ORIGINAL ARTICLE

DOI: 10.4274/jcrpe.galenos.2022.2022-1-1

J Clin Res Pediatr Endocrinol 2022;14(4):385-392

Evaluation of Glucose Metabolism and Cardiovascular Risk Factors in Prepubertal Girls with Premature Pubarche

Diğdem Bezen[1], Filiz Tütüncüler Kökenli[2], Emine Dilek[2], Didem Ağ Seleci[3], Hakan Erbaş[3]

[1]University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşçıoğlu City Hospital, Clinic of Pediatrics, Division of Pediatric Endocrinology, İstanbul, Turkey

[2]Trakya University Faculty of Medicine, Department of Pediatrics, Clinic of Pediatric Endocrinology, Edirne, Turkey

[3]Trakya University Faculty of Medicine, Department of Biochemistry, Edirne, Turkey

What is already known on this topic?

Isolated premature pubarche (PP) is regarded as a warning sign of intrauterine-programmed metabolic syndrome.

What this study adds?

PP is not a risk factor alone for impaired glucose metabolism and insulin resistance in non-obese girls with normal birth weight before puberty.

Abstract

Objective: Premature pubarche (PP) is a risk factor for metabolic syndrome (MS). The aim was to evaluate if glucose-insulin metabolism, cardiovascular risk factors, familial cardiovascular risk factors (FCVRF) created a risk for insulin resistance (IR) and if PP was a risk factor alone for MS in normal weight prepubertal girls with PP.

Methods: Thirty-five prepubertal, non-obese girls with PP with normal birth weight and 35 age-matched control girls were evaluated for FCVRF, anthropometric measurements, blood pressure, lipid profile, fasting blood glucose-insulin, hemoglobin A1c (HbA1c), sex hormone binding globulin (SHBG), leptin, adiponectin, tumor necrosis factor-alpha (TNF-α), androgen levels, and bone age. Oral glucose tolerance test was performed in PP participants. Homeostasis model of assessment of IR (HOMA-IR), fasting glucose/insulin ratio, atherogenic index (AI), and free androgen index (FAI) were calculated. PP participants were further stratified by FCVRF.

Results: HbA1c, lipid profile, testosterone, leptin, adiponectin, TNF-α, HOMA-IR, glucose/insulin ratio, AI, and fasting glucose-insulin levels were similar. In the PP group FAI was significantly higher ($p = 0.001$), whereas SHBG was significantly lower ($p = 0.010$) than the control group. Leptin levels of FCVRF + and FCVRF- subgroups were 15.2 ± 9.1 and 9.7 ± 7.2 ng/mL, respectively and the difference was significant ($p = 0.016$).

Conclusion: As PP does not appear to be a risk factor alone for impaired glucose metabolism and IR in prepubertal non-obese girls with normal birth weight, it is our opinion that it is unnecessary to examine in detail such cases before puberty. Low SHBG levels in the PP group and high leptin levels in FCVRF + subgroup might suggest that these may be predictive for MS in the future.

Keywords: Premature pubarche, prepubertal, leptin, glucose metabolism, adipocytokines, cardiovascular risk

Introduction

Puberty as a result of adrenal gland activity, known as adrenarche, is characterized by an increase in circulating androgen precursors, dehydroepiandrosterone (DHEA) and its sulfate ester (DHEA-S). Adrenarche is usually accompanied by pubarche; genital and/or axillary hair. If this situation occurs before the age of eight years in girls and before the age of nine years in boys, it is called, "premature pubarche" (PP)' (1). The incidence of PP, depending on societal and racial factors, varies between 5-8.6 % (2). In a study conducted in Turkey, the incidence of PP was reported to be 4.6 % (3). The female/male ratio in PP is approximately

Address for Correspondence: Diğdem Bezen MD, University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşçıoğlu City Hospital, Clinic of Pediatrics, Division of Pediatric Endocrinology, İstanbul, Turkey
Phone: + 90 532 628 37 71 **E-mail:** demboli4@yahoo.com **ORCID:** orcid.org/0000-0003-3977-5527

Conflict of interest: None declared
Received: 29.01.2022
Accepted: 25.05.2022

10/1 (4). Prematurity, intrauterine growth retardation, being overweight or obese predispose to PP (1,2,3,4,5,6).

Even though isolated (normal variant) PP is a benign condition, PP is currently accepted as a warning sign for intrauterine-programmed metabolic syndrome (MS), especially in obese children with a diagnosis of PP. Early diagnosis of MS and its components is important for detection, prevention, and early treatment because patients with MS are at risk of type 2 diabetes mellitus and cardiovascular diseases (5,7,8,9).

It has been shown that isolated PP predisposes to hyperinsulinemia and insulin resistance (IR), not only in obese children, but also in non-obese children. In these cases, low sex hormone binding globulin (SHBG) levels have been shown to be a useful marker for detecting IR (5). It has also been reported that the risk of MS is increased within this group and increased tumor necrosis factor-α (TNF-α) levels may be a predictive marker for MS (10). When compared to healthy controls, SHBG and insulin-like growth factor binding protein-1 have been found to be lower, whereas insulin-like growth factor-1 (IGF-1), TNF-α, adiponectin and insulin levels have been found to be higher (10,11). It is speculated that in these cases, hyperinsulinemia also causes dyslipidemia, and as a result, at an early age, cardiovascular risk begins to increase (5). Family history of type 2 diabetes mellitus and cardiovascular disease has been reported to be more frequent in girls with PP (12). In the light of this evidence, the aim of this study was to evaluate if glucose and insulin metabolism, cardiovascular risk factors, and familial cardiovascular risk factors (FCVRF) are associated with the risk of IR in normal-weight, prepubertal PP girls.

Methods

The patient group consisted of non-obese girls having no breast development and birth weights appropriate for gestational age (AGA), who were in follow-up with the diagnosis of PP from the outpatient clinic of Trakya University Medical Faculty Hospital, Department of Pediatric Endocrinology. Patients with breast development, chronic illnesses, any kind of drug use, congenital adrenal hyperplasia or virilizing tumor were excluded. An equal number of girls, born AGA, and who were non-obese and prepubertal were included as the control group. The patients and the families of the participants were informed about the study and signed informed consent forms were obtained from the mother or father of the participant and the child before they were recruited to the study. The study was conducted after approval was given by the Ethics Committee of Trakya University Faculty of Medicine (TÜTF-TÜBAPK date: 11.06.2013, approval no: 121).

Participants' data, including birth date, gestational age, birth weight, current height and weight measurements, waist-hip circumference measurements, and blood pressure (BP) measurements, and pubertal examination based on Tanner staging, were obtained and recorded. The presence or absence of cardiovascular risk factors, including type 2 diabetes mellitus, polycystic ovary syndrome, MS, dyslipidemia and familial cardiovascular disease (premature atherothrombotic cardiovascular disease, occurring in a first-degree male relative before 55 years of age or in a first-degree female relative before 65 years of age) were recorded (13). Height, weight measurements, and the body mass index (BMI) values and their standard deviation (SD) scores (SDS) were calculated using reference values for Turkish children (14).

Two mL of blood were drawn from all participants at 08.30 in the morning after 10 hours of fasting, and DHEA-S, androstenedione (AS), 17-hydroxyprogesterone (17-OHP), total testosterone (T), lipid profile [high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol, triglyceride (TG)], hemoglobin A1c (HbA1c), SHBG, TNF-α, leptin and adiponectin levels were measured. Free androgen index (FAI), defined as total T/SHBG, and atherogenic index (AI) defined as TG/HDL, were calculated. Oral glucose tolerance test (OGTT) (with 1.75 g/kg glucose, maximum of 75 g glucose) was performed in participants with PP, again at 8.30 in the morning after 10 hours of fasting and blood glucose and insulin values were obtained at baseline (0 minutes) and two hours (120 minutes). From the OGTT results, patients with hyperinsulinemia (those with fasting insulin >15 mIU/mL and/or 120th minute insulin level >75 mIU/mL) and IR [homeostasis model of assessment (HOMA-IR) >2.5] were identified. HOMA-IR was calculated using the standard formula: fasting blood glucose (mmol/L) x 18 x insulin (mIU/L)/22.5 and/or fasting glucose/insulin ratio <7 (15). For the determination of bone age (BA), a radiographic examination of the left wrist was completed for each participant, and BA was assessed by comparison with the Greulich-Pyle radiological atlas. BA SDS were calculated using the programme BoneXpert V3.1 (16). The study group was divided into two subgroups based on the presence (FCVRF+) or absence (FCVRF-) of FCVRF.

Blood glucose, LDL, HDL, TG, and total cholesterol levels were measured by spectrophotometry on an Advia 1800 device; insulin, DHEA-S, and T levels were measured by microparticle chemical immunoassay on an Abbott Architect i2000SR and leptin, adiponectin, and TNF-α levels were measured by immunoassay, also on the Architect i2000SR. SHBG and

AS levels were measured by immunoassay on the Siemens Immulite 2000 (Siemens Healthcare Diagnostics Inc. Flanders, HbA1c level was determined by high performance ion-exchange liquid chromatography using Adams HA-8180V analyzer (Arkray Factory Inc., Shiga, Japan) and 17-OHP levels were measured by radioimmunoassay on the gamma counter DPC Gambyt CR (DPC Diagnostic Products Corporation, Los Angeles, CA, USA) at the department of nuclear medicine. Left hand wrist radiographs were taken with the Philips Optimus Bucky Diagnost TS device.

Statistical Analysis

Normality of the distribution of the parameters was analyzed with Shapiro-Wilk test. Logarithmic or square root transformations were applied to non-normally distributed parameters to obtain normal distribution. Independent samples t-test was used for two group comparisons. All the results except for BA SDS were expressed as mean ± SD also for the data before the transformation was applied for easy understanding clinically. BA SDS data was expressed as median (minimum-maximum) because of normal distribution could not be obtained. Mann-Whitney U test was used for the comparison of BA SDS between two groups. All statistical analysis were performed by SPSS 20 statistical software (IBM Corp., Armonk, NY, USA). The value $p < 0.05$ was accepted as statistically significant.

Results

There were 35 patients in the PP group and 35 healthy girls in the control group. The mean ages of the PP and control groups at the time of the study were 8.3 ± 1.1 and 8.1 ± 1 years, respectively. Birth weights, gestational weeks, presence of FCVRFs, weight SDSs, height SDSs, waist/hip ratios, BA SDSs and BP values of the groups were similar. Although, the mean BMI SDS values were within normal ranges in both groups, they were significantly higher in the PP group than in the control group (Table 1).

There was no difference between the groups in terms of HbA1c level, lipid profiles, HOMA-IR scores, glucose/insulin ratios and AIs. In the PP group, serum DHEA-S, AS, and 17-OHP levels were significantly higher, whereas T levels were similar. Serum leptin, adiponectin, and TNF-α levels were similar in both groups. Fasting and 120th minute glucose and insulin levels of the PP participants and the fasting glucose and insulin levels of the control group participants were within normal limits, and there was no significant difference between the groups in terms of fasting glucose and insulin levels. FAI was significantly higher and SHBG was significantly lower in the PP group. Laboratory findings of the groups are shown in Table 2.

When the PP group was divided by the presence of FCVRF, the clinical and laboratory findings, except for leptin levels, were similar. The FCVRF+ PP group had significantly lower leptin levels than in FCVRP- PP group ($p = 0.016$). Comparisons of the clinical and laboratory findings of the PP sub-groups, stratified by the presence of FCVRF, are shown in Tables 3 and 4.

Discussion

Regardless of age and developmental stage, nutritional status is a physiological regulator of adrenarche. Starting from the age of five, an increase in fat tissue, insulin and IGF-1 levels associated with an increase in BMI enhances the expression of steroidogenic enzymes and the production of androgens in adrenocortical cells (17). Although, weight SDS, height SDS, and BMI SDS were within normal limits in our study, as previously reported (18,19), BMI SDS was found to be significantly higher in the group with PP compared to the control group. In contrast to an earlier study by Ibáñez et al. (20) conducted on participants with similar BMIs, in the present study mean waist/hip ratio was within normal limits and was similar between the groups. However, in the Ibáñez et al. (20) study, in which waist/hip ratio was increased their patients also had and hyperinsulinemia associated with an increase in central adiposity, whereas in our cohort the insulin levels of the PP patients were within normal limits.

The BA of young children normally averages within 33% of chronological age. BA advancement is early evidence of a hyperandrogenic condition, unless it is very mild or of very recent onset. However, BA may be normal early in the course of rapid virilization (21). In our study, BA SDS was similar in both groups, consistent with some literature (12,18) and it was within normal limits for age and pubertal stage. As suggested by Sopher et al. (22), in our study when BMI was within normal limits, PP alone does not appear to be a factor that increased BA, despite hyperandrogenemia.

Systolic and diastolic BP values are components of the MS criteria and are significant in cases with PP. In some studies, in which PP and healthy control participants were compared (10,18,19,23,24), blood pressure values were found to be within normal limits, similar to our study. Based on this evidence, it has been suggested that PP alone does not affect BP, if there is no increase in fat tissue, resulting in obesity or overweight in prepubertal period.

In the PP group, androgen precursors other than for T were significantly higher than in the control group. However, TNF-α, leptin, and adiponectin levels, all adipocytokines, were found to be similar in both groups. When glucose metabolism, another component of the MS, was evaluated

Table 1. Clinical findings of PP and control cases

Clinical findings	PP (n = 35)	Control (n = 35)	p
	Mean ± SD	Mean ± SD	
Birth weight (g)	3230 ± 405.9	3290.2 ± 371.7	NS
Gestation week (week)	39.4 ± 0.9	39.4 ± 0.8	NS
Family	n (%)	n (%)	
FCVRF +	16 (45.7)	14 (40)	NS
FCVRF-	19 (54.3)	21 (60)	NS
At the time of study	Mean ± SD	Mean ± SD	
Age (year)	8.3 ± 1.1	8.1 ± 1	NS
Weight SDS	0.56 ± 0.97	0.15 ± 0.95	NS
Height SDS	0.92 ± 1.11	0.65 ± 1.23	NS
BMI SDS	0.34 ± 0.83	-0.04 ± 0.78	**0.026**
Waist/Hip ratio	0.86 ± 0.04	0.85 ± 0.04	NS
Systolic BP (mmHg)	93 ± 3.47	93.14 ± 3.44	NS
Diastolic BP (mmHg)	63.29 ± 4.36	63.71 ± 3.5	NS
	Median (minimum-maximum)	Median (minimum-maximum)	
BA SDS	-0.40 (-2.5-2.1)	-0.90 (-3.8-2.3)	NS

PP: premature pubarche, SDS: standard deviation score, FCVRF: familial cardiovascular risk factor, BMI: body mass index, BA: bone age, BP: blood pressure, NS: not significant

Table 2. Laboratory findings of PP and control cases

Laboratory findings	PP (n = 35)	Control (n = 35)	p
	Mean ± SD	Mean ± SD	
Adipocytokine and adipokines			
TNF-α (pg/mL)	1.95 ± 0.84	1.81 ± 0.93	NS
Leptin (ng/mL)	12.27 ± 8.53	13.33 ± 13.03	NS
Adiponectin (µg/mL)	14.06 ± 5.42	15.81 ± 11.69	NS
Fasting lipid profile (mg/dL)			
Cholesterol	152.3 ± 26.6	155.4 ± 29.4	NS
Triglyceride	65.8 ± 31	67.7 ± 27.6	NS
LDL	90.2 ± 25.8	93 ± 22.8	NS
HDL	58 ± 12.4	57.9 ± 11.3	NS
OGTT			
Glucose (mg/dL)			
0.min	79.7 ± 8.2	80.6 ± 7.6	NS
120.min	97 ± 15	-	-
Insulin (µU/mL)			
0.min	6.6 ± 2.9	7.3 ± 4.1	NS
120.min	31.6 ± 18	-	-
HbA1c (%)	5.1 ± 0.3	5.1 ± 0.2	NS
HOMA-IR	1.2 ± 0.6	1.4 ± 0.8	NS
Fasting glucose/insulin ratio	15.2 ± 8.6	14.7 ± 8.8	NS
SHBG (nmol/L)	52.9 ± 24.2	72.9 ± 38.2	**0.010**
AI	1.2 ± 0.69	1.22 ± 0.62	NS
FAI	1.15 ± 0.62	0.85 ± 0.85	**0.001**

PP: premature pubarche, SDS: standard deviation score, TNF-α: tumor necrotizing factor-α, LDL: low density lipoprotein, HDL: high density lipoprotein, OGTT: oral glucose tolarence test, HbA1c: hemoglobin A1c, HOMA-IR: homeostasis model of assessment-insulin resistance, SHBG: sex homone binding globulin, AI: atherogenic indeks, FAI: free androgen index, NS: not significant

in PP participants, in many studies fasting glucose values (24,25,26,27,28), fasting insulin values, glucose/insulin ratio, HOMA-IR, postprandial glucose-insulin values (12,25,29,30) and HbA1c values (19) were within normal limits, and we obtained similar results. Liimatta et al. (31) evaluated patients diagnosed with PP twice, both at an average age of seven years and at an average age of 18 years. These authors showed that the factor affecting glucose metabolism was not the risk factors present in the prepubertal period, but the adipose tissue present in the pubertal stage. However, in some studies, fasting insulin levels and HOMA-IR were reported to be high and glucose/insulin ratio was reported to

Table 3. Comparison of clinical findings of the PP cases regarding the presence of FCVRF

Clinical findings	FCVRF + (n = 16) Mean ± SD	FCVRF- (n = 19) Mean ± SD	p
Birth weight (g)	3300 ± 445.5	3171 ± 371.1	0.357
Gestation week (week)	39.5 ± 0.8	39.3 ± 1	0.541
Diagnosis age (year)	7.2 ± 0.7	7.1 ± 0.9	0.817
At the time of the study			
Age (year)	8.3 ± 1.1	8.3 ± 1.1	0.960
Weight SDS	0.9 ± 0.81	0.28 ± 1.02	0.069
Height SDS	1.3 ± 1.22	0.59 ± 0.92	0.085
BMI SDS	0.61 ± 0.5	0.12 ± 0.99	0.159
BA SDS	0.15 ± 1.24	-0.52 ± 1.33	0.123
Waist/hip ratio	0.87 ± 0.48	0.86 ± 0.03	0.228
Systolic BP (mmHg)	92.8 ± 3.6	93.1 ± 3.4	0.774
Diastolic BP (mmHg)	62.5 ± 4.4	63.9 ± 4.2	0.336

SDS: standard deviation score, FCVRF: familial cardiovascular risk factor, BMI: body mass index, BA: bone age, BP: blood pressure, PP: premature pubarche

Table 4. Comparison of laboratory findings of the PP cases regarding the presence of FCVRF

Laboratory findings	FCVRF + (n = 16) Mean ± SD	FCVRF- (n = 19) Mean ± SD	p
DHEA-S (µg/dL)	124.9 ± 54.2	109.6 ± 48.4	0.329
17-OHP (ng/mL)	0.81 ± 0.3	0.96 ± 0.28	0.120
AS (ng/mL)	0.75 ± 0.37	0.7 ± 0.41	0.733
T (ng/dL)	16.3 ± 8.5	14.2 ± 3.3	0.341
SHBG (nmol/L)	47.7 ± 16.6	57.4 ± 28.8	0.312
TNF-α (pg/mL)	2.07 ± 0.78	1.84 ± 0.9	0.415
Leptin (ng/mL)	15.2 ± 9.1	9.7 ± 7.2	**0.016**
Adiponectin (µg/mL)	13.4 ± 5	14.5 ± 5.7	0.596
Cholesterol (mg/dL)	154.7 ± 26.8	150.3 ± 26.9	0.635
Triglyceride (mg/dL)	71.8 ± 35	60.6 ± 27.2	0.267
LDL (mg/dL)	97.7 ± 27.1	83.9 ± 23.6	0.117
HDL (mg/dL)	54.8 ± 11.5	60.6 ± 12.9	0.174
Fasting glucose (mg/dL)	79.6 ± 9.5	79.8 ± 7.3	0.765
120. min blood glucose (mg/dL)	96.5 ± 14.4	97.4 ± 15.9	0.778
Fasting insulin (µU/mL)	7.1 ± 3.3	6.1 ± 2.6	0.312
120. min blood insulin (µU/mL)	32.4 ± 14.8	30.9 ± 20.8	0.371
HbA1c (%)	5 ± 0.2	5.1 ± 0.3	0.435
HOMA-IR	1.39 ± 0.72	1.21 ± 0.58	0.508
Fasting glucose/insulin ratio	14.7 ± 9.9	15.7 ± 7.5	0.312
AI	1.38 ± 0.82	1.05 ± 0.53	0.208
FAI	1.34 ± 0.77	0.99 ± 0.41	0.085

SD: standard deviation, FCVRF: familial cardiovascular risk factor, DHEA-S: dehydroepiandrosterone-sulphate, 17-OHP: 17-hydroxyprogesterone, AS: androstenodione, T: total testosterone, SHBG: sex homone binding globulin, TNF-α: tumor necrotizing factor-α, LDL: low density lipoprotein, HDL: high density lipoprotein, HbA1c: hemoglobin A1c, HOMA-IR: homeostasis model of assessment-insulin resistance, AI: atherogenic indeks, FAI: free androgen index, PP: premature pubarche

be low in children with PP (26,32). The reason for impaired glucose metabolism and IR in these studies might possibly be related to the pubertal status of the cases. In our study, it was found that glucose, insulin, and HOMA-IR levels were similar between the PP and the control groups, and there was no impairment in glucose metabolism in the PP group, which could be due to the participants not being overweight or obese, participants being prepubertal and thus not yet experiencing any increase in adiposity. Thus we suggest that isolated PP in the prepubertal period might not pose a risk in terms of MS.

Dyslipidemia is an important biochemical disorder that causes cardiovascular risk to begin at an early age. In PP cases, some studies reported deterioration in lipid profile including an increase in total cholesterol, TG, LDL and decrease in HDL (18,25), whereas other studies reported the absence of dyslipidemia and the lipid profile to be within normal limits (19,29,32). In our study, lipid profile and AI were within normal limits in both groups. In studies in which dyslipidemia was detected, PP subjects were pubertal, and who were also obese and had hyperinsulinemia (18,25). It is possible that the reason lipid profiles were within normal limits, both in the PP group and in the control group in our study, was that the PP subjects were both prepubertal and of normal weight. We therefore speculate that isolated PP in the prepubertal period does not pose a strong risk for the development of dyslipidemia.

In our study, SHBG levels in the PP group were significantly lower than in the control group, and this finding was similar to other published studies (18,19,26,32). FAI was significantly higher in the PP group when compared to the control group. Although, this finding was similar to some studies (18,26,32), some of these studies included pubertal participants (26,32), while some of the others included obese PP participants, who were prepubertal. Ibáñez et al. (18) suggested that elevated FAI in prepubertal participants was a result of hyperinsulinemia. In our study, even though the participants in the PP group were prepubertal, non-obese and had normal birth weight, FAI was significantly elevated. This suggests that some mechanism(s) other than puberty, an increase in adipose tissue and hyperinsulinemia might be responsible for the occurrence of low SHBG and elevated FAI. One of these mechanisms may be intrauterine programming or genetic polymorphisms and other genetic variations that could affect enzyme expression, which plays a role in SHBG production in the liver. In order to test this hypothesis, studies with large numbers of participants, genetic studies and long-term follow-up are needed.

It has been shown that TNF-α, an adipocytokine, is a predictive marker for type 2 diabetes mellitus and coronary heart disease (33). Mathew et al. (10) reported that BP and TNF-α levels were high in both normal weight and overweight PP cases, and that this adipocytokine might be an important factor in the development of hypertension, a component of MS. In another study (32), it was shown that TNF-α levels in PP participants were similar to the control group. In our study, TNF-α level was found to be similar in both the PP group and the control group, and this similarity was primarily attributed to the presence of similar weight SDS and similar insulin levels in both groups. Leptin, also an adipokine, reflects the nutritional status of the body. Teixeira et al. (29) found that serum leptin levels were normal in PP cases with normal BMI and elevated in overweight cases. This finding led them to suggest that an increase in leptin level was not associated with PP but was directly related to increased BMI. Corvalán et al. (34) showed that obesity in 7-year-old children with normal birth weight was directly related to DHEA-S levels, whereas insulin, IGF-1 and leptin levels were only weakly associated with high DHEA-S, but strongly associated with obesity. In our study, serum leptin levels in PP participants were similar to the control group and this finding was attributed to the normal BMI SDS values of PP participants. Once again, we suggest that this is evidence that isolated PP does not lead directly to an elevation in serum leptin levels. It has been shown that adiponectin, another adipokine, increases insulin sensitivity and has a lower level in babies born small for gestational age (SGA) (8,35). Unlike in some studies (28,36), in our study serum adiponectin levels were normal in PP participants. Larqué et al. (28) found that postprandial adiponectin levels were lower in cases with PP when compared to the control group, yet they did not present birth weight data for their cases. Nieuwenhuis et al. (36) reported that adiponectin triggers puberty earlier in obese children. The serum adiponectin levels of the PP participants being similar to the control group in our study might be due to the fact that the study participants had normal birth weight, were non-obese and prepubertal without hyperinsulinemia.

A family history of cardiovascular disease is important for the development of MS, and it has been reported that it is more common in patients with PP than in healthy children (12). There are studies reporting the incidence of FCVRF in PP cases varies greatly, from 31.8% (23) to as high as 92.5% (25). In our study, there was no significant difference in the proportion reporting FCVRF between the PP group (45.7%) and the healthy control group (40%). When the PP group was divided into two subgroups, based on the presence or absence of FCVRF, it was found that mean leptin levels in the FCVRF+ subgroup were significantly higher than in the FCVRF- subgroup. The present study is the first published to divide and compare PP cases according to FCVRF history in

terms of clinical, biochemical, hormonal and adipocytokine statuses. The high serum leptin levels in the FCVRF+ PP group suggested that high serum leptin levels might be a predictive criterion for the development of obesity, MS or cardiovascular disease in the future. Once again, to test this hypothesis, studies with large numbers of participants and long-term follow-up are needed.

This study was conducted only in non-obese and prepubertal girls with normal birth weight, excluding SGA birth, puberty and obesity, which pose risks for the development of MS, independent of PP. The results appear to show that the prepubertal period in these PP patients does not pose a risk in terms of IR and cardiovascular risk.

Study Limitations

This study had several limitations. The sample size was small. OGTT was not performed in the control group and glucose metabolism was evaluated only with fasting glucose and insulin. Low SHBG levels and high leptin levels were found to be predictive factors but to support these findings long term follow up would be needed.

Conclusion

In conclusion, PP alone does not appear to be a risk factor for impaired glucose metabolism and IR in non-obese girls with PP with normal birth weight and before puberty. Additionally, low SHBG levels can be a predictive marker of hyperandrogenism in prepubertal girls with PP and high leptin levels in the FCVR+ subgroup may be a marker of future obesity risk but long term follow up studies are needed to test these hypotheses.

Ethics

Ethics Committee Approval: The ethics committee approval was obtained from Ethics Committee of Trakya University Faculty of Medicine (TÜTF-TÜBAPK date: 11.06.2013, approval no: 121).

Informed Consent: Informed consent was obtained from all parents/guardians and children included in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Diğdem Bezen, Filiz Tütüncüler Kökenli, Design: Diğdem Bezen, Filiz Tütüncüler Kökenli, Data Collection or Processing: Diğdem Bezen, Analysis or Interpretation: Diğdem Bezen, Filiz Tütüncüler Kökenli, Emine Dilek, Didem Ağ Seleci, Hakan Erbaş, Literature Search: Diğdem Bezen, Filiz Tütüncüler Kökenli, Writing: Diğdem Bezen.

Financial Disclosure: This study was supported by a project grant from the Trakya University Scientific Research Project Institution (TÜBAP date: 11.06.2013, approval no: 121).

References

1. Miller WL. The adrenal cortex and its disorders. In: Brook CGD, Clayton PE, Brown RS (Eds.). Brook's clinical pediatric endocrinology. 6th ed. UK: John Wiley&Sons Ltd, 2009;281-326.
2. Utriainen P, Laakso S, Liimatta J, Jääskeläinen J, Voutilainen R. Premature adrenarche--a common condition with variable presentation. Horm Res Paediatr 2015;83:221-231. Epub 2015 Feb 7
3. Atay Z, Turan S, Guran T, Furman A, Bereket A. The prevalence and risk factors of premature thelarche and pubarche in 4-to 8-year-old girls. Acta Paediatr 2012;101:e71-e75. Epub 2011 Sep 23
4. Saenger P, Dimartino-Nardi J. Premature adrenarche. J Endocrinol Invest 2001;24:724-733.
5. Ibáñez L, Dimartino-Nardi J, Potau N, Saenger P. Premature adrenarche--normal variant or forerunner of adult disease? Endocr Rev 2000;21:671-696.
6. Ibáñez L, Potau N, De Zegher F. Endocrinology and metabolism after premature pubarche in girls. Acta Paediatr Suppl 1999;88:73-77.
7. Alikaşifoğlu A. Erken puberte. Darendeliler F, Aycan Z, Kara C, Özen S, Eren E (eds). Çocuk Endokrinolojisi ve Diyabet. İstanbul: İstanbul Medikal Sağlık ve Yaşam Yayıncılık; 2021.
8. Chen X, Jia X, Qiao J, Guan Y, Kang J. Adipokines in reproductive function: a link between obesity and polycystic ovary syndrome. J Mol Endocrinol 2013;50:R21-R37.
9. Bideci A. Normal varyant erken puberte. Darendeliler F, Aycan Z, Kara C, Özen S, Eren E (eds). Çocuk Endokrinolojisi ve Diyabet. İstanbul: İstanbul Medikal Sağlık ve Yaşam Yayıncılık; 2021.
10. Mathew RP, Byrne DW, Linton MF, Vaughan DE, Fazio S, Russell WE. Evidence of Metabolic Syndrome In Lean Children With Premature Pubarche At Diagnosis. Metabolism 2008;57:733-740.
11. Ibáñez L, Potau N, Zampolli M, Riqué S, Saenger P, Carrascosa A. Hyperinsulinemia and decreased insulin-like growth factor-binding protein-1 are common features in prepubertal and pubertal girls with a history of premature pubarche. J Clin Endocrinol Metab 1997;82:2283-2288.
12. Silfen ME, Manibo AM, Ferin M, McMahon DJ, Levine LS, Oberfield SE. Elevated free IGF-I levels in prepubertal Hispanic girls with premature adrenarche: relationship with hyperandrogenism and insulin sensitivity. J Clin Endocrinol Metab 2002;87:398-403.
13. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK, Smith SC Jr, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Nishimura R, Ohman EM, Page RL, Stevenson WG, Tarkington LG, Yancy CW; American College of Cardiology Foundation; American Heart Association. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010;56:e50-e103.
14. Neyzi O, Günöz H, Furman A, Bundak R, Gökçay G, Darendeliler F, Baş F. Weight, height, head circumference and body mass index references for Turkish children. Çocuk Sağlığı ve Hastalıkları Dergisi 2008;51:1-14
15. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462-1470.

16. BoneXpert Version 3.1 [Internet]. 2021 [date of last access 10.04.2021]. Adress of Access: https://bonexpert.com/ahp/
17. Remer T, Manz F. Role of nutritional status in the regulation of adrenarche. J Clin Endocrinol Metab 1999;84:3936-3944.
18. Ibáñez L, Potau N, Chacon P, Pascual C, Carrascosa A. Hyperinsulinaemia, dyslipaemia and cardiovascular risk in girls with a history of premature pubarche. Diabetologia 1998;41:1057-1063.
19. Utriainen, P, Jääskeläinen, J, Romppanen J, Voutilainen R. Childhood metabolic syndrome and its components in premature adrenarche. J Clin Endocrinol Metab 2007;92:4282-4285. Epub 2007 Aug 14
20. Ibáñez L, Ong K, de Zegher F, Marcos MV, del Rio L, Dunger DB. Fat distribution in non-obese girls with and without precocious pubarche: central adiposity related to insulinaemia and androgenaemia from prepuberty to postmenarche. Clin Endocrinol (Oxf) 2003;58:372-379.
21. Rosenfield RL. Normal and premature adrenarche. Endoc Rev 2021;42:783-814.
22. Sopher AB, Jean AM, Zwany SK, Winston DM, Pomeranz CB, Bell JJ, McMahon DJ, Hassoun A, Fennoy I, Oberfield SE. Bone age advancement in prepubertal children with obesity and premature adrenarche: possible potentiating factors. Obesity (Silver Spring) 2011;19:1259-1264. Epub 2011 Feb 10
23. Uçar A, Saka N, Baş F, Hatipoğlu N, Bundak R, Darendeliler F. Reduced atherogenic indices in prepubertal girls with precocious adrenarche born appropriate for gestational age in relation to the conundrum of DHEAS. Endocr Connect 2012;2:1-10.
24. Çelik N, Alp H, Çamtosun E, Alp E, Çelik S, Berk E. The Association between premature adrenarche and cardiovascular risk may be greater than expected. Horm Res Paediatr 2017;87:7-14. Epub 2016 Nov 22
25. Siklar Z, Oçal G, Adiyaman P, Ergur A, Berberoğlu M. Functional ovarian hyperandrogenism and polycystic ovary syndrome in prepubertal girls with obesity and/or premature pubarche. J Pediatr Endocrinol Metab 2007;20:475-481.
26. Potau N, Williams R, Ong K, Sánchez-Ufarte C, de Zegher F, Ibáñez L, Dunger D. Fasting insulin sensitivity and post-oral glucose hyperinsulinaemia related to cardiovascular risk factors in adolescents with precocious pubarche. Clin Endocrinol (Oxf) 2003;59:756-762.
27. Williams KM, Oberfield SE, Zhang C, McMahon DJ, Sopher AB. The relationship of metabolic syndrome and body composition in children with premature adrenarche: is it age related? Horm Res Paediatr 2015;84:401-407. Epub 2015 Oct 30
28. Larqué E, Gil-Campos M, Villada I, Ramírez-Tortosa MC, Cañete R, Gil A. Postprandial plasma adiponectin response is reduced in prepubertal premature pubarche girls. Metabolism 2010;59:1319-1326. Epub 2010 Jan 21
29. Teixeira RJ, Ginzbarg D, Rodrigues Freitas J, Fucks G, Silva CM, Bordallo MA. Serum leptin levels in premature pubarche and prepubertal girls with and without obesity. J Pediatr Endocrinol Metab 2004;17:1393-1398.
30. Ibáñez L, Potau N, Francois I, de Zegher F. Precocious pubarche, hyperinsulinism, and ovarian hyperandrogenism in girls: relation to reduced fetal growth. J Clin Endocrinol Metab 1998;83:3558-3562.
31. Liimatta J, Utriainen P, Laitinen T, Voutilainen R, Jääskeläinen J. Cardiometabolic Risk Profile Among Young Adult Females With a History of Premature Adrenarche. J Endocr Soc 2019;3:1771-1783.
32. Livadas S, Dracopoulou M, Vasileiadi K, Lazaropoulou C, Magiakou MA, Xekouki P, Voutetakis A, Kanaka-Gantenbein C, Papassotiriou I, Stefanadis C, Chrousos GP, Dacou-Voutetakis C. Elevated coagulation and inflammatory markers in adolescents with a history of premature adrenarche. Metabolism 2009;58:576-581.
33. Rifai N, Ridker P. Inflammatory markers and coronary heart disease. Curr Opin Lipidol 2002;13:383-389.
34. Corvalán C, Uauy R, Mericq V. Obesity is positively associated with dehydroepiandrosterone sulfate concentrations at 7 y in Chilean children of normal birth weight. Am J Clin Nutr 2013;97:318-325. Epub 2013 Jan 2
35. Kamoda T, Saitoh H, Saito M, Sugiura M, Matsui A. Serum adiponectin concentrations in newborn infants in early postnatal life. Pediatr Res 2004;56:690-693. Epub 2004 Sep 15
36. Nieuwenhuis D, Pujol-Gualdo N, Arnoldussen IAC, Kiliaan AJ. Adipokines: A gear shift in puberty. Obes Rev 2020;21:e13005. Epub 2020 Jan 30