markers, interleukin-6 (IL-6), highly sensitive C-reactive protein (hs-CRP), and fetuin-A, in patients with premature adrenarche (PA) and the control group.

Materials and Methods: This single-center cross-sectional study included 85 non-obese and pre-pubertal children. After 8–12 h of fasting, blood glucose, HDL, LDL, triglyceride, cholesterol, insulin, dehydroepiandrosterone sulfate, total testosterone, 17-OH PG, IL-6, hs-CRP, and Fetuin-A levels were measured and compared in a convenience sample of PA (n=35) and a healthy volunteers of control (n=50) group.

Results: The mean age (7.34±0.62 years vs. 7.09±0.77 years, respectively) and sex (82% girl vs. 80% girl, respectively) of the PA and control groups were similar (p>0.05). Fasting insulin levels (10.9±6.21 Uu/mL vs. 7.4±5.9 Uu/mL; p<0.001), HOMA-IR (2.06±0.63 vs. 1.36±1.00; p=0.017), FGIR (11.31±5.60 vs. 16.46±8.52; p=0.004), and QUICKI (0.35±0.02 vs. 0.37±0.03; p<0.001) levels were different in PA and control groups. IL-6 level higher in PA group than controls [2.7 (3.30) pg/mL vs. 3.02 (1.31) pg/mL, p=0.035], while plasma Fetuin-A [522.02 (715.86) mg/L; 519.4 (945.97) mg/L, p=0.434] and hs-CRP [0.73 (1.02) mg/dL; 1.0 (1.12) mg/dL, p=0.439] levels were similar. IL-6 cutoff value for PA was calculated as 2.06 with 72.7% sensitivity and 48.8% specificity for all study groups (AUC=0.641, p=0.036).

Conclusion: The high IL-6 levels may be an indicator of chronic subclinical inflammation in PA cases. These children should be followed closely in terms of metabolic disorders.

Keywords: Fetuin-A, highly sensitive c-reactive protein, inflammation, interleukin-6, premature adrenarche

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INTRODUCTION

Premature adrenarche (PA) is defined as the presence of isolated genital and/or axillary hair in younger than 8-year-old girls, and younger than 9-year-old boys. Precocious puberty, congenital adrenal hyperplasia, androgen-secreting tumors, and exogenous androgen exposure should be ruled out for the diagnosis of PA (1). Although the pathogenesis is unknown, it has been reported that PA may be related to genetic and epigenetic (intrauterine fetal programming) factors or the early activation of the zona reticularis (1, 2). A typical laboratory finding of the adrenarche is that the dehydroepiandrosterone Sulfate (DHEA-S) level is higher than 40 µg/dl (1). In a study, the prevalence of PA was found to be 8.6% in girls and 1.8% in boys (3).

Although PA has been accepted as a normal variant, emerged studies showed that it may precede many disorders such as polycystic ovary syndrome (PCOS), hyperinsulinemia, cardiovascular diseases, and metabolic syndrome (MeS) (2, 4, 5). The association between PA and the aforementioned diseases has not been clearly explained; it may be related to chronic subclinical inflammation in PA cases. There is a limited study with conflicting reports in the literature investigating subclinical inflammation in children with PA (6–8).

It has been shown that interleukin-6 (IL-6) is the main marker in chronic inflammation and its level increases in inflammatory diseases (9, 10). One of the other well-known markers for inflammatory processes especially in cardiovascular diseases is highly sensitive C-reactive protein (hs-CRP) (11, 12). Fetuin-A, a multifunctional glycoprotein that is synthesized chiefly by the liver, has varied effects on human health (13). It has been shown that Fetuin-A plays an important role in inflammatory processes by regulating cytokine secretions and adipocyte functions (14). It has also been related to some endocrine conditions such as obesity, insulin secretion and effects, and diabetes, as well as calcium and phosphate mineralization (15).

This study aimed to compare the serum inflammatory markers, IL-6, hsCRP, and Fetuin-A, in patients with PA and the control group. To the best of our knowledge, there is no study in the literature comparing Fetuin-A level in PA and their control group. The secondary aim is to compare MeS risk factors (insulin resistance, dyslipidemia, hypertension, and obesity) between groups, and to investigate their correlations with inflammatory markers.

MATERIALS and METHODS

This single-center cross-sectional study was conducted by Sivas Cumhuriyet University Pediatric Endocrinology Department from September 2020 to March 2021. A convenience group of PA and healthy volunteers of the control group were included in the study. Independent t-test power analysis was performed with PASS 2008 software. The sample size was calculated as 40 individuals in each group (α=0.05, β=0.10), according to the effect size of 0.727 determined by our clinical expectations by taking into account the mean and standard deviation statistics of a previous study (6).

The Diagnosis of PA

- The presence of genital and/or axillary hair in girls younger than 8 years, boys younger than 9 years
- Breast Tanner stage one for girls, testicular volume <4 ml for boys
- Exclusion of androgen-secreting tumors, congenital adrenal hyperplasia, and exogenous androgen exposure.

The Exclusion Criteria in both PA and Control Group

The following criteria were excluded from the study:

- Chronic disease history
- Cardiovascular disease risk factors (hypertension, hyperlipidemia, impaired glucose tolerance, and obesity)
- History of chronic drug use
- Obesity or malnutrition
- Fever or signs of infection

Auxological Measurements

Height was measured by the same person with a Harpenden stadiometer, without shoes, and head in the Frankfurt plane. Bodyweight was measured with a Braun branded electronic scale with 0.1 kg precision by removing the thick clothes. Obesity was defined as a BMI above the 95th percentile for the appropriate age- and sex-based Turkish children (16). Blood pressure was measured with an Erka brand sphygmomanometer. Radiography of the left-hand wrist was obtained for bone age determination. Bone age was estimated using the Greulich-Pyle atlas.

Laboratory Analysis

After 8–12 h of fasting, blood was taken from all cases. Blood glucose, HDL, LDL, triglyceride, cholesterol, insulin, DHEA-S, total testosterone, a,d 17-hydroxyprogesterone (17-OHP) levels were measured immediately. Then after centrifugation for 15 min at 3500 rpm, the serum from all the participants was stored at –20°C for analysis of IL-6, hs-CRP, and Fetuin-A levels.

Fasting blood glucose, cholesterol, triglyceride, HDL, and LDL values were evaluated by spectrophotometric method (Roche Cobas c702, Germany). Serum hsCRP concentration was determined by the turbidimetry method (Beckman Coulter, California, USA). Insulin, IL-6, total testosterone, and DHEA-S levels were evaluated using the electrochemiluminescent assay method (Roche Diagnostics, e801, Germany). 17-OHP levels were determined by LC-MS (Thermo Scientific, TSQ Quantum Acess Max). Fetuin-A was studied using the quantitative sandwich enzyme-linked immunosorbent assay method from Shanghai Sunred Biological Technology Co., Ltd, China.

Calculations (17–19)

- Homeostasis Model Assessment for Insulin Resistance (HOMA-IR): (Fasting blood glucose (mg/dL) × fasting insulin (μU/mL)/405)
- Fasting glucose insulin ratio (FGIR): [(Fasting glucose (mg/dL)/fasting insulin (μU/mL)]
- Quantitative Insulin Sensitivity Check Index (QUICKI): [(1/(log (insulin) + log (plasma glucose (mg/dL)]
- Plasma atherogenic index (PAI): log (triglyceride/HDL)

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS/PC 22.0) for Windows software (SPSS, Chicago, IL, USA) was used for statistical analyses. The values were expressed as the mean±standard deviation (SD) for parametric tests, medians (interquartile ranges) for non-parametric tests, or percentage for qualitative results. The normality of data was assessed using Shapiro–Wilks test. The Chi-square test was used for comparisons of gender differences between groups. To compare mean or median, the independent samples t-test or Mann–Whitney U-test were used as appropriate. Pearson or Spearman rank correlation values were used for the evaluation of quantitative data correlations. P<0.05 was accepted as statistically significant.

Cumhuriyet University Clinical Research Ethics Committee approved the study protocol (dated 17.9.2020 and numbered 2020–09/03). Informed assent was taken from children, and informed consent was taken from parents.

RESULTS

Eighty-five non-obese, pre-pubertal children [PA (n=35), and Control Group (n=50)], aged 5–8 years old, included the study. The mean age (7.34±0.62 years vs. 7.09±0.77 years, respectively) and sex (82% girl vs. 80% girl, respectively) of the PA (n=35) and control (n=50) groups were similar (p=0.573). PA group had higher weight (27.6±4.7 kg vs. 23.4±5.03 kg, respectively), height (126.08±5.84 cm vs. 121.3±8.22 cm, respectively), and BMI (17.3±2.2 kg/m^2, 15.7±1.7 kg/m^2) than control group (p<0.001; p=0.005; p=0.001, respectively). The systolic blood pressure (100±10 mmHg vs. 94.4±16.9) and the percent of small for gestational age (8.6% vs. 2%) were higher in the PA group than in control; however, the differences were not statistically significant (p=0.095; p=0.301, respectively) (Table 1).

When we compared PA and control group's biochemical parameters; fasting blood glucose (88.62±7.6 mg/dL vs. 86±7.0 mg/dL, p=0.223), HDL (53.5±13.3 mg/dL vs. 57.9±14.9 mg/dL, p=0.184), LDL (98.09±24.5 mg/dL vs. 98.1±41.88 mg/dL, p=0.980), cholesterol (153.6±26.9 mg/dL vs. 156.5±32.3 mg/dL, p=0.330), triglyceride (78.4±36.9 mg/dL, 84.7±50.4 mg/dL, p=0.922), and PAI levels (0.13±0.24 vs. 0.12±0.299, p=0.764) were similar.

Table 1. Anthropometric, biochemical, and physiological characteristics of the cases included in the study

	PA (n=35)	Control (n=50)	p
Age, year	7.34±0.62	7.09±0.77	0.129
Sex, girl %	82	80	0.573
SGA, %	8.6	2	0.301
Bodyweight, kg	27.6±4.7	23.4±5.03	<0.001
Bodyweight-SDS	0.58±0.75	-0.17±0.80	<0.001
Height, cm	126.08±5.84	121.3±8.22	0.005
Height-SDS	0.39±0.77	-0.18±0.76	<0.001
BMI, kg/cm^2	17.3±2.2	15.7±1.7	0.001
BMI-SDS	0.54±0.78	-0.04±0.77	<0.001
SBP, mmHg	100±10	94.4±16.9	0.095
DBP, mmHg	58.7±8.1	60±8.6	0.523
Glucose, mg/dL	88.62±7.6	86±7.0	0.223
Insulin, Uu/mL	10.9±6.2	7.4±5.9	0.006
Cholesterol, mg/dL	153.63±26.9	156.5±32.3	0.330
HDL, mg/dL	53.5±13.3	57.9±14.9	0.184
LDL, mg/dL	98±24.5	98.1±41.88	0.980
Triglyceride, mg/dL	78.4±36.9	84.7±50.4	0.922
PAI	0.13±0.24	0.12±0.29	0.764
DHEA-S, µg/dL	68.8 (196.5)	17.8 (212.2)	<0.001
17-OH PG, ng/mL	0.36±0.31	1.15±1.44	0.440

SDS: Standard deviation, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HDL: High density lipoprotein, LDL: Low density lipoprotein, DHEA-S: Dehydroepiandrosterone-sulfate, 17-OH PG: 17-hydroxyprogesterone PAI: Plasma atherogenic index

Fasting insulin levels (10.9±6.21 Uu/mL vs. 7.4±5.9 Uu/mL; p<0.001), HOMA-IR (2.06±0.63 vs. 1.56±1.00; p=0.017), FGIR (10.70±5.59 vs. 16.46±8.52; p=0.004), and QUICKI (0.35±0.02 vs. 0.37±0.03; p<0.001) levels were different in PA and control groups (Fig. 1). In addition, serum DHEA-S level was higher in case group [68.8 (196.5) µg/dL] than control group [17.8 (212.2) µg/dL] as expected, p<0.001).

Inflammatory parameters were also compared in PA and control groups; IL-6 level higher in PA group than controls [2.7(3.30) pg/mL vs. 3.02 (1.31) pg/mL, p=0.035], while plasma Fetuin-A [522.02 (715.86) mg/L; 519.4 (945.97) mg/L, p=0.434], and hs-CRP [0.73 (1.02) mg/dL; 1.0 (1.12) mg/dL, p=0.439] levels were similar (Fig. 2). IL-6 cutoff value for PA was calculated as 2.06 with 72.7% sensitivity and 48.8% specificity for all study groups (AUC=0.641, p=0.036) (Fig. 3).

The correlations between inflammatory markers (IL-6, Fetuin-A and hsCRP), androgen levels (DHEA-S and 17-OHP), insulin resistance parameters (HOMA-IR, QUICKI and FGIR), and lipid profiles were evaluated. There were no significant correlations between inflammatory markers and the other parameters. However, HOMA-IR level as an insulin resistance parameter was significantly correlated with triglyceride (r=0.34, p<0.001) and PAI (r=0.38, p<0.001) levels.

DISCUSSION

The major outcome of the study was a higher level of IL-6 in children with PA than healthy age- and sex-similar controls. We also found that the IL-6 cutoff value for PA was 2.06 with 72.7% sensitivity and 48.8% specificity. However, it should be taken into account that the calculated AUC value was 0.641, indicating a moderate diagnostic accuracy. In addition, these children had higher HOMA-IR and fasting insulin levels with lower FGIR and QUICKI

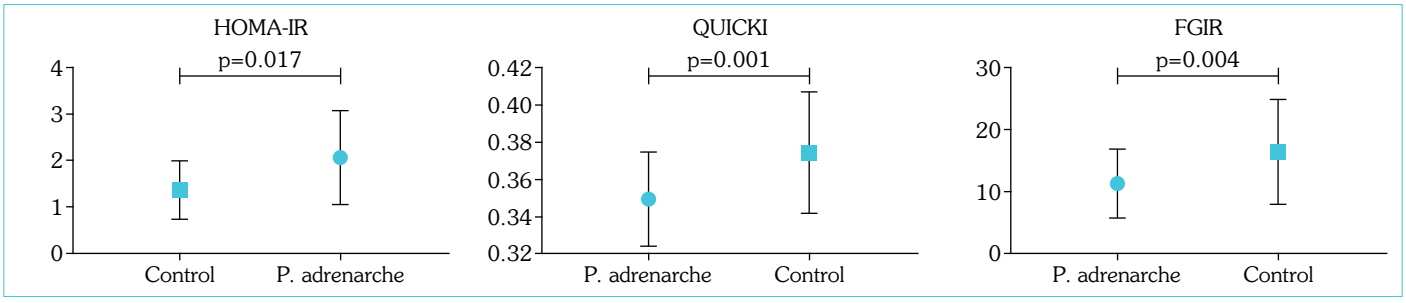

Figure 1. HOMA-IR, QUICKI, and FGIR values as an indicator of insulin resistance of the PA and Control Groups (Error Bar represent mean±SD)

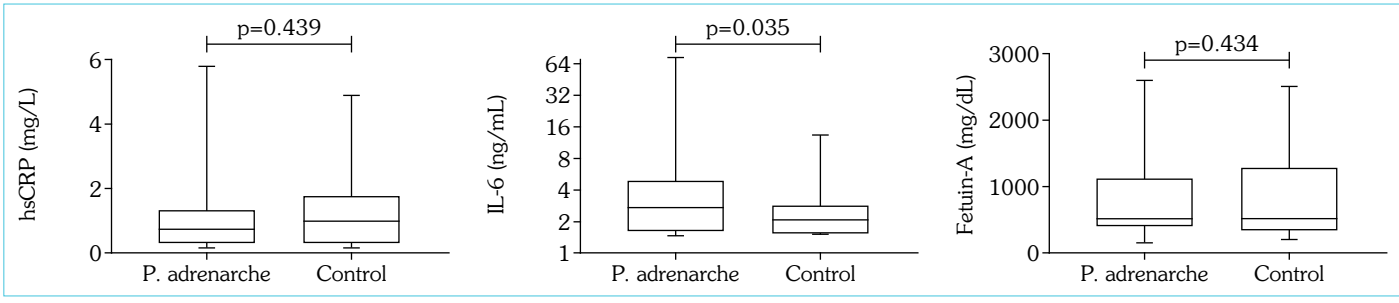

Figure 2. Level of Inflammatory markers (Interleukin-6, high sensitive c-reactive protein, and fetuin-a) in Patients with PA and Control Groups

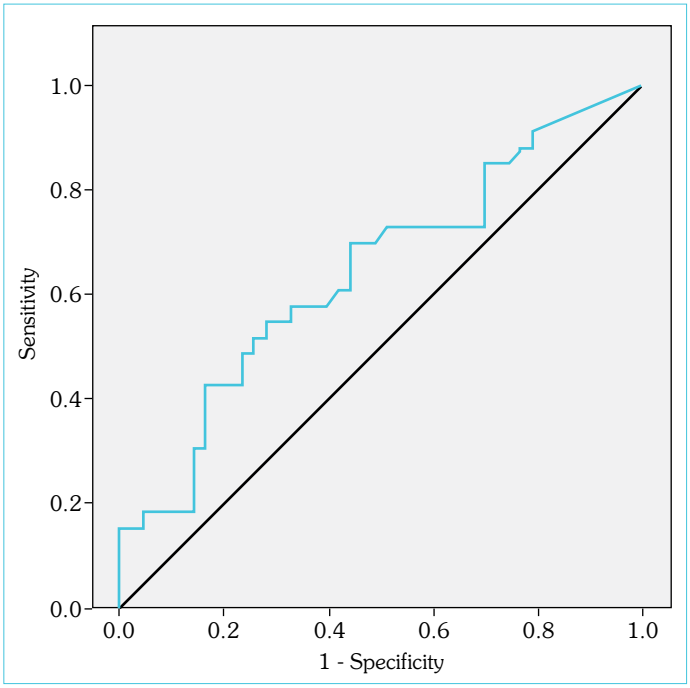

Figure 3. Receiver operating characteristic (ROC) curve of the IL-6 level on detection of Premature Adrenarche. The cutoff value was calculated as 2.06 with 72.7% sensitivity and 48.8% specificity (AUC=0.641, p=0.036)

levels, suggesting a tendency for increased insulin resistance. As a matter of fact, although the PA and the control groups were selected among non-obese children, the BMI level of the PA group was slightly higher than the control group. Hence, high IL-6 levels in the PA group may be related to BMI level. However, there was no significant correlation between IL-6 level and BMI-SDS in this cohort. Hence, we thought that increased IL-6 level in the PA group was independent of BMI. However, more comprehensive studies are needed on this subject.

PCOS and MeS risk factors (dyslipidemia, insulin resistance, hypertension, and obesity) are more common in individuals with a history of PA (4, 20, 21). This association may be related to chronic subclinical inflammation in cases with PA (21, 22). There are conflicting reports in a limited number of studies investigating the role of chronic subclinical inflammation in patients with PA. These studies were conducted either in children with a diagnosis of PA (6) or in adolescent and adult women with a history of PA (8).

Firstly, in a study with limited number of patients with pre-pubertal PA (n=10), Mathew et al. (7) showed that TNF-α and IL-8 levels were high in the lean pre-pubertal PA group, whereas IL-6 and CRP levels were not different. Similarly, in another study, comparing TNF-α and IL-6 levels in a pre-pubertal group of 73 PA and 98 control, it has been found that TNF-α levels were higher in the PA group, whereas the mean serum IL-6 concentrations between the study groups were similar (6).

Livadas et al. (8), in a study, conducted on 45 adolescents with a history of PA with a mean age of 13.1±3.4 and 19 healthy controls of similar age showed that CRP, androgen, and plasminogen activator inhibitor type-1 (PAI-1) levels, insulin resistance indices were higher, and tissue plasminogen activator levels were statistically lower than PA group than controls. In this study, levels of TNF-α and IL-6 were higher in the PA group but were not statistically significant. Based on these findings, the authors speculated that adolescents with a history of PA may have subclinical inflammation and fibrinolytic abnormalities. The most important limitation of this study is the small number of cases, especially in the control group. Furthermore, the coexistence of pre-pubertal, pubertal, and post-menarchial cases was additional important limitation that may affect the results. On the other hand, Mauras et al. (23) showed that hs-CRP, IL-6, and PAI-1 were higher in obese pre-pubertal children than the non-obese peers, indicating the higher pro-inflammatory and prothrombotic state was independent of puberty. In our study, we similarly showed that IL-6 level is high in pre-pubertal and non-obese children with PA.

Ibanez et al. (4) showed that TNF-α and CRP values in non-obese hyperinsulinemic and hyperandrogenemic adolescents (n=31, mean age 16 years) were significantly higher than the control group. However, the PA history of the patients was not questioned in this study. In another study, they showed that increased BMI and leptin levels were associated with low birth weight and insulin resistance in patients with PA in a study of 42 non-obese children and adolescents (24). It has also been shown that the PAI-1 levels of 33 PA girls (6–11 years old) were higher than the control group and suggested that a high level of PAI-1 in children with PA may be an indicator for PCOS development in their later life (25).

In our study, we also found that HOMA-IR, QUICKI, and FGIR values as an indicator of insulin resistance of the PA group were different from the control group. This finding was consistent with the previous studies (4, 26, 27). However, there were some studies showed that insulin resistance parameters were similar in cases with PA and their controls (28, 29).

CONCLUSION

The high IL-6 levels may be an indicator of chronic subclinical inflammation in PA cases. These children are at increased risk for MeS, and PCOS in their later life. Therefore, children with PA should be followed closely in terms of metabolic disorders. Prospective studies with an increased number of cases are needed on this subject.

Ethics Committee Approval: The Cumhuriyet University Clinical Research Ethics Committee granted approval for this study (date: 17.09.2020, number: 2020–09/03).

Informed Consent: Written informed assent and consent were obtained from all participants and their parents before any procedures.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – NÇ; Design – NÇ, GK; Supervision – NÇ; Resource – NÇ, GK, HOD; Materials – NÇ, HOD; Data Collection and/or Processing – GK; Analysis and/or Interpretation – NÇ, GK; Literature Search – NÇ, GK, HOD; Writing – NÇ; Critical Reviews – NÇ, GK, HOD.

Conflict of Interest: The authors have no conflict of interest to declare.

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