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Evaluation of Insulin Resistance in Patients with Premature Adrenarche

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ABSTRACT:
Purpose: There is a conflicting result in terms of insulin resistance (IR) in children with Premature Adrenarche (PA). The study aimed to investigate the IR and Trıglycerıde-Glucose (Ty-G) index in patıents wıth PA.
Material and Methods: This cross-sectional study was conducted in a tertiary pediatric endocrinology clinic with 160 children aged 6-8 years old. The study group (n=75) were selected cases diagnosed with PA. Seventy-nine age and sex-matched children were also selected as a control group. Ty-G İndex Homeostasis Model of Insulin Resistance (HOMA-IR), and atherogenic index of plasma (AIP) were calculated.
Results: Trıglycerıde-Glucose index, AIP, and HOMA-IR were similar (p>0.05). Ty-G İndex was positively correlated with AIP (r=0.61, p<0.001), BMI-SDS (r=0.26, p=0.002), and HOMA-IR (r=0.33, p<0.001) levels. The DHEA-S level was correlated with the AIP (r=0.24, p=0.005), and BMI-SDS (r=0.17, p=0.03) levels. BMI-SDS was correlated with HOMA-IR (r=0.28, p=0.02) levels.
Conclusion: Non-obese children with PA have similar IR parameters compared with control groups. Therefore, additional evaluation for IR parameters in lean children with PA is not required.
Keywords: *Premature Adrenarche, Insulin Resistance, Triglyceride Glucose index, Homeostasis Model of Insulin Resistance, Plasma atherogenic index*

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INTRODUCTION

Premature adrenarche (PA) is defined as the appearance of the onset of sexual hairs (pubic and/or axillary) before eight years of age in girls, and nine years of age in boys (Ibáñez et al., 2017). For the diagnosis, the other androgen excess conditions (such as Congenital Adrenal Hyperplasia, and exogenous androgen source) should be excluded. It is seen 4-9 times more in girls than in boys (Rosenfield, 2021). Although considered a benign condition, It has been shown that children with PA are at risk for future metabolic syndrome, polycystic ovary syndrome (PCOS), hirsutism, and cardiovascular complications (Çelik et al., 2017; Ibáñez et al., 2017; Oberfield et al., 2011).

Insulin resistance (IR) is described as the deterioration of glucose balance in hepatic cells and peripheral tissue due to decreased insülin sensitivity. The hyperinsulinemic-euglycemic clamp test(HEC) is considered the main method for insulin resistance (Cersosimo et al., 2014). On the other hand, studies have shown that it has a high correlation with the Homeostasis Model of Insulin-Resistance (HOMA-IR) levels and the clamp test(Keskin et al., 2005). It was also determined that the Triglyceride Glucose (Ty-G) index, that is another method for measuring IR, also strongly correlated with HOMA-IR and HEC (Ashraf et al., 2014; Guerrero-Romero et al., 2010)

There is a conflicting result in terms of IR in children with PA. In the literature, some of the studies

investigating IR in patients with PA indicate that IR is present, and some are not. (Kaya et al., 2018; Utriainen et al., 2007). Moreover, to our knowledge, there is no study evaluating the Ty-G index in patients with PA. We aimed to investigate Ty-G and IR indexes among children diagnosed with PA.

MATERIAL and METHODS

Purpose and Type of the Study

The was a cross-sectional study in design. We evaluated 160 children aged 6-8 years old in a tertiary pediatric endocrinology clinic. The study aimed to investigate the IR and Trıglyceride-Glucose (Ty-G) index in patıents wıth PA.

Sampling and participant

The study group (n=75) were selected cases diagnosed with premature adrenarche. Seventy-nine children who were brought to the hospital for routine control were also selected as a control group. The exclusion criteria were obesity/overweight (Body Mass Index (BMI) levels higher than the 90th percentiles), having a chronic disorder, being pubertal, or using any medication.

Diagnostic criteria for Premature Adrenarche;

• Early sexually hair (pubic and/or axillary) development (eight-year for girls, and nine-year for boys)

• Being prepubertal; no breast development in girls (Tanner grade 1), testicular volume lower than 4 mL in boys,

• Other causes of increased androgen levels such as late-onset congenital adrenal hyperplasia or adrenal/gonadal tumor should be ruled out.

Data Collection Tools

Fasting blood samples were taken from all study groups by 09:00 hours. Fasting glucose levels and lipid profiles (cholesterols, triglycerides) were evaluated with the colorimetric method (Germany, Roche-Cobas, c702). Dehydroepiandrosterone Sulfate and insülin levels were also determined by the ECL method (Germany, Roche-Cobas e801)

Calculations

1. Triglyceride-Glucose Index (Ty-G Index)(Simental-Mendía et al., 2008): Ln["Fasting-triglyceride level in mg/dL" × "fasting plasma glucose in mg/dL"/2])
2. Homeostasis Model of Insulin Resistance (HOMA-IR) (Keskin et al., 2005): *HOMA-IR=["Fasting insulin level in µU/mL" x" Fasting glucose level in mg/dL"]/405]*
3. Atherogenic Index of Plasma (AIP) (Sapunar et al., 2018): log (triglyceride / HDL)

Statistical Analysis

SPSS 13.0 for Windows (SPSS, Inc., Chicago, Illinois, U.S.A.) was used for statistical calculations. Kolmogorov-Smirnov was performed to check for normality. Student t test, and the chi-square test were used to investigate associations between Continuous and categorical variables, respectively. Correlations among parameters were estimated using the Pearson correlation coefficient analysis. Values except gender were expressed as the mean±standard deviation (SD); $p < 0.05$ was considered statistically significant.

Ethical Approval

Sivas Cumhuriyet University ethics board approved the study protocol. (16.02.2022/2022-02/12)

RESULTS

The mean ages and percent of the sex were similar in the control and PA groups (p=0.18, and p=0.24, respectively). Body weight (p<0.001), Body-weight-SDS (p<0.001), Height (p=0.001) Height-SDS (p=0.001) , BMI (p=0.001), and BMI-SDS (p=0.001) were significantly different (Table 1).

Concentrations of dehydroepiandrosterone sulfate were higher in the PA group than in the comparison group, expectedly (89.6±59.0 vs 41.3±39.7; p<0.001). However, AIP, HOMA-IR, and TyG Index were similar (p>0.05) (Table 2).

We also investigated the correlations between TY-G, HOMA-IR, AIP BMI-SDS, and DHEA-SO4 levels: Ty-G index was correlated with AIP (r=0.61, p<0.001), BMI-SDS (r=0.26, p=0.002), and HOMA-IR (r=0.33, p<0.001) levels. The DHEA-S level was correlated with the AIP (r=0.24, p=0.005) and BMI-SDS (r=0.17, p=0.03) levels. BMI-SDS was correlated with HOMA-IR (r=0.28, p=0.02) levels (Figure 1).

Table 1. Socio-demographic characteristics of the study and control groups

	Study Group (n=75)	Control Group (n=75)	p
Age, *year*	7.5±0.9	7.3±1.1	0.18
Sex (% Girl)	83.5	75.3	0.24
Body-weight, *kg*	26.2±4.3	23.2±4.4	<0.001
Body-weight-SDS	0.4±0.9	-0.2±0.9	<0.001
Height, *cm*	126.2±6.6	122.3±7.9	0.001
Height-SDS	0.3±08	-0.1±0.9	0.001
BMI, *kg/cm²*	16.6±1.9	15.6±1.7	0.001
BMI-SDS	0.2±0.8	-0.2±0.8	0.001

Data are given as mean ± SD. BMI, body mass index

Table 2. Basal Metabolic Parameters of the study and control groups

	Study Group (n=75)	Control Group (n=75)	p
Glucose, *mg/dL*	87.5±7.5	86.7±6.6	0.46
Insulin, *Uu/mL*	9.5±6.5	7.4±5.5	0.07
AIP	0.03±0.2	-0.02±0.2	0.20
HOMA-IR	2.0±1.4	1.5±1.3	0.06
Ty-G index	8.0±0.3	7.9±0.4	0.45
DHEA-S, *µg/dL*	89.6±59.0	41.3±39.7	<0.001
Cholesterol, *mg/dL*	156.2±28.9	153.4±29.0	0.57
HDL, *mg/dL*	71.3±29.8	78.4±40.7	0.23
LDL, *mg/dL*	75.1±28.6	69.0±21.6	0.15
TG, *mg/dL*	76.5±34.4	75.3±43.0	0.84

Data are given as mean ± SD. AIP, Atherogenic index of plasma; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; Ty-G index, Triglyceride-Glucose index; DHEA-S, Dehydroepiandrosterone Sulfate; HDL, High-Density Lipoprotein; LDL, low-density lipoprotein; TG, Triglyceride

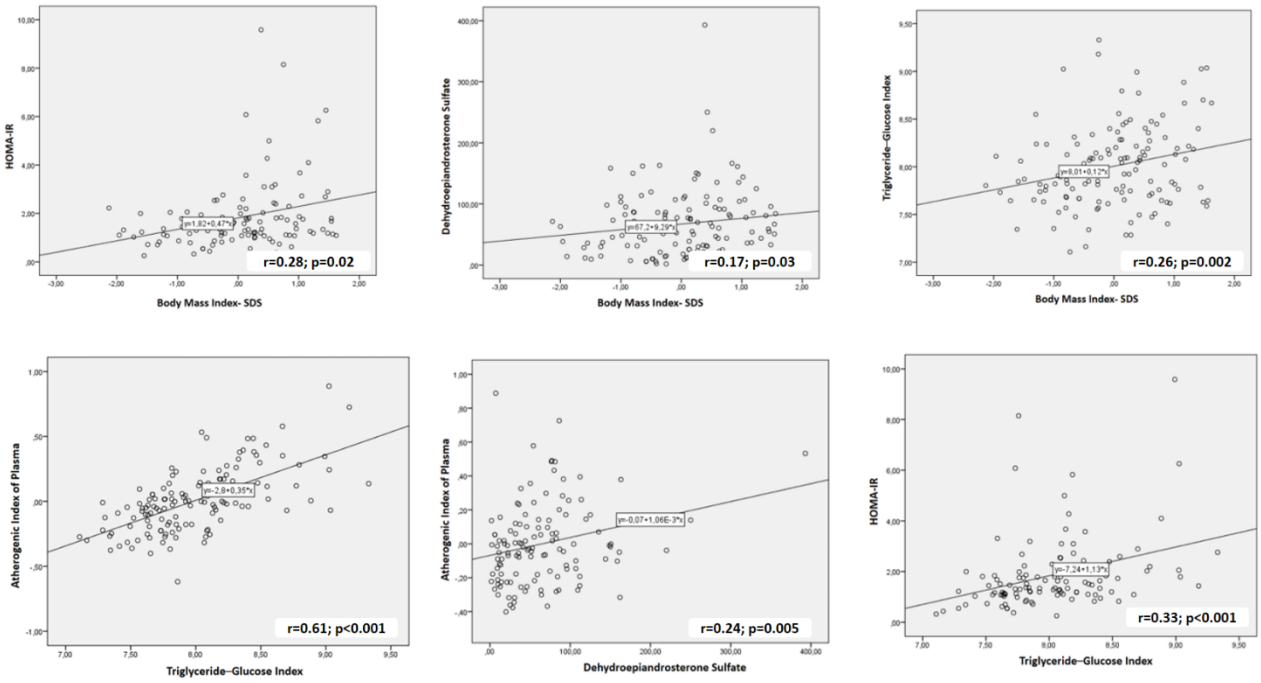

Figure 1. Correlations beween Atherogenic index of plasma, Homeostatic Model Assessment of İnsulin Resistance, Triglyceride-Glucose index, and Dehydroepiandrosterone Sulfate levels

DISCUSSION

The primary conclusion of this study is that insulin resistance parameters are similar in prepubertal non-obese children with and without PA. There is a conflicting result in terms of insulin resistance in children with PA(Kaya et al., 2018; Utriainen et al., 2007). In parallel with our study, Kaya et al.(Kaya et al., 2018) showed that the HOMA-IR level in lean prepubertal children was similar to the control group. However, they also suggested that the level was statistically higher in the obese and PA group than obese children without PA. So, they speculated that BMI at the onset of the diagnosis may be an important risk factor for IR. When we subdivided according to BMI-SDS as below and above the 50th percentiles (data is not given), there were no differences in terms of HOMA-IR. On the contrary, it has been shown that 7.5-8 years old finish children with PA had higher HOMA-IR levels than controls(Utriainen et al., 2007).

Studies about the Ty-G index developed by Simental-Mendia and colleagues have shown that it is highly correlated with the HEC method and HOMA-IR (Guerrero-Romero et al., 2010; Simental-Mendía et al., 2008; Vasques et al., 2011; Wan et al., 2015). A lot of studies conducted on the Ty-G index in the pediatric age group, such as obesity, PCOS, Type 2 diabetes, and metabolic syndrome (Aslan Çin et al., 2020; Taştanoğlu et al., 2021; Yoon et al., 2022). To our knowledge, there is no literature review of the Ty-G index in the PA. We showed that Ty-G index as a surrogate marker for insulin resistance was similar in non-obese children with or without PA. However, this index was correlated with the HOMA-IR level and the AIP index.

In our study, although the subjects were selected from non-obese children, BMI and BMI-SDS were increased in the PA group than in the control group. In line with the study, Ibanez et al.(Ibáñez et al., 2003) showed that girls with diagnosed PA aged 6-18 years old had increased BMI and total fat mass. They also suggested that adiposity is related to insulin and androgen levels in this cohort. We found that BMI-SDS was positively correlated with DHEA-SO4, HOMA-IR, and Ty-G. Corvalan et al.(Corvalán et al., 2013) showed that obese children two-fold risk for highly DHEA-SO4 levels in seven years old non-obese, prepubertal children.

Childhood lipid disorders are a well-known risk factor for metabolic syndrome and cardiovascular complications(Mosca et al., 2022). Dyslipidemia has been investigated in many studies in patients with PA; While some studies have found that the blood lipid profile is similar to the control group(Bezen et al., 2022; de Jesus Teixeira et al., 2004; Utriainen et al., 2007), the others showed that patients with PA have dyslipidemia(Ibáñez et al., 1998, 2000). These different results may be related to the study groups. As a matter of fact, in some studies, as in our study, prepubertal and non-obese children were evaluated, while in some studies, adolescents or adults with a history of PA were included in the study. In our study, blood lipid levels and AIP of children with PA were similar to the control group. We also found that the DHEA-SO4 level was correlated with AIP.

There were certain limitations in the study. First, we have a relatively small sample size. Secondly, gold-standard tests for detection of the IR such as the euglycemic clamp test or oral glucose tolerance test were not applied.

In conclusion, when non-obese children with PA were compared with the control group, these children did not have insulin resistance. Therefore, no additional evaluation for IR parameters is required initially when evaluating these children. More extensive studies are needed to investigate this issue.

Conflict of Interest

The Submitters do not declare any competing interests.

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