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The association between metabolic complications and arterial hypertension in obese adolescents

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Abstract

OBJECTIVE: There is increasing evidence for the contribution of obesity and its metabolic sequels in the development of arterial hypertension (AH).
METHODS: The casual blood pressure (CBP), 24hABPM, ambulatory arterial stiffness index (AASI) and symmetric (sAASI) ambulatory arterial stiffness index (both derived from a 24 h ABPM) and selected laboratory tests were performed in 130 obese (mean BMI SDS 4.2) adolescents at the mean age of 13.7 years.
RESULTS: AH was diagnosed in 36.2%, and in 33.8% patients on the basis of CBP and 24hABPM respectively. There were significant correlations between: CBP-SBP insulin level (fasting r=0.19, p=0.03 and post glucose load r=0.18, p=0.04), HOMA-IR (r=0.18, p=0.04), and uric acid (UA) level (r=0.35, p<0.001); CBP-DBP and UA level (r=0.23, p=0.01). There were significant correlations between 24hABPM parameters and cortisol secretion: dSBP and urinary free cortisol (r=0.3, p=0.03), nDBP and nMAP and cortisol rhythm (r=0.21, p=0.03). There a correlation between sAASI and creatinine level (r=0.29, p=0.002) and negative correlation between AASI and eGFR (r=–0.23, p=0.009).
CONCLUSIONS: The increase of the CBP parameters is associated with insulin resistance and hyperuricemia, while the increase of ABPM results is proportional to the cortisol secretion in obese adolescents.

INTRODUCTION

The prevalence of primary arterial hypertension (AH) has recently increased among pediatric population. While the reported prevalence in the late 1970s was about 1%–2%, the rates reported in the early 2000s have increased up to 13–17% (Fixler *et al.* 1979; Sorof *et al.* 2002; Maldonado *et al.* 2011; Mazor-Aronovitch *et al.* 2014). The similar trend has been observed for obesity and its metabolic complications (Muntner *et al.* 2004). There is an increasing evidence for the association of these both disorders. The results of the NHANES study show that the increase of the BMI may cause an increase in systolic blood pressure (SBP) by 29% and diastolic blood pressure (DBP) by 12% (Muntner *et al.* 2004). That may explain high prevalence of AH in overweight or obese pediatric patients,

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reaching up to 30% in comparison to <5% in slim peers (Fixler *et al.* 1979; Sorof *et al.* 2002; Maldonado *et al.* 2011; Mazor-Aronovitch *et al.* 2014).The development of the metabolic and hormonal complications in obese children is a long lasting process. The critical moment for the development of overt metabolic complications such as insulin resistance and subsequent type 2 diabetes, lipid disorders and non alcoholic fatty liver disease and sub-clinical hormonal abnormalities is puberty. At that age many patients present already with AH. That suggest, that even sub-clinical metabolic abnormalities may contribute to the development of the AH. The diagnosis of AH in children and adolescents is based on the average SBP and/or DBP that is measured on at least 3 occasions (casual blood pressure, CBP) and it's comparison to the normal values for gender, age, and height. Since 2008 24-h ambulatory blood pressure monitoring (ABPM) has also been applied to children and adolescents (Urbina *et al.* 2008; Flynn *et al.* 2014). Also ABPM derived ambulatory arterial stiffness index (AASI) and symmetric AASI (s-AASI) are newly recognized cardiovascular risk factors (Dolan *et al.* 2006). The present study is a first attempt to compare CBP and ABPM results in obese adolescents, and to analyze their association with selected metabolic and hormonal complications of the obesity.

MATERIAL AND METHODS

The study included 130 (71 girls, 59 boys) obese (mean BMI SDS 4.2, [Q_1=3.2; Q_3=5.5]) adolescents at the mean age of 13.7 [Q_1=11.9; Q_3=15.3] years. All participants were at the pubertal age (Tanner stage III–V). Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using a stadiometer (Harpenden, UK) and a balanced scale. As the standard of reference for calculating SDS for waist and hip circumference, normal values from the local population were used. Casual blood pressure measurement was done auscultatory, with a standard clinical sphygmomanometer, with a cuff appropriate to the size of the child's upper right arm. It was repeated three times, on three different ambulatory visits. SBP and DBP were calculated as the mean value of these three results (National High Blood Pressure Education Program Working Groupon High Blood Pressure in Children and Adolescents, 2004). 24-hour BP monitoring was performed using an Ambulatory BP Monitor (Spacelabs 90217,USA), with a cuff which was the same size as the one used to measure casual blood pressure. It was set to take a reading every 15 minutes (day 6 a.m.–10:59 p.m.), and every 30 minutes (night 11:00 p.m.–5:59 a.m.). The monitoring was performed in a standard setting, patients went to sleep at 9–10 p.m. and got up at 6–7 a.m. Sleep and activity periods were established based on a diary completed by the child's parents. Recordings with at least 70% valid readings and at least one reading every hour were considered for the analysis. The following parameters were analyzed: mean 24-h systolic, diastolic, and mean arterial pressure (MAP), mean day-time systolic (dSBP), diastolic (dDBP), and MAP (dMAP), mean night-time systolic (nSBP), diastolic (nDBP), and MAP (nMAP). Blood pressure load was calculated separately for sleep and awake periods. BP load was defined as the percentage of valid ambulatory BP measurements above a set threshold value (95th percentile for sex and height) (Wühl *et al.* 2002). Loads in excess of 30% were considered elevated. Loads in excess of 50% were considered severely elevated. The calculation of nocturnal dipping was based on a formula by the American Heart Association: [(dSBP–nSBP)/dSBP] × 100. Normal dipping was defined as a ≥10% decline in SBP (Urbina *et al.* 2008). White coat AH was defined as AH observed in CBP but not in ABPM. Masked AH was defined as a CBP within the normal range, but AH in ABPM. AASI was calculated according to the following formula: 1– the regression slope of diastolic pressure on systolic BP, sAASI was calculated according to the following formula: 1–(correlation coefficient/regression slope of systolic on diastolic BP) (Wühl *et al.* 2002, Sorof & Potrman 2000). Uric acid (UA), triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol concentrations were estimated in the fasting blood sample by the dry chemistry method with a Vitros 5.1.FF machine (Ortho-Clinical Diagnostics, Rochester, NY, USA). Urinary free cortisol was measured in the 24-h urine collection. Standard oral glucose tolerance tests were performed with the assessment of fasting and post-load glucose and insulin levels. HOMA-IR was calculated using the formula: [fasting insulin level (μIU/mL) × fasting glucose level (mmol/L)]/22.5. Blood cortisol levels were assessed twice: in the morning (8.00 a.m.) and evening (8.00 p.m.).

Statistics

Categorical variables were expressed as counts and percentages. Empirical distribution of continuous variables was described using median, quartiles (notation used: M_e [Q_1;Q_3]) and mean, standard deviation (notation used: mean (SD)). Statistical significance of differences between two independent groups was assessed using the Mann-Whitney test or chi-square test as appropriate. Associations between continuous variables were examined by the Spearman's rank correlation coefficient. An association between a binary variable and a continuous variable adjusted for other variables was assessed by the use of a logistic regression model and reported using odds ratio (OR) with a 95% confidence interval (CI). A *p*-value less than 0.05 was considered an indication of a statistically significant result. All statistical analyses were performed using R 3.0 (R Development Core Team, 2010).

Ethics

The investigation was conducted according to the principles expressed in the Declaration of Helsinki.

The study has been approved by Jagiellonian University Bioethical Committee (decision number KBET/38/B/2008); all participants and their parents signed informed consent.

RESULTS

Arterial hypertension, diagnosed on the basis of the mean value of SBP and DBP of three independent CBP measurements (>95th centile), was confirmed in 47 (36.2%) of the study participants, 30 (42.3%) girls and 17 (28.8%) boys. High normal BP (>90th centile) was recognized in 13 (10%) patients; 6 (8.4%) girls, 7 (11.9%) boys. Based upon CBP 28.4% of the subjects were classified as having systolic AH and 13.8 % were classified as having diastolic AH. On the basis of 24hABPM, AH was diagnosed in 44 patients (33.8%), 25 (35.2%) girls and 19 (32.2%) boys. White coat hypertension was recognized in 22 participants (9 boys, 13 girls; 46.8% of the patients with AH) and masked hypertension in 21 (13 boys, 9 girls). Analysis of the 24hABPM results revealed significantly higher mean 24-hour values of BP parameters in patients with AH in CBP (24h SBP SDS: median value 1.07 [0.38;1.66] vs. 0.51 [–0.35;1.26], p<0.001, 24h DBP SDS: 0.22 [–0.40;0.82] vs. –0.28 [–0.85;0.31], p=0.02, 24h MAP SDS: 0.62 [0.30;1.15] vs. 0.26 [–0.55;0.82], p=0.01). Also median values of SBP and MAP during the activity period (06.00 am. –10.59 pm.) were higher in AH patients (dSBP SDS: 0.76 [0.10;1.54] vs. 0.16 [–0.53;0.96], p=0.01, dMAP SDS: 0.28 [–0.15;1.15] vs. –0.07 [–0.72;0.57], p=0.01). Nevertheless there were no significant differences between patients with and without AH concerning DBP during the activity period (dDBP SDS: –0.36 [–0.72;0.64] vs. –0.61 [–1.09;–0.02], p=0.05), BP parameters during the sleep period (11.00 p.m. – 05.59 a.m.) (nSBP SDS: 1.13 [0.46;1.73] vs. 0.65 [0.04;1.46], p=0.06, nDBP SDS: 0.46 [–0.17;1.22] vs. 0.39 [–0.18;1.07], p=0.73, nMAP SDS: 1.00 [0.46;1.40] vs. 0.77 [0.15;1.36], p=0.14) and night dip percentage (10.9 [8.07;15.0] vs. 8.87 [6.39;12.6] , p=0.05) (Table 1). There were no significant differences concerning the percentage of elevated cases of MAP (>2.0 SD) in patients with and without AH – 6.38% vs. 4.82%, p=0.7. Patients with AH diagnosed on the basis of CBP presented with a significantly higher incidence of elevated SBP load (42.6% vs. 22.9%, p=0.03). Surprisingly, there were no significant differences between patients with and without AH concerning a higher incidence of elevated DBP (21.3% vs. 10.8%, p=0.17) extremely elevated SBP load (17.0% vs. 9.6%, p=0.34), extremely elevated DBP load (2.13% vs. 1.2%, p=0.999) or abnormal night dip (42.6% vs. 60.2%, p=0.08). Patients with AH diagnosed on the basis of CBP presented at a higher median age (14.5 [12.5;16.2] vs. 13.0 [11.6;14.6] years, p=0.01) and BMI-SDS (5.20 [3.33;6.22] vs. 3.87 [3.16;5.01], p=0.01). The analysis of girls and boys confirmed the difference concerning age in both groups, but BMI SDS was only higher in girls (a detailed comparison of the two groups is presented in Table 1). There was a significant correlation between SBP measured by CBP and fasting and 120' post load insulin levels in OGTT (r=0.19, p=0.03 and r=0.18, p=0.04 respectively), and HOMA-IR (r=0.18, p=0.04). There were also a significant correlation between SBP and DBP measured in CBP and UA levels (r=0.35, p<0.001, R=0.23, p=0.01 respectively). Moreover, patients with AH diagnosed on the basis of CBP presented with higher levels of UA (median 384 [323;432] vs.335 [300;397] μmol/L, p=0.02). This finding was confirmed in girls with AH (386 [324;428] vs. 324 [289;361] μmol/L, p=0.01), but not in boys (376 [327;436] vs. 354 [308;426] μmol/L, p=0.39). The odds ratio (OR) for boys was 1.42 (0.61; 3.31), p=0.41 for AH associated with each 100 unit increase of uric acid. After adjusting for age and BMI SDS the odds ratio (OR) was 1.13 (0.40; 3.23) with a p=0.82. OR for girls was 2.88 (1.31; 6.30), p=0.01 for AH associated with each 100

Tab. 1. Comparison of the ABPM results in both investigated groups: with and without AH in CBP.

Parameter	Arterial Hypertension	Without Arterial Hypertension	*p*-value
N	47	83	
Age (years)	14.1 (2.85) 14.5 [12.5;16.2]	12.8 (2.60) 13.0 [11.6;14.6]	0.002
BMI SDS	5.29 (2.39) 5.20 [3.33;6.22]	4.16 (1.43) 3.87 [3.16;5.01]	0.005
24hSBP SDS	1.10 (1.21) 1.07 [0.38;1.66]	0.48 (1.24) 0.51 [–0.35;1.26]	0.009
24hDBP SDS	0.07 (1.17) 0.22 [–0.40;0.82]	–0.22 (0.87) –0.28 [–0.85;0.31]	0.024
24hMAP SDS	0.72 (0.99) 0.62 [0.30;1.15]	0.26 (0.88) 0.26 [–0.55;0.82]	0.005
dSBP SDS	0.88 (1.19) 0.76 [0.10;1.54]	0.20 (1.19) 0.16 [–0.53;0.96]	0.002
dDBP SDS	–0.25 (1.01) –0.36 [–0.72;0.64]	–0.54 (0.85) –0.61 [–1.09;–0.02]	0.054
dMAP SDS	0.45 (0.96) 0.28 [–0.15;1.15]	–0.10 (0.94) –0.07 [–0.72;0.57]	0.002
nSBP SDS	111 (7.53) 111 [106;116]	108 (9.17) 108 [103;113]	0.057
nDBP SDS	0.48 (0.92) 0.46 [–0.17;1.22]	0.46 (0.96) 0.39 [–0.18;1.07]	0.734
nMAP SDS	1.00 (0.80) 1.00 [0.46;1.40]	0.81 (0.86) 0.77 [0.15;1.36]	0.143
Night dip %	11.0 (5.43) 10.9 [8.07;15.0]	9.26 (4.93) 8.87 [6.39;12.6]	0.052
AASI	0.43 (0.15) 0.43 [0.35;0.50]	0.43 (0.15) 0.41 [0.31;0.50]	0.558
sAASI	0.06 (0.15) 0.08 [–0.04;0.17]	0.04 (0.15) 0.08 [–0.05;0.12]	0.403

Notation used mean (SD) and median [Q1;Q3].

unit increase of uric acid. After adjusting for age and BMI SDS the OR=2.63 (0.93; 7.43), p=0.07 (Figure 1). There was a correlation between dSBP measured by ABPM and UFC (r=0.30, p=0.026). There were also correlations between cortisol rhythm (8.00 a.m./8.00 p.m.) cortisol ratio and nDBP and nMAP (r=0.21, p=0.029), (r=0.21, p=0.034). There were no significant differences in AASI and sAASI values between patients with and without HA (Table 1). There was no correlation between AASI and BMI SDS (r=0.07, p=0.419), neither between sAASI and BMI SDS (r=0.06, p=0.485) . There was no correlation between AASI and biochemical parameters (Table 2). There was a correlation between sAASI and creatinine level (r=0.29, p=0.002) and negative correlation between sAASI and eGFR (r=–0.23, p=0.009). There was no significant correlation between sAASI and other biochemical parameters (Table 2).

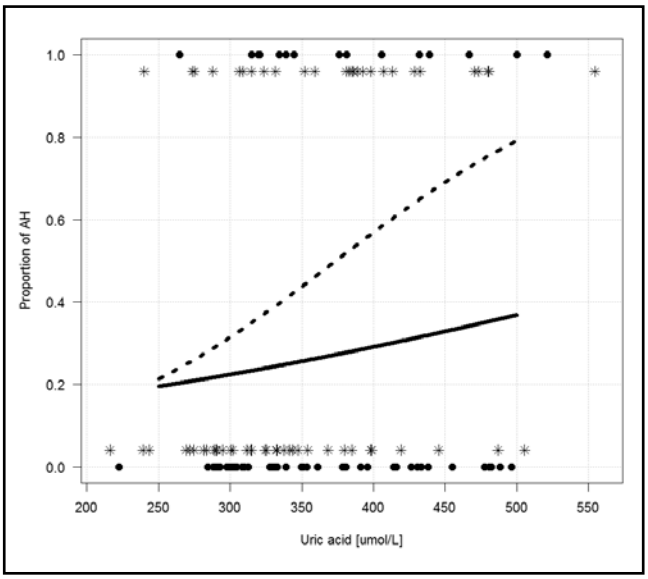

Fig. 1. Association between AH and uric acid, separately for girls (dashed line, stars) and boys (solid line, dots).

Tab. 2. Correlation between AASI and sAASI and selected biochemical parameters.

Selected biochemical parameters	AASI		sAASI	
	r	*p*-value	r	*p*-value
creatinin	0.02	0.79	0.29*	0.001
eGFR	0.04	0.66	–0.23*	0.009
fasting glucose	0.01	0.88	–0.01	0.93
120′ post-load glucose	0.07	0.41	0.11	0.2
fasting insulin	0.04	0.63	0.1	0.28
120′ post-load insulin	0.01	0.93	–0.001	0.97
HOMA IR	0.05	0.55	0.08	0.35
Total cholesterol	0.02	0.78	0.02	0.82
LDL cholesterol	0.05	0.60	0.03	0.74
HDL cholesterol	–0.001	0.96	–0.1	0.25
Triglicerides	0.04	0.68	0.08	0.39
Uric acid	0.08	0.36	0.08	0.36
Urinary free cortisol	0.01	0.96	0.13	0.35
Morning (8 a.m.) blood cortisol level	–0.06	0.49	0.03	0.35
Evening (8 p.m.) blood cortisol level	–0.14	0.16	0.15	0.13

*p<0.05

DISCUSSION

The incidence of obesity in the pediatric population has recently increased. As a consequence metabolic disturbances and AH are diagnosed more often at a younger age (Muntner *et al.* 2004; Maldonado *et al.* 2011). Although many studies have been done in this field, the details of the association between metabolic consequences of obesity and the development of AH remain unclear. Another important issue is the assessment and interpretation of BP measurements in obese adolescents owing to the fact that it differs from measurements in adults in various aspects (Flynn *et al.* 2014). According to the AHA recommendations issued in 2008 and updated in 2014, ABPM may be useful in the assessment of pediatric AH, however additional data evaluating the efficacy of ABPM in measuring the effect of interventions and effectiveness of ABPM-driven BP control in reversing target-organ damage are needed. In the adult population it is well proven, that ABPM measurements are more valuable in the assessment of end-organ damage than casual blood pressure (CBP) measurements (Perloff *et al.* 1989; White *et al.* 1989; Staessen *et al.* 1999; Cuspidi *et al.* 2001; National High Blood Pressure Education Program Working Groupon High Blood Pressure in Children and Adolescents, 2004). It should be also used as a complementary diagnostic tool in pediatric patients with obesity. The present study is a first attempt to compare CBP and 24h ABPM results and metabolic complications in obese adolescents in order to assess the suitability of these methods for the diagnosis of AH in selected groups of patients. There was no significant difference in the prevalence of AH diagnosed on the basis of the two analyzed methods: 36.2% vs. 33.8% in CBP and 24h ABPM respectively. The incidence of AH diagnosed on the basis of CBP was higher (17–20%), than by 24h ABPM, which was lower (75%) compared to previously published data (Figueroa-Colon *et al.* 1997; Babinska *et al.* 2012; Mazor-Aronovitch *et al.* 2014). 24h ABPM revealed the presence of white-coat hypertension in 46.8% of patients diagnosed with AH on the basis of CBP, that percentage is higher in pediatric, but not obese patients (29% according to the results published by of Jones et al.) and adult patients (Hornsby *et al.* 1991; Sorof & Portman 2000; Babinska *et al.* 2012).

This data may suggest the strong impact of the emotional factors on blood pressure in obese adolescents. What is even more interesting, 25% of the patients with normal CBP results presented masked hypertension, and elevated BP load during sleep time. According to the data in the literature, it might be associated with sleep disturbances and/or sympathetic nervous system hyperactivity present in obese patients (Eguchi *et al.* 2011; Feber *et al.* 2014). Another possible cause, that was not analyzed in this context yet, is abnormal cortisol rhythm and hypercortisolemia. It has been proven that any abnormalities in 24-h cortisol profiles may affect BP rhythm (Wojcik *et al.* 2013). Moreover, recently published studies showed that cortisol levels were related to obesity and the development of insulin resistance in children (Reinehr *et al.* 2014). The present study revealed significant correlations between morning /evening cortisol ratio and nDBP and nMAP during the sleep period (r=0.21, p=0.03), (r=0.21, p=0.03). The results of the present study show, that mean 24h-SBP, dSBP and dMAP during the activity period were higher in AH patients. Nevertheless there were no significant differences between patients with and without AH concerning dDBP during the activity period, BP parameters during the sleep period or night dip percentage. Therefore the usefulness of CBP and 24h ABPM in the diagnosis of AH in obese adolescents is comparable, however 24h ABPM additionally may indicate white coat AH and masked AH. CBP measurements correspond with 24-hSBP and dMAP during the activity period, but is not a good enough marker to diagnose BP profile abnormalities during the sleep period and nDBP. Urinary free cortisol, that reflects cortisol secretion was correlated with dSBP. Interestingly there were no significant differences in AASI and sAASI between patients with and without HA. Altered AASI is a recognized risk factor of cardiovascular disorders in adult people (Dolan *et al.* 2006). Its clinical significance in children remains unclear. The present study revealed significant correlations between SBP measured by CBP and metabolic abnormalities secondary to obesity (elevation of creatinine and uric acid levels as well as insulin resistance parameters). Of particular interest is the increase of UA levels in patients with AH. Among adults, the association between uric acid levels and BP has been known for decades, however the independent role of serum uric acid as a marker of cardiorenal risk is debated (Mellen *et al.* 2006; Perlstein *et al.* 2006; Krishnan *et al.* 2007; Jones *et al.* 2008; Viazzi *et al.* 2014). Among participants in the Bogalusa Heart Study, UA levels measured during childhood were significantly associated with childhood and adult SBP as well as DBP (Alper *et al.* 2005). Moreover, multivariate logistic regression analysis revealed that UA levels were associated with a positive history of cardiovascular events and a high Framingham risk score even after adjusting for metabolic syndrome and its components (OR=1.10, 95% CI 1.03–1.18; p=0.01; OR-1.28, 95% CI 1.15–1.42; p<0.001) (Viazzi *et al.* 2014). The study by Bombelli *et al.* (2014) revealed, that an increase in uric acid levels independently predicted new-onset out-of-office hypertension, and long-term cardiovascular and all-cause mortality [30]. In the present study the increase of UA levels was significantly associated with AH in girls (OR=2.88, p=0.01). Contrary to previously published results, UA levels did not correlate with 24h ABPM parameters (Jones *et al.* 2008).

We can conclude, that while the usefulness of CBP and 24h ABPM in the diagnosis of AH in obese adolescents is comparable, 24h ABPM may indicate white coat AH. The increase of the CBP parameters is associated with insulin resistance and hyperuricemia, while the increase of 24h ABPM results is proportional to the cortisol secretion in obese adolescents.

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Conflict of interest

The authors declare no competing interests.

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