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Evidence of metabolic syndrome in lean children with premature pubarche at diagnosis

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Abstract

We investigated for evidence of early metabolic syndrome irrespective of body mass index (BMI) in subjects with premature pubarche (PP). Ten children with PP were compared with controls matched for age, sex, ethnicity, and BMI. Congenital adrenal hyperplasia and other known causes of PP were excluded by standard methods. Anthropometry, blood pressure (BP), dual-energy x-ray absorptiometry body scan, fasting blood lipid profile, and cytokines were obtained. The children were divided into 2 groups: (1) the total group of children with PP, and their age-, sex-, ethnicity-, and BMI-matched controls and (2) those with PP and normal BMI (<19 kg/m^2) and their matched controls selected from the original groups. The PP subjects with normal BMI (S_1) showed significantly higher systolic BP ($P = .028$), diastolic BP ($P = .028$), and mean arterial pressure ($P = .018$) compared with matched controls (C_1). Nevertheless, for both groups, all the above parameters were statistically not significant when corrected for height. Fat distribution in PP subjects indicated significantly higher android ($P = .047$) and android-gynoid ratio ($P = .013$). Normal-BMI PP children had significantly higher android-gynoid ratio fat distribution compared with their matched controls ($P = .037$). Trunk fat percentage (p: 0.04) and trunk fat (grams) ($P = .007$) were significantly elevated in PP children compared with matched controls. Again, for both groups, all the above parameters were not statistically significant when corrected for height. The PP subjects had significantly higher tumor necrosis factor (TNF)–α ($P = .038$) and interleukin-8 (picograms per milliliter) ($P = .05$) compared with matched controls. Normal-BMI PP children also had higher TNF-α ($P = .028$) compared with matched controls. When corrected for height, TNF-α was higher in the total ($P = .037$) and normal-BMI ($P = .043$) PP children. Premature pubarche can be linked to markers of the metabolic syndrome in lean children.
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1. Introduction

Premature pubarche (PP), the early appearance of pubic hair before the age of 8 years (9 years in boys) [1], is almost 10 times more common in girls than in boys [2]. Traditionally, PP has been considered a benign process [2]. Adolescent girls with a history of PP, however, have an increased incidence of polycystic ovary syndrome [3], which is usually associated with obesity, hyperinsulinemia, hyperandrogenism, and dyslipidemia [4,5]. The metabolic syndrome (visceral obesity, dyslipidemia, hyperglycemia, and hypertension) has become one of the major public health challenges worldwide [6].There is no universally accepted or defined criteria for diagnosing metabolic syndrome in children [7]. As a result, different groups, for their studies or analyses, used their own modifications of adult criteria, usually those of Adult Treatment Panel III [8] but, occasionally, a combination of criteria from different definitions [9-12].

The ultimate importance of early diagnosis of metabolic syndrome is that it helps identify individuals at high risk of both type 2 diabetes mellitus and cardiovascular disease (CVD) [13] and should lead to early implementation of prevention strategies including lifestyle changes [14,15]. Hyperinsulinemia and obesity are common features in prepubertal and pubertal girls with a history of PP [5]. In addition, boys with PP show reduced insulin sensitivity

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independent of obesity [16]. Ibanez et al [17] have shown that PP girls had excess total body and central fat throughout all pubertal stages, and increased central fat was related to hyperinsulinemia and hyperandrogenemia.

The importance of fat distribution, in addition to total fat, as a risk factor for CVD is recognized in both adults [18] and children [19]. An android or male fat pattern, with relatively greater fat in the upper body region, is associated with negative metabolic predictors [19,20]. A gynoid or female fat pattern, with relatively greater fat in the hip and thigh areas, is associated with less metabolic risk [21]. Similarly, a pattern of fat deposits favoring trunk relative to extremities has also been linked to health risks [22,23]. Differences in body and extremity fat composition have not been previously reported in children with PP and normal body mass index (BMI).

Clinical studies in children have demonstrated that an atherogenic pattern of risk factors can start in childhood [24,25]. Such a pattern has been noted in children with PP [24], but that study was limited to girls. Obesity and cardiovascular risk factors track from childhood into adulthood [25,26]. Thompson et al [26] have shown that CVD risk factors are present in overweight children at the age 9 of years, but this has not been demonstrated in lean children with PP.

In this study, we demonstrate that both boys and girls with PP have significantly higher total cholesterol (TC) to high-density lipoprotein (HDL) ratios compared with controls matched for age, sex, ethnicity, and BMI. Furthermore, increased adiposity, serum dehydroepiandrosterone sulfate (DHEAS), and plasma cytokine levels as early markers of metabolic syndrome were found in lean children with PP. These findings are consistent with early onset of metabolic syndrome in children with PP and normal BMI (<19 kg/m^2).

2. Methods

2.1. Subjects: informed consent

All children enrolled in the study and their parents were thoroughly familiarized with the protocols, including any risks of the procedure described below and the potential benefits gained as a result of the study. The study was approved by the Vanderbilt University Institutional Review Board Human Subjects Committee. Participants were permitted to terminate their involvement in the project at any time during their enrollment. Written informed consent was obtained from parents or guardians of all participants, and assent was also obtained from the participant child.

3. Recruitment of subjects

3.1. Eligibility criteria

Girls before the age of 6 years, if African American, or before the age of 8 years, if white [27], and boys below the age of 9 years in either ethnicity with isolated PP (Tanner stage II or more pubic hair development in either sex, Tanner stage 1 breast in girls, and testicular volume of less than 4 mL in boys) at diagnosis were included in the study.

3.2. Exclusion criteria

Before enrollment in the study, all patients with PP underwent an adrenocorticotropic hormone stimulation test to exclude those with late-onset forms of congenital adrenal hyperplasia, and IV leutinizing hormone releasing hormone (LHRH) [28] and radiological investigations, if indicated, to exclude adrenal and ovarian tumors and central precocious puberty. These tests are standard in the evaluation of children with PP and not part of the experimental design for this study. Children with PP secondary to any of the above diagnoses were excluded from the study.

3.3. Final subject group

There were 10 PP subjects (S_T): 7 girls and 3 boys (mean age ± SD, 7.3 ± 1 years; age range, 5.9-8.98 years). Seven of the total group of 10 children (5 girls and 2 boys [S_1]) were separately analyzed because of their normal BMI (<19 kg/m^2, ie, <95th percentile at age 7 years) (mean age ± SD, 7.2 ± 1.2 years; age range, 5.9-8.98 years).

4. Controls

Prepubertal controls without PP, but matched for age (±2 years), sex, ethnicity, BMI (±2 kg/m^2), and maternal history of gestational diabetes were identified for each of the PP subjects. Hence, 3 control groups were matched one to one for each of the subjects: (*a*) prepubertal girls younger than 6 years if African American, (*b*) prepubertal girls younger than 8 years if white, and (*c*) prepubertal boys of either ethnic origin younger than 9 years.

4.1. Method of recruitment

Control children were recruited from the General Pediatric or Adolescent Clinic, local elementary schools, private pediatric practices, or through advertisement in the Vanderbilt University media.

4.2. Exclusion criteria

Controls were screened for hyperlipidemia, and those with fasting cholesterol >200 mg/dL and/or triglycerides >150 mg/dL were excluded as controls.

4.3. Final control group

There were 7 girls and 3 boys in the matched total control group (C_T) (mean age ± SD, 7.3 ± 1.6 years; age range, 3.49-9.25 years), from which 5 girls and 2 boys were selected based on their match to normal-BMI PP group (S_1) and called *normal-BMI control group* (C_1) (mean age ± SD, 7.3 ± 2 years; age range, 3.49-9.25 years).

Table 1
Anthropometric characteristics

Parameter	All		Normal BMI	
Subjects	PP[a] (S_T)	Controls[a] (C_T)	PP[a] (S_1)	Controls[a] (C_1)
n	10	10	7	7
Age (y)	7.3 ± 1.0	7.3 ± 1.6	7.2 ± 1.2	7.3 ± 2.0
Sex F/M	7:3	7:3	5:2	5:2
Weight SD	1.2 ± 1.1	0.8 ± 0.9	0.6 ± 0.7	0.4 ± 0.3
Weight percentile	78.2 ± 23.8	69.5 ± 19.1	69.5 ± 23.5	61.1 ± 13
Height SD	1.2 ± 0.8	0.6 ± 0.7	0.9 ± 0.6	0.6 ± 0.6
Height percentile	81.9 ± 13.1	61.6 ± 25.8 *	76.1 ± 11.2	61.3 ± 24
Body surface area (m^2)	1.06 ± 0.2	1.04 ± 0.2	1 ± 0.1	1 ± 0.2
Waist-hip ratio	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1 ± 0.2
BMI (kg/m^2)	18.8 ± 4.7	19.0 ± 4.8	16.3 ± 2	16.4 ± 1.5
BMI (SD)	1.3 ± 0.8	1.2 ± 0.8	0.9 ± 0.5	0.8 ± 0.4
Systolic BP (mm Hg)	109.5 ± 9	102.0 ± 6.7	110.7 ± 10.3	99.3 ± 2.9 *
Systolic BP corrected for height (mm Hg/m)	84.7 ± 8	80.2 ± 8.8	86.7 ± 7.9	80.6 ± 9.1
Diastolic BP (mm Hg)	59.4 ± 6.3	53.0 ± 5.6 *	61.4 ± 6.5	52.2 ± 1.6 *
Diastolic BP corrected for height (mm Hg/m)	46 ± 6.3	41.8 ± 6.6	48 ± 6.2	42.5 ± 5.8
MAP (mm Hg)	79.7 ± 10.4	70.9 ± 3.9 *	83.1 ± 10.8	70.7 ± 2.7 *
MAP corrected for height (mm Hg/m)	61.6 ± 8.9	55.9 ± 7	64.9 ± 8.3	57.4 ± 6.8

[a] Continuous variables are presented as means ± SD. MAP indicates mean arterial pressure.
* $P \leq .05$.

4.4. Initial evaluation of the phenotype

All subjects and controls underwent initial clinical evaluation by the principal investigator including pubertal staging according to Marshall and Tanner [29] to confirm that both groups were prepubertal.

4.5. Height and weight measurements

Height was measured 3 times using a Harpenden stadiometer, and the average was taken in deciding the actual height. Weight was measured without shoes using a digital weighing machine once. Weight and height SD scores, BMI [30], surface area, and waist-hip ratio were calculated.

5. Blood pressure measurements

Blood pressure (BP) in the recumbent position was determined 3 separate times over a span of 15 minutes using the Dinamap (Critikon Corp, Tampa, FL) and once manually by the nurse coordinator: the average of the above 4 readings was recorded for comparison of systolic, diastolic, and mean arterial BP between PP subjects and their matched controls.

6. Measurement of plasma lipids, adiponectin, and C-reactive protein

Fasting blood samples were collected for the measurements. Determination of cholesterol was based on a modification of the method published by Allain et al [31], that of triglyceride was based on the method of Fossati and Prencipe [32], and that of HDL cholesterol (HDL-C) was based on the method of Teitz [33] (Alpha Wasserman, ACE HDL-C).

Atherogenic index was calculated from the following formula: (TC − HDL)/HDL [34]. Adiponectin and C-reactive protein (CRP) levels were determined by a double antibody sandwich enzyme-linked immunosorbent assay method.

6.1. Dehydroepiandrosterone sulfate

The measurement of DHEAS was accomplished using a kit from Diagnostic Systems Laboratories, Webster, TX, according to the manufacturer's instructions. The sensitivity of the assay was around 1.7 μg/dL, and between-assay coefficient of variation was 10%. There is a 40% cross-reactivity with dehydroepiandrosterone.

6.2. Cytokines

Tumor necrosis factor (TNF)–α, interleukin (IL)-8, IL-1B, IL-10, IL-12p70, and IL-6 were assayed by human inflammation cytokine cytometric bead array kit (BD Biosciences Pharmingen, San Diego, CA).

7. Dual-energy x-ray absorptiometry scans

The dual-energy x-ray absorptiometry (DEXA) scanner used was a Lunar Prodigy model (software version 8.1 GE Lunar Prodigo Pro, MA). The raw scan data, which include values of tissue and bone, were captured and sent to a computer for quantitative assessment. The term *android* is used for central obesity, and *gynoid* is used for obesity of the lower body often seen in women [35]. The radiation exposure for the DEXA was 7 mrem.

8. Correction of data for height

To control for height, systolic, diastolic, and mean arterial pressures were recalculated for individual patient height (meters) [36]. In addition, serum lipids, DHEAS, biometric measurements, and biochemical markers (cytokines, CRP, and adiponectin) were corrected for height (meters); and significant corrected-for-height values ($P \leq .05$) were included in the tables.

8.1. Statistics

We assessed pairwise differences between PP subjects and controls using the McNemar test for categorical variables, and a paired t test for continuous variables, when normally distributed. Wilcoxon signed rank test was used when the data were skewed. P values less than .05 or less were considered statistically significant. All tests were 2-tailed. Statistical analyses were performed on a personal computer with the statistical package SPSS for Windows (Version 11.5; SPSS, Chicago, IL) and the statistical language R (www.r-project.org).

9. Results

9.1. Clinical findings

Despite matched BMI in subjects and controls, PP subjects (S_T) had a significantly higher height percentile ($P = .046$) and mean arterial pressure ($P = .037$) compared with matched controls (C_T). The PP subjects with normal BMI (S_1) also showed significantly higher systolic BP ($P = .028$), diastolic BP ($P = .028$), and mean arterial pressure ($P = .018$) compared with matched controls (C_1) (Table 1). Nevertheless, for both groups, despite the trends, all the above parameters were not significant when corrected for height (S_T: mean arterial pressure, 0.13; C_T: systolic BP, $P = .177$; diastolic BP, $P = .15$; mean arterial pressure, 0.123).

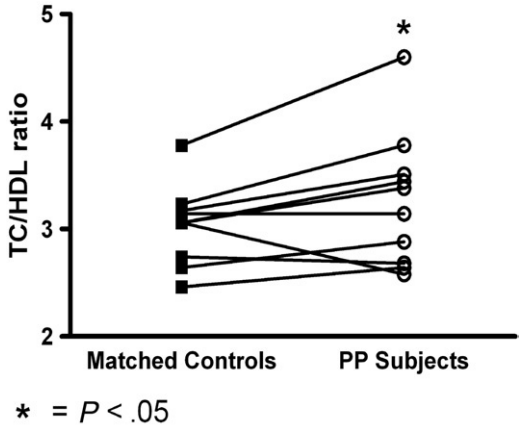

Fig. 1. The TC/HDL ratio in controls and subjects.

9.2. Biochemical data

The PP subjects in either group (S_T and S_1) had significantly higher DHEAS compared with their respective matched controls (C_T and C_1, respectively) ($P = .043$) even after correction for height in both groups (S_T vs C_T total group, $P = .021$; S_T vs C_T normal-BMI group, $P = .028$) (Table 2), confirming our previously described adrenal source of the androgens [28].

The PP subjects also had higher TC/HDL ratio (p: 0.042) (Fig. 1) and atherogenic index ($P = .0.042$). The TC/HDL ratio ($P = .059$) and atherogenic index (p: 0.059) in PP subjects were not significantly elevated when corrected for height. There were nonsignificant trends in increased plasma TC, low-density lipoprotein (LDL), and triglycerides (TG) in PP subjects; and the LDL cholesterol (LDL-C) (milligrams

Table 2
Serum lipid and DHEAS characteristics

Parameter	All		Normal BMI	
Subject	PP [a] (S_T)	Controls [a] (C_T)	PP [a] (S_1)	Controls [a] (C_1)
n	10	10	7	7
TC (mg/dL) [b]	158.7 ± 31.2	140.1 ± 14.3	147.1 ± 25.7	141.1 ± 16.7
HDL-C (mg/dL) [b]	47.2 ± 11	46.4 ± 8.3	50.6 ± 11.4	49.6 ± 8.9
LDL-C (mg/dL) [b]	94.5 ± 22.6	82.6 ± 10.6	84.7 ± 14.9	82.6 ± 9.7
LDL/HDL ratio	2.1 ± 0.6	1.8 ± 0.3	2.2 ± 0.5	1.9 ± 0.3
TC/HDL ratio	3.53 ± 0.8	3.1 ± 0.4 *	3.0 ± 0.4	2.9 ± 0.3
Atherogenic index	2.5 ± 0.8	2.1 ± 0.4 *	2.0 ± 0.4	1.9 ± 0.3
TG (mg/dL) [c]	85.2 ± 44.8	55.9 ± 20.5	62.6 ± 22.7	46.1 ± 7.7
TG/HDL ratio	1.69 ± 1.04	1.42 ± 0.61	1.83 ± 1.21	1.46 ± 0.54
DHEAS (μg/dL) [d]	80.8 ± 39.6	33.9 ± 21.1 *	74.8 ± 46.9	29.3 ± 16.2 *
DHEAS (μg/dL)/height (meter)	61.6 ± 31.2	24.9 ± 14.5 *	57.9 ± 38.0	22.0 ± 11.0 *

[a] Continuous variables are presented as means ± SD.
[b] Cholesterol in milligrams per deciliter × 0.0259 = millimoles per liter.
[c] Triglycerides in milligrams per deciliter × 0.01 = grams per liter.
[d] Dehydroepiandrosterone sulfate in micrograms per deciliter × 0.026 = micromoles per liter.
* $P \leq .05$.

Table 3
Variations in extremity and trunk fat and fat distribution by DEXA, and abdominal skin fold thickness

Parameter	All		Normal BMI	
Subject	PP[a] (S_T)	Controls[a] (C_T)	PP[a](S_1)	Controls[a] (C_1)
N	10	10	7	7
Left arm fat (g)	518.5 ± 408.5	443.8 ± 383.3 *	283.4 ± 142.5	222.4 ± 82.6
Total left-sided tissue fat (g)	5808.1 ± 4383.6	4879.1 ± 4033.8 *	3334.6 ± 1466.8	2623.4 ± 779.2
Right arm fat (g)	509.8 ± 421.7	406.6 ± 430	272.7 ± 145.6	218.9 ± 96.7
Total right-sided tissue fat (g)	5720.4 ± 4301.7	4681.2 ± 3822.2 **	3292.3 ± 1394.8	2538.1 ± 785.4
Arms fat (g)	1028.6 ± 827.4	904.6 ± 814.7 *	556.6 ± 287.2	441.4 ± 177.7
Fat distribution: android	37.5 ± 15.2	31.6 ± 15.4 *	30.2 ± 11.8	22.6 ± 5.7
Fat distribution: A/G	0.88 ± 0.2	0.76 ± 0.2 *	0.8 ± 0.2	0.65 ± 0.2 *
Trunk fat %	30.6 ± 14.1	25.8 ± 13.9 *	23.6 ± 9.8	17.8 ± 4.8
Trunk fat (g)	5635.7 ± 4914.3	4158.9 ± 3847.1 **	2850 ± 1307.9	2014.4 ± 810.1
Total fat (g)	11528.6 ± 8684.4	9560.4 ± 7855.4	6627 ± 2859.1	5161.7 ± 1563.2
Total body fat distribution %	31.3 ± 12.8	27.5 ± 11.9	25.1 ± 9.1	20.6 ± 3.5
Abdominal skin fold (mm)	21.6 ± 13.2	14. 9 ± 9.2	17.2 ± 10.4	10.2 ± 3.5

A/G indicates android:gynoid ratio.
[a] Continuous variables are presented as means ± SD.
* $P \leq .05$.
** $P \leq .01$.

per deciliter) was 94.5 ± 22.6 in PP subjects vs 82.6 ± 10.6 in controls ($P = .123$) (Table 2).

9.3. Biometric parameters

The PP subjects had higher fat (grams) in arms ($P = .023$), total left side fat tissue (grams) ($P = .011$), and total right side fat tissue (grams) ($P = .004$). Fat distribution in PP subjects indicated significantly higher android ($P = .047$) and android-gynoid ratio ($P = .013$). Normal-BMI PP children had significantly higher android-gynoid ratio fat distribution compared with their matched controls ($P = .037$). Trunk fat percentage ($P = 0.04$) and trunk fat (grams) ($P = .007$) were significantly elevated in PP children compared with matched controls (Table 3). None of the biometric parameters were significantly elevated when corrected for height (fat [grams] in arms, $P = .177$; total left side fat tissue [grams], $P = .139$; total right side fat tissue [grams], $P = .459$; android fat distribution, $P = .207$; android-gynoid ratio, $P = .175$; trunk fat percentage, $P = .193$; and trunk fat [grams], $P = .328$) in PP children compared with matched controls in the total and normal-BMI groups.

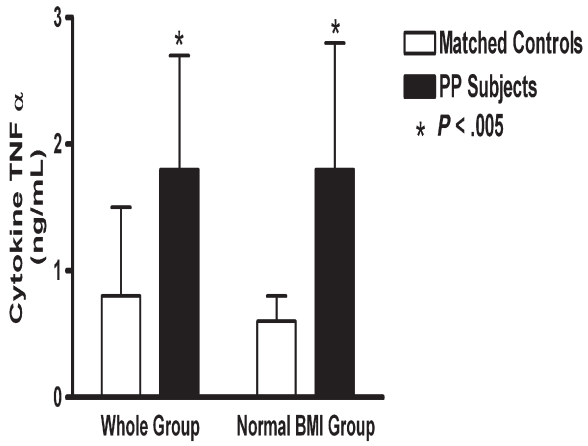

Fig. 2. Differences in cytokine TNF-α in controls and subjects.

9.4. Cytokines

The PP subjects had significantly higher TNF-α ($P = .038$) (Fig. 2) and IL-8 (picograms per milliliter) ($P = .05$) cytokines compared with matched controls. Normal-BMI PP children also had higher TNF-α ($P = .028$) (Fig. 2) compared with matched controls. The TNF-α was significantly higher in PP subjects compared with controls in both total and normal-BMI groups when corrected for height (total group, $P = .037$; normal-BMI group, $P = .043$) (Table 4). The IL-8 (picograms per milliliter) levels in PP subjects were not statistically different when corrected for height ($P = .546$).

Table 4
Serum cytokines (picograms per milliliter), CRP (nanograms per milliliter), and adiponectin (nanograms per milliliter)

Parameter	All		Normal BMI	
Subject	PP[a] (S_T)	Controls[a] (C_T)	PP[a] (S_1)	Controls[a] (C_1)
n	10	10	7	7
TNF-α	1.8 ± 0.9	0.8 ± 0.7 *	1.8 ± 1	0.6 ± 0.2 *
TNF-α/ height (m)	1.5 ± 0.6	0.6 ± 0.5 *	1.4 ± 0.7	0.5 ± 0.5 *
IL-8	2.6 ± 0.4	1.7 ± 1.3 *	2.6 ± 0.4	1.4 ± 0.5
IL-1B	5.6 ± 1.2	3.8 ± 2.4	5.6 ± 1.3	3.8 ± 2.9
IL-10	2.7 ± 1.5	2.2 ± 1.6	2.5 ± 1.8	1.8 ± 1.7
IL-12p70	1.2 ± 0.2	1 ± 0.8	1.2 ± 0.2	0.9 ± 1
IL-6	2.8 ± 0.7	3.0 ± 1.2	2.8 ± 0.8	2.8 ± 1.4
CRP	830.7 ± 923.3	1332.7 ± 1529.8	640.5 ± 923.4	1332.7 ± 1529.8
Adiponectin	14012.7 ± 8165.8	14068.97 ± 8339.2	16256.5 ± 8965.6	17329.9 ± 7567.1

[a] Continuous variables are presented as means ± SD.
* $P \leq .05$.

10. Discussion

After having excluded tumors and central or peripheral activity of the gonads, we confirmed in the study that the principal cause of PP was adrenal hyperandrogenism, as implied in the term *premature adrenarche* (PA). We found that PP subjects had a significantly higher ratio of cholesterol to HDL; greater peripheral, truncal, and total body fat; and higher plasma levels of cytokines TNF-α and IL-8 than BMI-matched controls. Of these, only TNF-α was significantly and consistently elevated in total and normal-BMI groups of PP children when compared with matched controls and when corrected for height in both groups. These changes in serum cytokines in PP children with normal BMI have not been previously reported.

Premature adrenarche was previously considered to be a benign condition; but more recently, it has been associated with hyperinsulinemia, dyslipidemia, and hypertension [37]. Elevated serum triglycerides and an increased ratio of LDL-C to HDL-C have been found in girls with PA [24]. The dyslipidemia of insulin resistance has been proposed to be a precursor to the development of atherosclerosis [38]. Ibanez et al [24] showed that girls with PA have higher triglyceride, cholesterol, LDL-C, and VLDL levels than their healthy peers through the prepubertal and pubertal periods. Hyperinsulinemia and insulin resistance, both independently and together, have been hypothesized to result in dyslipidemia in subjects with both normal and impaired glucose tolerance [39,40]. Hyperinsulinemia enhances hepatic VLDL synthesis [38] and could directly contribute to the increased triglyceride and cholesterol values in these subjects. Laws and Reaven [41] showed that a high triglyceride and a low HDL-C concentration are strong indicators of insulin resistance [42]. In our study, TC/HDL and atherogenic index were significantly elevated in the total group of PP subjects. Nevertheless, the above findings for both groups did not reach significance when corrected for their respective heights.

Guven et al [34], in a study of Turkish girls, demonstrated that those with PA have higher BMI, elevated LDL-C and VLDL-C levels, hyperinsulinemia, and higher BP than their healthy peers. However, cholesterol differences have not been previously demonstrated in a mixed group of children with PP matched with controls for BMI, in addition to age, ethnicity, and sex.

There have been major advances in the noninvasive assessment of body composition. In this study, we used supine DEXA to assess body composition [43]. Along with underwater weighing and isotope dilution, DEXA is considered the most accurate method for measurement of body composition [44]. To provide consistency in body composition measurements, all PP subjects and controls in our study underwent DEXA scan measurement of body composition in supine position. We have shown higher android-gynoid ratio fat distribution in PP children with normal BMI compared with matched controls. This is likely to be directly related to increased DHEAS levels in PP. Sex steroids play important roles in determining body fat mass and its distribution [45] including body fat patterning [46-48]. It has also been suggested that intraadipose sex steroid metabolism is also a determinant of android vs gynoid patterns of body fat [45]. These differences in body and extremity fat composition in children with PP and normal BMI indicate the influence of fat metabolism in PP subjects even when lipid profiles and BMI are in the reference range and comparable with matched controls.

Adipose tissues secrete a variety of molecules and adipocytokines, including TNF-α and IL-8 [49]. Previous studies have shown that elevated serum levels of CRP, IL-6, and TNF-α precede type 2 diabetes mellitus [50] and coronary heart disease [51]. In our study, we found marked elevations in TNF-α and IL-8 initially and elevation of TNF-α alone for both groups when corrected for their individual height. Elevation of TNF-α in PP children regardless of BMI suggests a possible direct correlation to later development of essential hypertension in metabolic syndrome. Further studies are needed to confirm this hypothesis. In addition, TNF-α was consistently elevated in obese and nonobese children with PP and, if confirmed in bigger studies, may be an early predictor of metabolic syndrome at PP diagnosis.

In children with PP, our results support the contention that the cluster of risk factors for CVD starts in childhood [26,52]. The increased insulin concentrations concurrent with altered lipid profile may initiate this process in the prepubertal period [53]. Based on our data, the development of PP regardless of BMI should be interpreted as indicative of insulin resistance, a proinflammatory environment, and a risk for development of metabolic syndrome. Metformin has been advocated for use in children with insulin-resistant syndromes and is considered safe [54,55]. Tumor necrosis factor–α down-regulation may be accomplished by an antibody to TNF-α (as infliximab in rheumatoid arthritis) [56], although the sole use of TNF-α antibody failed to reverse insulin resistance in humans. Our data suggest that additional therapeutic targets may be identified for the inflammatory cytokines that are elevated in children with PP.

In conclusion, children with PP, even those with normal BMI, show early signs of the metabolic syndrome and should be targeted with early lifestyle interventions. Our study suggests that TNF-α levels are markers of metabolic syndrome at PP diagnosis.

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