Blood Pressure in Obese and Overweight Children and Adolescents

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ABSTRACT: **Background:** The prevalence of obesity in children and adolescents has increased dramatically in the last few decades. Primary hypertension, a known secondary complication among obese adults, has been considered rare in children.

Objectives: To investigate the prevalence of hypertension and its relation to body mass index (BMI) in obese children aged 9–17 years in Israel.

Methods: Weight, height, BMI, and systolic and diastolic blood pressure (BP) (twice) were measured in children attending general and pediatric endocrine clinics. Obesity was defined as BMI ≥ 95th percentile and overweight as BMI ≥ 85th percentile. Pre-hypertension and hypertension were defined as systolic and/or diastolic BP ≥ 90th percentile for age, gender and height and BP ≥ 95th percentile respectively. In children with pre-hypertension or hypertension, repeated measurements were performed.

Results: We evaluated 264 children of whom 152 had BMI ≥ 85th percentile (study group). Their mean age was 12.5 years. The prevalence of elevated BP (both pre-hypertension and hypertension) in the study group was 44.1% and 31% at the first and second measurements respectively, compared to 11.6% and 1.9% in the normal-weight group. Hypertension was documented in 17.2% of the study group at the second measurement.

Conclusions: Elevated BP was diagnosed in 31% of overweight and obese children and adolescents. Increased awareness and early diagnosis and treatment are essential.

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KEY WORDS: obesity, hypertension, adolescence, childhood

The prevalence of obesity in children and adolescents has increased dramatically over the last few decades [1,2]. In Israel a threefold increase in prevalence of obesity was observed in schoolchildren between 1990 and 2004 [3]. The prevalence of secondary morbidity such as type 2 diabetes mellitus, dyslipidemia and non-alcoholic fatty liver among children is increasing in parallel [4]. The prevalence of hypertension, a known secondary complication among obese adults and once considered rare in children, has been increasing recently among children. While in the late 1980s the reported prevalence was about 1%–2% [5], the recently reported rate in certain populations in the United States and other countries in the world is 13–17% [6,7]. Moreover, while in the past the majority of pediatric patients with hypertension had secondary hypertension, most commonly caused by renal disease, and only 16% of all cases of pediatric hypertension had primary hypertension [8], today nearly 50% of patients seen in a specialized pediatric hypertension clinic have primary hypertension [9].

There are few data on the prevalence of hypertension in children and adolescents in Israel. In the 1980s Zadik et al. [10] reported its prevalence among children aged 5–14 years. The prevalence of systolic blood pressure above the 97th percentile was 1%, and of diastolic blood pressure 0.6%. It was concluded that there is no need for blood pressure screening in children. In another study, conducted in 1993 among 4500 Israeli-Arab children aged 6–17 years, hypertension was found in 2.2% [11].

Known complications of hypertension in adults have been described also in children. These include increased left ventricle mass and diastolic dysfunction [12], fatty streaks and fibrous plaques in the aorta and coronary arteries in autopsies [13], retinopathy and glomerular hyperfiltration [14], and decreased cognitive function secondary to pre-hypertension (> 90th percentile) [15,16].

In view of the rising prevalence of obesity in Israel, we investigated the prevalence of hypertension and pre-hypertension in obese children aged 9–17 years as compared with normal-weight children.

PATIENTS AND METHODS

All children referred to a hospital-based pediatric endocrine clinic at their first visit as well as children from community-based general pediatric clinics were included. The children recruited in the community attended the clinics for routine checkups, including doctor's certificates for sport activities and scheduled visits for well-child assessment. Children

*The first two authors contributed equally to this study

with chronic diseases, kidney disease, a known syndrome, chronic medical treatment, or suffering from any acute illness were excluded. The study population comprised 264 children aged 9–17 years. The research protocol was approved by the Helsinki Committee of the Sheba Medical Center.

We measured height and weight in each child at the first visit. Body mass index was calculated as the weight in kg divided by the height in meters squared. Obesity was defined as BMI above the 95th percentile for age and gender (> 1.645 standard deviation score) according to the Centers for Disease Control and Prevention health data (CDC growth charts, US National Center for Health Statistics: http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/charts.htm). Since there are no Israeli national data, the CDC data were selected by the Israel Ministry of Health as the routine reference for anthropometric data for children. The new CDC growth charts are reportedly adequate for assessing Israeli children [17]. Overweight was defined as 85th ≤ BMI < 95th percentile (1.036 < BMI SDS < 1.645).

Blood pressure was measured by trained personnel according to the recommendations of the Task Force on Blood Pressure Control in Children [18]. BP was measured by auscultation using a mercury sphygmomanometer on the right arm after the patient had been seated quietly for 5 minutes, with the back supported, feet on the floor, right arm supported and cubital fossa at heart level. BP for each child was defined as the average of measurements performed in the child at that visit (two to three measurements). Patients with systolic and/or diastolic BP > 90th percentile for age, gender and height were classified as having normal BP. Patients with systolic and/or diastolic BP > 90th but < 95th percentile were classified as showing pre-hypertension. Patients with systolic and/or diastolic BP ≥ 95th percentile were designated as manifesting hypertension. Children with BP ≥ 90th percentile for age, gender and height (elevated BP) were scheduled for a second visit 2 weeks later.

Eighty children were recalled for a second visit because of elevated measurements obtained at the first visit (systolic and/or diastolic BP ≥ 90th percentile). Of these, 66 were reexamined, 47 were recalled for a third visit because of elevated results at the second visit, and 27 of them were reexamined. The differences between BP measurements were examined using the McNemar-Bowker test. A significant statistical difference in systolic values ($P = 0.001$) was found between the first and second visits; no significant difference was found between the diastolic values ($P = 0.15$). No significant difference was found between the second and the third visits for both the systolic ($P = 0.246$) and the diastolic values ($P = 0.779$), and we therefore used the measurements of the second visit for further analyses.

BMI = body mass index
CDC = Centers for Disease Control and Prevention
SDS = standard deviation score
BP = blood pressure

STATISTICAL ANALYSIS

The size of the cohort was determined based on the assumption that the difference in the prevalence of hypertension between obese and normal-weight children is 10% and the prevalence of hypertension among normal-weight children 2%. Using a paired *t*-test with two-sided alpha of 0.05 and statistical power of 80%, the study group should have comprised 204 children (at least 102 patients in each group).

Categorical data were expressed as numbers (percentages) and continuous variables as the mean value ± SD. For group comparison, ANOVA was used for continuous variables and the chi-square test for linear trend for categorical variables. All *P* values refer to two-tailed tests of significance; $P < 0.05$ was considered significant. Multivariable logistic regression analysis was performed to determine predictors of hypertension. The following variables were included in the final model: age, gender, weight group (normal, overweight), and blood pressure (normal, pre-hypertension). The results of the logistic regression analysis are presented as odds ratio with the appropriate 95% confidence intervals. All statistical analyses were performed with SPSS software.

RESULTS

The study population comprised 264 children of whom 152 were obese or overweight (BMI percentile ≥ 85) (the study group), and 112 were normal weight. There was no difference in mean age (12.55 ± 2.02 vs. 12.51 ± 2.03 years) and gender (57% females vs. 54%) between the groups. Mean BMI SDS in the study group was 3.12 compared to -0.01 in the normal-weight group.

In a logistic model, significant correlation was found between obesity and both elevated BP and hypertension ($P < 0.001$ for both). Correlation was significant both for systolic BP ($P < 0.001$) and diastolic BP ($P = 0.002$). In multiple variant logistic regression analyses for all subjects a significant correlation was found with BMI SDS ($P < 0.001$, odds ratio 1.548, confidence interval 1.303–1.838). In logistic regression studies in the study group, a significant correlation was found with male gender ($P = 0.048$, OR 1.986, CI 1.007–3.920).

In a linear model, there was a significant positive correlation between systolic BP and BMI SDS ($R = 0.453$, $P < 0.001$) [Figure 1], and between diastolic BP and BMI SDS ($R = 0.382$, $P < 0.001$) [Figure 2]. In multiple linear regression analyses for systolic BP, significant correlations were found with BMI SDS ($P < 0.001$) and age ($P = 0.015$) but not with gender. In multiple linear regression analyses for diastolic BP, a significant correlation was found with BMI SDS ($P < 0.001$).

OR = odds ratio
CI = confidence interval

Figure 1. The correlation between body mass index SDS and systolic blood pressure

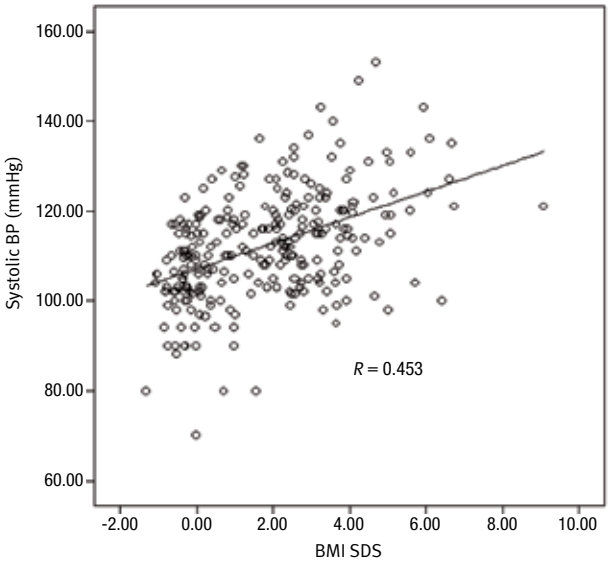
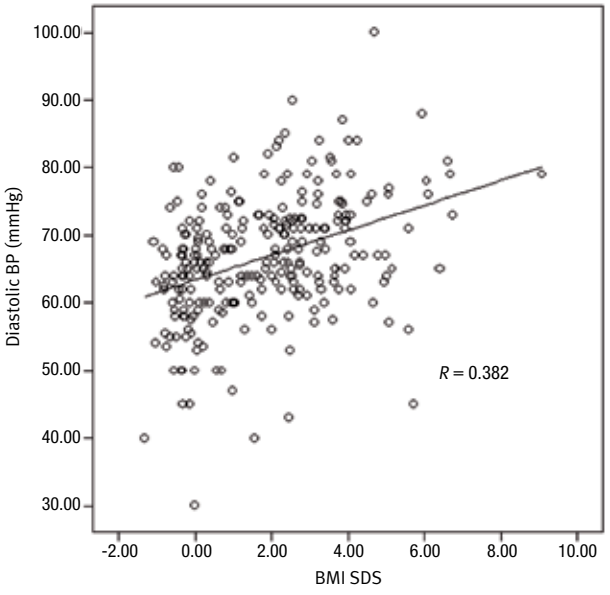


Figure 2. The correlation between body mass index SDS and diastolic BP



BP measurements at the first visit showed a significantly higher occurrence of elevated BP in the study group compared with the normal-weight group (44.1% vs. 11.6%). These findings were consistent for both systolic and diastolic measurements [Table 1]. In the normal-weight group most subjects with abnormal measurements had pre-hypertension, whereas in the study group the majority had hypertension tenfold higher than in the normal-weight group (34.2% vs 3.6%).

Table 1. Blood pressure at the first visit

	Study group BMI ≥ 85th percentile (n=152)	Normal-weight group BMI < 85th percentile (n=112)	*P* value
Percent of children with BP > 90th percentile (no. of children)	44.1 (67)	11.6 (13)	
Percent of children with systolic BP > 90th percentile	40.1	9.9	< 0.001
Percent of children with diastolic BP > 90th percentile	21.1	4.5	0.001
Percent of children with pre-hypertension (90–95th percentile)	9.9	8	NS
Percent of children with hypertension (systolic and/or diastolic BP ≥ 95th percentile)	34.2	3.6	< 0.001

Table 2. Occurrence of elevated BP and hypertension in overweight compared with normal-weight children (after the 2nd BP measurement visit)

	Study group BMI ≥ 85th percentile (n=145)	Normal-weight group BMI < 85th percentile (n=105)
Percent of children with BP > 90th percentile (no. of children)	31% (45)	1.9% (2)
Percent of children with hypertension (≥ 95th percentile) (no. of children)	17.2% (25)	1.9% (2)

Final score: The second measurement in those children for whom it was available, and the first measurement in all the others (7 patients from each group were not included in the final analysis, since they had elevated BP at the first visit and BP measurement was not repeated at the second visit)

At the second visit, of 60 overweight patients 45 (76%) had elevated BP (elevated systolic BP in 65%, elevated diastolic BP in 35%, and both elevated systolic BP and diastolic BP in 25%). Of six normal-weight patients, two had hypertension and they were referred to their primary physician.

In the final analysis of all subjects after the second visit, 31% of overweight children had elevated BP and 17.2% had hypertension [Table 2]. The occurrence of elevated BP was 16-fold higher in the study group compared to the normal-weight group, and the occurrence of hypertension was nine-fold higher respectively.

DISCUSSION

Thirty-one percent of obese and overweight children and adolescents referred to the pediatric endocrine clinic had elevated BP (pre-hypertension and hypertension) compared with only 2% of normal-weight children and adolescents. Hypertension was found in 17% of overweight children compared with 1.9% in the normal-weight group. We found a positive correlation between severity of obesity as expressed by BMI SDS and both

systolic and diastolic BP. Moreover, 27% of overweight children (1.036 < BMI SDS < 1.645) had hypertension at both the first and second visits. This finding emphasizes the importance of measuring BP at well-child care visits, considering that about one-fifth of the children in the western population are considered overweight [19].

Zadik and co-authors [10] reported in the 1980s that among children aged 5–14 years with BMI above the 97th percentile the prevalence of systolic BP above the 97th percentile was 1%, and the prevalence of diastolic BP above the 97th percentile 0.6%. They concluded that there was no need for BP screening in children. However, it appears that hypertension in children is often undiagnosed today. Hansen et al. [20] reported that in their study hypertension was missed in about 75% of children with persistently elevated BP readings and that pre-hypertension was missed in about 89% [20].

Our results are in concordance with other recent reports showing an increasing prevalence of hypertension among obese and overweight children [6,7,21]. The reported prevalence in the school-age population ranged between 10% and 12%. The reported prevalence in the obese children was 33–38% at the first visit and 21% at the second visit.

Not all investigators have demonstrated an increasing prevalence of BP in obese children [22]. The wide variability among studies on the prevalence of hypertension in children may be due to several methodological differences. Firstly, in some studies only a single set of BP measurements was performed, increasing the prevalence of hypertension [23]. Secondly, some studies report the prevalence of hypertension only [21], while others report the prevalence of both pre-hypertension and hypertension [23]. Furthermore, the age range is markedly different in these studies, some including children aged 5–17 years. Since the prevalence of hypertension in young children is very low, the total prevalence is low [15].

Interestingly, a recent report in Israel examined whether blood pressure levels of children with a history of intrauterine growth retardation are higher than in children without such a history [24]. Children born with IUGR had lower systolic BP levels than matched controls at age 8–12 years. There was no difference in diastolic BP values. In the IUGR group, systolic BP correlated significantly with current weight and body mass index. None of the blood pressure values correlated with birth weight. The authors concluded that postnatal weight gain in this group had a greater impact on systolic blood pressure than birth weight.

The importance of measuring blood pressure at a second visit is to eliminate incidentally elevated BP. Although a single measurement is not diagnostic and may be elevated as a result of the 'white coat hypertension' phenomenon, it is still important to follow these patients. White coat hypertension is no longer considered benign, with new reports suggesting that it carries a higher risk for cardiovascular morbidity in the future [25].

In adults, hypertension is more prevalent in men than in women. Elevated BP and hypertension have been reported in some studies to be more prevalent in boys than in girls [21]. Similarly, in our study among overweight subjects, male gender had a stronger impact on the risk of hypertension than the degree of obesity.

Although our results are in concordance with previous research in western countries, already showing the appearance of early complications associated with obesity in childhood, our study has several limitations. We lack data from the second visit in seven of the overweight children and seven of the normal-weight children who had elevated BP at the first visit. To calculate the total prevalence of elevated BP and hypertension, those children were excluded from the total calculation and therefore the severity of the problem may have been underestimated. We also conducted a third visit for 60% of the children who had had elevated BP at the second visit. Although we did not find a significant difference between the second and the third visits, there were still children with normal BP at this visit.

In conclusion, elevated BP (pre-hypertension and hypertension) was diagnosed in 31% of obese and overweight children and adolescents. We believe that increased awareness and early diagnosis and treatment are essential.

IUGR = intrauterine growth retardation

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Capsule

Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis

Metabolites from intestinal microbiota are key determinants of host-microbe mutualism and, consequently, the health or disease of the intestinal tract. However, whether such host-microbe cross-talk influences inflammation in peripheral tissues, such as the lung, is poorly understood. Trompette et al. found that dietary fermentable fiber content changed the composition of the gut and lung microbiota, in particular by altering the ratio of firmicutes to bacteroidetes. The gut microbiota metabolized the fiber, consequently increasing the concentration of circulating short-chain fatty acids (SCFAs). Mice fed a high fiber diet had increased circulating levels of SCFAs and were protected against allergic inflammation in the lung, whereas a low fiber diet decreased levels of SCFAs and increased allergic airway disease. Treatment of mice with the SCFA propionate led to alterations in bone marrow hematopoiesis that were characterized by enhanced generation of macrophage and dendritic cell (DC) precursors and subsequent seeding of the lungs by DCs with high phagocytic capacity but an impaired ability to promote T helper type 2 (T_H2) cell effector function. The effects of propionate on allergic inflammation were dependent on G protein-coupled receptor 41 (GPR41, also called free fatty acid receptor 3 or FFAR3), but not GPR43 (also called free fatty acid receptor 2 or FFAR2). Our results show that dietary fermentable fiber and SCFAs can shape the immunological environment in the lung and influence the severity of allergic inflammation.

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Capsule

In vivo discovery of immunotherapy targets in the tumor microenvironment

Recent clinical trials showed that targeting of inhibitory receptors on T cells induces durable responses in a subset of cancer patients, despite advanced disease. However, the regulatory switches controlling T cell function in immunosuppressive tumors are not well understood. Zhou et al. show that such inhibitory mechanisms can be systematically discovered in the tumor microenvironment. The authors devised an in vivo pooled short hairpin RNA (shRNA) screen in which shRNAs targeting negative regulators became highly enriched in murine tumors by releasing a block on T cell proliferation upon tumor antigen recognition. Such shRNAs were identified by deep sequencing of the shRNA cassette from T cells infiltrating tumor or control tissues. One of the target genes was *Ppp2r2d*, a regulatory subunit of the PP2A phosphatase family. In tumors, *Ppp2r2d* knockdown inhibited T cell apoptosis and enhanced T cell proliferation as well as cytokine production. Key regulators of immune function can therefore be discovered in relevant tissue microenvironments.

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