Prehypertension in Outpatient Obese Children

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BACKGROUND

The aim of the study was to analyze the prevalence of prehypertension (PH) in obese (OB) children and its relation with estimated glomerular filtration rate (eGFR) and left ventricular (LV) function.

METHODS

The study included 447 OB and 131 normal-weight children. PH was defined according to the criteria proposed by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. Insulin sensitivity was evaluated by $HOMA_{IR}$, and eGFR was calculated by Schwartz's formula. LV function was analyzed by echocardiography in 165 OB children.

RESULTS

PH was observed in 79 OB children (17.7%) and in 2 (1.5%) controls. Among OB children, those with PH had greater percentage of males ($P < 0.05$), higher level of body mass index (BMI) ($P < 0.001$), waist circumference (WC) ($P < 0.005$), and $HOMA_{IR}$ ($P < 0.001$), compared to PH^- children. The two groups did not differ for eGFR and LV function. At logistic regression analysis, PH was independently associated with male gender ($P < 0.025$) and $HOMA_{IR}$ ($P < 0.002$). Gender analysis showed that boys with PH presented higher levels of BMI ($P < 0.005$), WC ($P < 0.01$), $HOMA_{IR}$ ($P < 0.001$), and triglycerides ($P < 0.005$) compared to PH^- boys. Females with PH were older and in more advanced postpubertal stage, had higher BMI, WC ($P < 0.05$, for all), and $HOMA_{IR}$ ($P < 0.025$), compared to PH^- girls.

CONCLUSIONS

In a population of outpatient OB children, the prevalence of PH was 17.7% and boys were more likely than girls to have PH. This condition is characterized by insulin resistance in both sexes but no impairment in glomerular and LV function.

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The increasing prevalence of obesity among young people has generated much concern, as pediatric obesity has been recognized as a risk factor for the development of coronary heart disease later in life.[1] Several studies have evidenced a strong association between body mass index (BMI) and blood pressure (BP) in the pediatric population.[2–4] In view of these data, measurement of BP is strongly recommended as a regular practice in overweight/OB children to prompt intensive lifestyle modifications and prevent adverse cardiovascular consequences in adulthood.[5]

The guidelines published by the National High Blood Pressure Education Working Group on High Blood Pressure in children and adolescents have introduced a new category, the so-called prehypertension (PH), which is defined by BP values >90th and <95th percentile for age, gender, and height. In adolescents, the 90th percentile may be higher than the adult threshold for PH of 120/80 mm Hg (ref. 6). This condition is characterized by a high risk to progress toward manifest hypertension, as demonstrated by the National Childhood Blood Pressure database, which reports a progression rate in adolescents as high as 7% per year.[7] To date, very limited information is available on the prevalence of PH in OB children; in addition, whether pediatric PH is associated with preclinical manifestations of organ damage is at present unknown. Accordingly, this study was undertaken to evaluate the prevalence of PH in a large sample of outpatient OB children and its relation with glomerular and LV function.

METHODS

Subjects. The study population included 447 Caucasian OB children with ages ranging between 6 and 16 years. All children were consecutively observed at the Outpatient Metabolic Unit of the Pediatric Department of Pozzuoli Hospital from March 2004 to March 2009. Obesity was defined by individual BMI ≥95th percentile for age and gender.[8] PH was defined according to criteria published by the National High Blood Pressure Education Working Group on High Blood Pressure in children and adolescents[6] The diagnosis of PH was confirmed in a subsequent visit, performed within 2 weeks from the previous one, before starting the nutritional intervention. Exclusion criteria were gastrointestinal, liver, and kidney disease; alcohol consumption; and hypertension (systolic BP or diastolic BP ≥95th percentile for gender, age, and height), which was diagnosed in 40 children (8%).

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The control group consisted of 131 non-OB children (66 boys, 65 girls), comparable to the OB group for age and gender distribution, randomly selected among children attending the same Outpatient Unit for allergy-related problems. All had a body weight <85th percentile.

The study was approved by the Local Ethics Committee and informed consent was obtained from the parents of all the participants.

Measurements. Weight was determined to the nearest 0.1 kg on a medical balance; height was measured to the nearest 0.1 cm with a wall-mounted stadiometer. Waist circumference was measured using a flexible tape at the high point of the iliac crest at minimal respiration, with the participant in a standing position.[9] Children's sexual maturity was evaluated by the Tanner staging for pubic hair (I–V).[10] Postpubertal stage was defined by Tanner stage IV and V. BP was measured according to standard criteria[6] at the right arm in the supine position after a 5-min rest, using a mercury sphygmomanometer with an appropriately sized cuff, and a stethoscope placed over the brachial artery pulse; three readings were taken 2 min apart and the average of the two last values was used in the analyses.

Fasting blood samples were taken from all participants, for the determination of biochemical parameters in the centralized laboratory of Pozzuoli Hospital.

Fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein–cholesterol, plasma creatinine, and insulin were determined according to standard procedures using a Roche analyzer (Modular Analytics Serum Work Area; Roche, Mannheim, Germany). Low-density lipoprotein–cholesterol was calculated with the Friedwald formula. Insulin sensitivity was evaluated by the homeostasis model assessment of insulin resistance ($HOMA_{IR}$) index using a standard formula: fasting insulin (U/l) × fasting glucose (mmol/l) divided by 22.5.

Plasma creatinine was analyzed with Jaffe method. Estimated glomerular filtration rate (eGFR) was calculated according to international guidelines using the Schwartz formula: 0.55 × height (cm)/serum creatinine (mg/dl). In adolescent boys, the value of the constant was 0.70 (ref. 11).

Echocardiography. A total of 165 OB children and 30 non-OB children were randomly selected within each group to undergo echocardiography. Standard echocardiograms were obtained by a commercially available echocardiographic system with tissue Doppler imaging capabilities (Power Vision 8000; Toshiba, Tokyo, Japan). All measurements were analyzed according to the Recommendations of the American Society of Echocardiography.[12] Left ventricular mass (LVM) was calculated according to the Penn convention and indexed for height$^{2.7}$ (LVM index). As there is no general agreement on the criteria of LV hypertrophy in children, we used two cutoffs: a value of LVM index >38.6 g/height$^{2.7}$ and a value of LVM-for-height above 95th percentile (LVM/h 95th percentile).[13,14] Relative wall thickness (RWT) was calculated from posterior wall thickness (PWT), interventricular septum thickness (IVST), and LV diastolic diameter (LVDD) using the following formula: (PWT + IVST)/LVDD. RWT was normalized for age (RWT_a) by the following equation: $RWT_a = RWT - 0.005 \times (age - 10)$ (ref. 15)

LV function was analyzed by conventional and tissue Doppler imaging echocardiography as described elsewhere;[16] transmitral peak rapid filling velocity (E), peak atrial filling velocity (A), E/A ratio and isovolumic relaxation time were obtained as measures of diastolic function.

For tissue Doppler imaging echocardiography, three major velocities were recorded at the annular site: peak positive systolic velocity (S_a), and two peak negative velocities during the early (E_a) and late (A_a) phases of diastole. E_a/A_a ratio were also calculated. All readings were made online.

Statistics. Data are expressed as mean ± s.d. or number. Given the skewed distribution of plasma insulin, $HOMA_{IR}$, triglycerides, the statistical analysis of these variables was applied after log-transformation. Means were compared by unpaired Student's t-test. χ^2 or Fisher's exact test, as appropriate, were used to compare proportions. Logistic regression analysis was applied to evaluate the independent role of variables significantly associated with PH. A two sided P value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS for Windows, version 13.0 (SPSS, Chicago, IL).

RESULTS

PH was present in 2 control children (1.5%) and 79 out of 447 OB children (17.7%) ($P < 0.001$). As reported in **Table 1** (left panel), the OB group showed higher waist circumference, fasting plasma glucose, insulin, $HOMA_{IR}$, triglycerides, systolic BP, and lower levels of high-density lipoprotein ($P < 0.001$, for all parameters) than non-OB children. No difference was observed for age, Tanner stage, cholesterol, eGFR, and diastolic BP. OB children showed a higher LVM index ($P < 0.001$) compared to non obese children, whereas no difference was observed between the two groups as to systolic and diastolic function evaluated with both conventional and tissue Doppler imaging echocardiography.

The OB group with PH showed greater percentage of boys ($P < 0.005$), older age ($P < 0.005$), higher levels of BMI ($P < 0.001$), waist circumference ($P < 0.005$), fasting plasma glucose ($P < 0.05$), fasting plasma insulin ($P < 0.001$), and $HOMA_{IR}$ ($P < 0.001$) than normotensive children (**Table 1**, right panel). No difference was observed in eGFR between the two groups. As for the cardiac parameters, no difference was observed in LV geometry or function, except for a weak, albeit statistically significant, difference in isovolumic relaxation time, which was more prolonged in prehypertensive than in normotensive children ($P < 0.05$).

At logistic regression analysis, PH was independently associated with $HOMA_{IR}$ ($P < 0.002$) and male gender ($P < 0.025$) (**Table 2**). In addition, no significant relation was observed between PH and isovolumic relaxation time after correction for age and gender.

Analyzing the features of prehypertensive children by gender, boys with PH exhibited higher levels of age ($P < 0.05$),

Table 1 | Anthropometric, biochemical, and echocardiographic features of the control and obese group, and obese children without and with prehypertension

			Obese group	
	Control group	Obese group	PH$^-$	PH$^+$
Clinical variables				
n	131	447	368	79
Boys (%)	66 (50)	220 (49)	170 (46)	50 (63)†
Postpubertal stage (%)	12 (9)	66 (14)	42 (11)	14 (18)
Age (years)	10 ± 3	10 ± 3	10 ± 3	11 ± 3†
Body mass index (kg/m^2)	17 ± 2	27 ± 4*	27 ± 4	29 ± 4††
Waist circumference (cm)	74 ± 7	88 ± 11*	88 ± 11	92 ± 11†
Fasting plasma glucose (mg/dl)	83 ± 6	86 ± 7*	85 ± 7	87 ± 8**
Fasting plasma insulin (mU/l)	5 ± 2	15 ± 10*	14 ± 8	19 ± 15††
$HOMA_{IR}$	0.8 ± 0.6	3.1 ±2.3*	2.9 ± 1.8	4.3 ± 3.6††
Cholesterol (mg/dl)	155 ± 24	162 ± 30	161 ± 30	162 ± 34
HDL-cholesterol (mg/dl)	56 ± 9	51 ± 12*	51 ± 11	49 ± 13
Triglycerides (mg/dl)	66 ± 29	89 ± 45*	87 ± 39	95 ± 51
LDL-cholesterol (mg/dl)	89 ± 21	93 ± 28	93 ± 27	93 ± 30
eGFR (ml/min/1.73 m^2)	150 ± 23	149 ± 25	150 ± 24	149 ± 30
Systolic blood pressure (mm Hg)	99 ± 8	104 ± 10*	102 ± 9	117 ± 7††
Diastolic blood pressure (mm Hg)	59 ± 6	61 ± 10	59 ± 8	70 ± 12††
Echocardiographic variables				
N	30	165	134	31
Relative wall $thickness_a$ (mm)	0.34 ± 0.07	0.35 ± 0.05	0.35 ± 0.05	0.35 ± 0.06
Left ventricular mass (g/h$^{2.7}$)	23 ± 3	37 ± 10*	37 ± 9	38 ± 10
Ejection fraction (%)	62 ± 5	63 ± 5	63 ± 5	64 ± 6
Isovolumic relaxation time (ms)	65 ± 13	66 ± 10	65 ± 10	69 ± 9**
E/A ratio	2.0 ± 0.8	2.1 ± 0.7	2.1 ± 0.7	2.1 ± 0.9
E_a/A_a ratio	2.6 ± 0.8	2.4 ± 0.7	2.3 ± 0.7	2.5 ± 0.7
S_a velocity (cm/s)	10 ± 2	10 ± 2	10 ± 2	10 ± 2
LVMi >38.6 g/h$^{2.7}$	0 (0)	63 (36)*	48 (36)	14 (45)
LVM/h 95th percentile	0 (0)	22 (12)*	17 (13)	5 (16)

Data are expressed as mean ± s.d. or number.
A, peak atrial filling velocity; *E*, transmitral peak rapid filling velocity; E_a/A_a, ratio between peak negative velocities during the early (E_a) and late (A_a) phases of diastole; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; LVM, left ventricular mass; LVMi, LVM index; PH, prehypertension; S_a, peak positive systolic velocity.
*$P < 0.001$: control vs. obese group, **$P < 0.05$, $^\dagger P < 0.005$, $^{\dagger\dagger}P < 0.001$: normotensive vs. prehypertensive obese children.

BMI ($P < 0.005$), waist circumference ($P < 0.01$), fasting plasma glucose ($P < 0.01$), insulin ($P < 0.001$), $HOMA_{IR}$ ($P < 0.001$), triglycerides ($P < 0.005$), compared to normotensive boys. No difference was observed for eGFR or cardiac parameters. Among girls, PH was associated with older age ($P < 0.05$), more advanced postpubertal stage ($P < 0.05$), higher BMI ($P < 0.05$), insulin ($P < 0.001$), and $HOMA_{IR}$ ($P < 0.025$) as compared to normotensive girls. The two groups did not differ for other metabolic, glomerular, or LV variables (Table 3).

DISCUSSION

Our study demonstrates that in an outpatient population of Caucasian OB children the prevalence of PH is elevated (17.7%). This condition is characterized by insulin resistance, but no impairment of glomerular and LV function.

The prevalence of PH in adolescents is highly heterogeneous, ranging from 8% in a Canadian rural population[17] to >40% in an Israeli population;[18] this wide variability may be due to common demographic factors such as ethnic group, age, and obesity status, all known to influence BP. Only a single study has evaluated the prevalence of PH in a multiethnic population of OB children, reporting a prevalence of 27.9% (ref. 19). In our sample, we found a prevalence of 17.7%; of note is the finding that it was higher in boys than in girls (22.7% vs. 12.8%, $P < 0.001$) confirming previous studies performed in children[19] and young adults.[18]

Currently, there is still debate whether PH in the pediatric population should be considered a condition of high risk to progress toward hypertension, or as a pathological status itself. Although from longitudinal studies it can be predicted that as many as 7% of PH children per year will progress to hypertension,[7] whether PH in OB children has adverse clinical consequences is still unexplored. In the Strong Heart Study, prehypertensive OB subjects aged 14–39 years showed higher LVM, eccentric hypertrophy, and impaired LV function compared to their normotensive counterparts.[20] However, these findings are not directly comparable to ours, as the population examined in that study included American-Indian young adults with a higher degree of obesity. To the best of our knowledge, this study is the first to investigate the relation between PH and LV function in Caucasian OB children. The absence of LV functional abnormalities in our OB children with PH, however, does not diminish the clinical significance of this condition, which might cause adverse consequences over time. In fact, longitudinal data on adult populations have shown that the persistence of PH over time is associated with a significantly increased occurrence of LV hypertrophy and diastolic dysfunction, suggesting that PH amplifies the typical age-related adaptation of the heart.[21] However, as the data are the result of a cross-sectional study, it cannot be excluded that pediatric PH sustained over time may increase cardiovascular risk. It is also possible that progression of PH may not necessarily involve alterations of LV structure but may rather pass through endothelial dysfunction. This view is supported by a recent study showing abnormalities of coronary flow reserve in prehypertensive adult subjects in the presence of normal LVM.[22] In this context, it is important to recall that endothelial dysfunction is considered an early manifestation of atherosclerosis and a prognostic factor of cardiovascular events.[23]

Although pediatric hypertension is known to impair renal function,[24,25] the impact of PH on glomerular function is unknown. We found a normal eGFR, which is in line with the findings by Cordero *et al.* who reported that in an adult population PH was not associated with renal dysfunction but only with insulin resistance.[26] However, only longitudinal studies will clarify whether the persistence of PH over time may deteriorate glomerular function.

Table 2 | Independent predictors of PH among obese children

	β Coefficient	95% CI	*P* value
$HOMA_{IR}$	1.780	1.95–18.06	0.002
Male gender	0.637	1.12–3.18	0.016
Age	0.033	0.89–1.20	0.66
Body mass index	0.021	0.94–1.11	0.63
Postpubertal stage	0.022	0.41–2.56	0.97
Waist circumference	0.005	0.97–1.04	0.78

CI, confidence interval; $HOMA_{IR}$, homeostasis model assessment of insulin resistance; PH, prehypertension.

Table 3 | Comparison between normotensive and prehypertensive obese children by gender

	Boys (*n* = 220)			Girls (*n* = 227)		
	PH⁻	PH⁺	*P* value	PH⁻	PH⁺	*P* value
N	170	50		198	29	
Postpubertal stage (%)	13 (8)	5 (10)	0.81	29 (15)	9 (31)	<0.05
Age (years)	10 ± 2	11 ± 3	<0.05	10 ± 3	11 ± 3	<0.05
Body mass index (kg/m^2)	27 ± 4	29 ± 5	<0.005	28 ± 4	30 ± 4	<0.05
Waist circumference (cm)	88 ± 11	93 ± 12	<0.01	88 ± 11	91 ± 10	0.08
Fasting plasma glucose (mg/dl)	86 ± 7	89 ± 7	<0.01	85 ± 8	85 ± 8	0.65
Fasting plasma insulin (mU/l)	12 ± 7	17 ± 12	<0.001	15 ± 9	23 ± 18	<0.001
$HOMA_{IR}$	2.7 ± 1.5	3.8 ± 3.1	<0.001	3.2 ± 2.0	5.0 ± 4.7	<0.025
Cholesterol (mg/dl)	159 ± 30	168 ± 37	0.09	163 ± 29	161 ± 23	0.72
HDL-cholesterol (mg/dl)	51 ± 11	48 ± 12	0.17	51 ± 11	51 ± 15	0.87
Triglycerides (mg/dl)	82 ± 38	101 ± 54	<0.005	91 ± 39	86 ± 45	0.53
LDL-cholesterol (mg/dl)	92 ± 28	99 ± 35	0.12	95 ± 26	87 ± 19	0.11
eGFR (ml/min/1.73 m^2)	151 ± 25	150 ± 32	0.82	149 ± 24	147 ± 27	0.68
N	65	18		69	13	
IRT (ms)	64 ± 11	68 ± 9	0.15	66 ± 10	71 ± 11	0.11
E_a/A_a ratio	2.3 ± 0.7	2.3 ± 0.7	0.82	2.2 ± 0.7	2.4 ± 0.6	0.34
S_a velocity (cm/s)	9.9 ± 1.7	10.2 ± 2.6	0.56	10.3 ± 1.9	10.0 ± 1.7	0.12
Left ventricular mass (g/h$^{2.7}$)	39 ± 10	40 ± 9	0.90	35 ± 8	36 ± 12	0.79

Data are expressed as mean ± s.d. or number (%).
E_a/A_a ratio, ratio between peak negative velocities during the early (E_a) and late (A_a) phases of diastole; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; $HOMA_{IR}$, homeostasis model assessment of insulin resistance; IRT, isovolumic relaxation time; LDL, low-density lipoprotein; PH, prehypertension; S_a, peak positive systolic velocity.

Although PH was associated with an increased risk of cardiovascular events in an adult population,[27] the clinical significance of PH in pediatric obesity remains to be established. Our data indicate that in OB children PH does not impact organ function, but is rather associated with the typical metabolic traits clustering with visceral obesity, particularly insulin resistance. It is of interest to note that boys exhibit a worse metabolic profile than girls. This observation suggests that sex steroids and the different fat distribution in the two genders may play a role in the regulation of BP levels. Interestingly, a recent study has shown that fat accumulation is associated with high BP and higher sympathetic activity in adolescent boys but not girls.[28]

The limitations of our study include the cross-sectional design, which does not allow to define the clinical significance of PH in relation to the cardiovascular risk in adulthood. In addition, the possibility that our study may be underpowered to appreciate gender differences with regard to LV function cannot be excluded; therefore, the findings derived from gender analysis should be interpreted with caution. Lastly, we defined insulin resistance on the basis of a static measure such as the HOMA index. However, this index is recognized to highly correlate with the hyperinsulinemic–euglycemic clamp and is widely used in clinical epidemiological studies.

In conclusion, PH is present in a quite large number of outpatient OB children, particularly boys, and is associated with insulin resistance. This observation supports the need to actively detect this condition among OB children in order to prevent the progression toward hypertension.

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