Metabolic syndrome frequency in longitudinally followed children with premature adrenarche during pubertal ages

Gamze Kaya[1], Şükran Poyrazoğlu[2], Oğuz Bülent Erol[3], Seha Saygılı[1], Mine Şükür[2], Firdevs Baş[2], Rüveyde Bundak[2], Feyza Darendeliler[2]

[1]I.U. İstanbul Faculty of Medicine, Department of Pediatrics, [2]I.U. İstanbul Faculty of Medicine , Pediatric Endocrinology Unit, [3]I.U. İstanbul Faculty of Medicine , Pediatric Radiology Unit

Introduction: Premature pubarche is defined as the appearance of pubic hair before age 8 years in girls and 9 years in boys, without other sexual development indicators. An important cause of premature pubarche is premature adrenarche (PA). PA is a benign situation which does not require treatment. However, follow-up in PA is needed for morbidities with increasing age, including metabolic syndrome, type 2 diabetes and polycystic ovary syndrome (PCOS).

Objective: To evaluate metabolic syndrome parameters in PA children during presentation in prepuberty and afterwards in puberty.

Methods: Fifty-four patients (48 girls, 6 boys) (mean age 12.5±2.4 years) diagnosed with PA and followed until puberty were included in our study; as the control group 28 (22 girls, 6 boys) (age, sex, puberty matched) healthy children (mean age 13.5±2.2 years) were taken. The study population consisted of children who were followed with the diagnosis of PA until inclusion in the study protocol. Congenital adrenal hyperplasia (CAH) was ruled out in all PA children. Exaggerated adrenarche was defined as DHEAS level >130 µg/dL at presentation. Data of birth and presentation (anthropometric and hormonal) of cases were taken from the files. During investigation, anthropometric measurements, lipid levels, hormonal parameters, adipocytokines (adiponectin, leptin, ghrelin, visfatin, resistin, RBP-4, TNF-α, IL-6) were evaluated and oral glucose tolerance test (OGTT) was done. Pelvic US (female) and Carotid Doppler US were performed in all patients. Body adiposity index was calculated as hip (cm)/height(m) $^{1.5}$ -18. Atherogenic index(AI) was calculated as log(TG/HDL). Different indices for insulin resistance (IR) were calculated. In PA children, prepubertal and pubertal results and also pubertal PA and control cases were compared. Cases with PA were examined in subgroups according to Tanner stages, body mass index (BMI) SDS, presence of IR, hyperandrogenemia and PCOS(Rotterdam criteria). The study was approved by the local ethical committee. Informed consent was taken from all parents. Statistical analyses were done using SPSS 20.0. Parametric and nonparametric tests were utilized. p<0.05 was accepted as statistically significant.

Results: In PA cases; onset of adrenarche was 7.0±0.9 years, onset of puberty was 9.7±0.8 in girls, 10.7±0.9 in boys and menarcheal age was 11.8±0.9 years. The age of puberty and menarche were earlier, compared with the data of Turkish children. History of SGA rate was 15.1%. There was a high rate of diabetes (47.2%) in the family history in PA group. Birth weight (BW) SDS, height SDS, waist/hip ratio, diastolic blood pressure parameters of the study and control groups were similar (Table 1). Gestational week (GW) SDS was over 37 weeks in both groups, however was lower in the PA group (p=0.007). Mean BMI SDS was normal in the PA group at presentation and in puberty but was significantly higher than in the controls (p=0.007). Waist circumference (WC) SDS was significantly higher in pubertal PA than in the controls (p=0.007). IR parameters were higher in puberty in PA than in prepuberty and higher than the controls. At first presentation, 7 patients (25.9%) had IR and 4 patients (15.4%) had dyslipidemia; during the study 34 patients (63%) had IR, 6 patients (11.1%) impaired glucose tolerance, 2 patients (3.7%) diabetes, 14 patients (27.5%) dyslipidemia and PCOS was present in 8 patients (33.3%) with menstruation.

Table 1. Anthropometric and laboratory findings in premature adrenarche children in pre- and pubertal period

	Premature Adrenarche (prepuberty) n=54 (1)	P(1.2)	Premature Adrenarche (puberty) n=54 (2)	P(2.3)	Controls n=28 (3)
Age (years)	8.0 ±1.2	-	12.5±2.4	0.072	13.5±2.2
Birth data					
Gestational age (weeks)	-	-	38.5±3.2	**0.007**	39.6±1.2
Birth weight (gram)	-	-	2908±671	**0.015**	3218±437
Birth weight SDS	-	-	-0.4±1.4	0.923	-0.3±1
Menarcheal age (years)	-	-	11.8±0.9	0.322	12.4±1.5
Anthropometric data (SDS)					
Weight	0.7±1.07	0.919	0.7±1.3	**0.005**	-0.3±1.4
Height	0.5±1.3	0.006	-0.02±1.01	0.200	-0.4±1.1
Body mass index (BMI)	0.7±1	0.419	0.8±1.2	**0.007**	-0.03±1.1
Sitting height/height ratio	-1.4±1.1	**0.003**	-0.7±1	-	-
Waist circumference	-	-	2.6±1.7	**0.007**	1.5±1.6
Waist hip ratio	-	-	0.9±0.06	0.419	0.9±0.05
Body adiposity index	-	-	27.5±5.2	**0.001**	23.1±3.5
BMI SDS groups n(%)					
Normal [< (+1)]	33 (61.1)	0.119	30 (55.6)	**0.024**	20 (71)
Overweight [+1-(+2)]	19 (35.2)		16 (29.6)		8 (29)
Obese [>(+2)]	2 (3.7)		8 (14.8)		
Blood pressure profile					
Systolic blood pressure SDS	-0.1±0.9	0.593	-0.06±0.84	**0.037**	-0.47±0.62
Diastolic blood pressure SDS	0.3±0.8	0.791	0.3±0.6	0.603	0.2±0.8
OGTT-derived data					
Fasting glucose (mg/dl)	87.4±8.6	**<0.001**	78.2±7	**<0.001**	87.8±6.2
Fasting insulin (µU/ml)	8.3±3	0.721	14.1±7.3	**0.002**	9±4.7
HOMA-IR	1.9±0.8	**0.001**	2.8±1.5	**0.023**	1.7±1.2
FGIR	11.62±4.3	**<0.001**	6.9±3.4	**<0.001**	11.9±5.4
OGTT 2 h glucose (mg/dl)	-	-	110.6±22.3	-	-
OGTT 2 h insulin (µU/ml)	-	-	86.5±66	-	-
Insulin total (µU/ml)	-	-	370.8±210.4	-	-
ISIcomp (Matsuda index)	-	-	4.14±1.9	-	-
HOMA-IR high n (%)	7 (25.9)	0.324	9 (16.7)	0.533	2 (8.3)
Lipid profile					
Triglyceride (mg/dl)	66.5±24.7	0.094	78.6±31.1	0.069	65.4±25.2
Total Cholesterol (mg/dl)	166.6±28.4	0.352	173.1±29.2	**0.028**	159.7±21.9
LDL-C (mg/dl)	89.3±21.5	0.288	95.3±23.3	0.103	85.7±22.9
HDL-C (mg/dl)	64±14.9	0.721	62.8±13.5	0.678	61.4±11.6
VLDL-C (mg/dl)	13.7±6	0.093	15.7±5.6	0.097	13.4±5.6
HDL/total cholesterol ratio	0.4±0.07	0.404	0.36±0.07	0.281	0.39±0.09
Atherogenic index (AI)	-0.004±0.2	0.066	0.08±0.22	0.338	0.02±0.2
Dyslipidemia n (%)	4 (15.4)	0.284	15 (29.4)	**0.024**	1 (4)
Adipocytokines					
Leptin (ng/ml)	-	-	4.80±3.31	**0.011**	2.97±2.34
Ghrelin (pg/ml)	-	-	107.10±115.59	0.063	117.82±81.61
Adiponectin (ng/ml)	-	-	6.54±3.51	0.322	7.33±3.13
Resistin (pg/ml)	-	-	1533.42±799.6	0.163	1869.97±1364.7
Visfatin (pg/ml)	-	-	144.29±82.49	0.055	181.09±78.08
RBP-4 (pg/ml)	-	-	1732.56±721.6	0.372	1889.11±797.65
IL-6 (pg/ml)	-	-	0.99±4.6	0.902	0.97±3.14
TNF-α (pg/ml)	-	-	123.97±181.4	0.462	156.34±213.17

SDS, standard deviation score; HOMA-IR, homeostasis modeling assessment for insulin resistance; FGIR, fasting glucose insulin ratio; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; VLDL-C, very low-density lipoprotein-cholesterol

In PA children IR was present in 53% of patients with BMI SDS <+1, in 68.8% of patients with BMI SDS +1-(+2) and in 87.5% of patients with BMI SDS >+2. While lipid profiles were similar between groups, total cholesterol (TC) was higher in the PA group (p=0.028). Subgroup analysis showed higher AI in the PCOS and hyperandrogenemia subgroups, higher IR in BMI subgroup. Adiponectin, ghrelin, visfatin, resistin, RBP-4, TNF-α, and IL-6 levels were similar between the groups, but leptin was higher in PA group (p=0.011). Carotid Intima-media thickness results were positively correlated with BMI SDS (r=0.281; p=0.043), WC (r=0.287; p=0.043) and waist/hip ratio (r=0.305; p=0.031). The most important factors for the development of IR in pubertal PA as shown in logistic regression analysis were WC SDS, BW and presence of exaggerated adrenarche.

Conclusions: We showed that hyperinsulinaemia is common in PA children in prepubertal period and increases with age especially with increasing WC and BMI, even within normal ranges.

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