Hypertension in children (12–14 years) – a case–control study in Bursa, Turkey

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The aim of this study was to determine the cardiovascular disease risk factors (risk of overweight/overweight, dyslipidemia, paraoxonase-1 activity, positive family history, physical inactivity, smoking) that accompany hypertension and investigate the relationship between hypertension and some of these risk factors.

This study included 118 hypertensives and 118 age- and sex-matched non-hypertensive controls aged 12-14 years.

Among controls, 64.4% had no risk factor. Among cases, 34.8% had no risk factor other than hypertension, and 65.2% had two or more risk factors.

The adjusted odds ratio (OR) (95% confidence interval [CI]) of hypertension was 5.65 (2.88–11.09) for risk of overweight/overweight. Body mass index, paraoxonase and arylesterase activities were significantly higher in hypertensives than those of the control group.

We conclude that it would be useful to routinely evaluate blood pressure and body weight at schools and, additionally, considering that hypertension alone is encountered rarely, it would be appropriate to examine the hypertensive students for other risk factors.

Key words: hypertension, overweight, dyslipidemia, paraoxonase-1 activity, children.

Hypertension is defined as a risk factor for cardiovascular diseases (CVD) in both adults and children[1]. The risk of CVD is related to increment in blood pressure (BP) and presence of other CVD risk factors[2]. Other cardiovascular risk factors, such as dyslipidemia, high blood glucose and obesity, usually accompany hypertension[3], and prospective and retrospective studies reveal that CVD risk factors are rooted in childhood[4-6].

The association between obesity and hypertension is well known. Physiopathological mechanisms of hypertension in obesity are complex, multifactorial and unclear. Many human and animal studies revealed that the interaction between hypertension and obesity is the retention that might be related to insulin resistance, anatomical changes in the kidneys, disturbances in vascular functions and sympathetic nerve system, activation of the renin-angiotensin system, and changes at the hypothalamo–hypophyseal–adrenal axis[7]. The nature of interaction between hypertension and dyslipidemia is unclear[3]. The combination of obesity, high BP and dyslipidemia makes an additional contribution to atherosclerotic lesions in adolescents[4].

In recent years, besides the known risk factors for CVD, studies have been conducted to investigate paraoxonase-1 (PON-1) activity. It is claimed that PON-1 activity is related to CVD[8]. PON-1 is reported to have a protective role in the atherosclerotic process, by contributing to the protective effect of high density lipoprotein (HDL) and preventing the oxidation of low density lipoprotein (LDL) cholesterol[9]. PON-1 activity varies among healthy individuals. PON-1 exhibits two common polymorphisms

at amino acids 55 (leucine–methionine change) and 192 (glutamine–arginine change)[8]. Leucine (L) at position 55 and arginine (R) at position 192 have been associated with increased cardiovascular risk[10,11]. The mechanism by which these PON-1 polymorphisms increase susceptibility to CVD is unclear. Both polymorphisms give rise to different enzyme activities toward paraoxon, with 192R and 55L alleles being associated with high PON-1 activity[11,12]. The 192 polymorphism results in two different isoforms that have high (B) and low (A) activity towards paraoxon. The population can be subdivided into three phenotypes: AA (low activity), AB (intermediate activity) and BB (high activity)[13,14]. The effect of the 192 polymorphism is not altered toward phenylacetate (arylesterase activity). The use of phenylacetate as substrate is therefore considered as an index of PON-1 mass[11].

The prevalence of hypertension shows an increasing trend among children and adolescents[1]. Awareness of CVD risk factors that accompany hypertension is necessary for protective precautions.

The aim of this study was to determine the CVD risk factors (risk of overweight/overweight, dyslipidemia, PON-1 activity, positive family history, physical inactivity, smoking) that accompany hypertension and investigate the relationship between hypertension and some of these risk factors on middle school students aged 12-14 years.

Material and Methods

This case–control study was conducted between 1 April and 31 May 2006 and was approved by the Ethics Committee of the Uludağ University Medical Faculty (2006-5/29).

Determination of Cases

The cases in this study were found in a cross-sectional study conducted among middle school students aged 12–14 years, aiming to determine hypertension prevalence among them[15].

This former cross-sectional study was conducted among 12–14-year-old schoolchildren at Bursa provincial center between February and June 2006. This study was conducted at 16 middle schools with 2,478 students. Schools and students were chosen using stratified random sampling[15].

A questionnaire, including information about age, sex, family history of CVD, physical activity, and smoking status, was applied. The children who smoked at least one cigarette per week were considered to be at risk of CVD. To encourage truthful answers, children were reassured that parents and teachers would not receive the information about their smoking status. One of the questions was asked to evaluate the students' leisure-time physical activity patterns. State of physical activity was determined using the questions used for adults in various Scandinavian studies and modified by Ucar et al.[16] for the Turkish population[17,18]. Students were classified into three physical activity groups according to their answers: (1) Sedentary activity: students who ride to school, by vehicle, and do activities that do not require physical effort, such as watching television, reading a book; (2) Moderate activity: students who walk or ride a bicycle to school and do moderate physical activities; (3) Active: students who do regular training in school sports teams, and do heavy gardening.

A team consisting of three doctors and one health officer went to schools in the morning. An Omron 705 IT automatic sphygmomanometer was used to measure BP[19]. The cuff size was approximately 140x480 mm. BP of students was measured from the right arm at heart level three times with a minimum of five-minute breaks after allowing them to rest. Average systolic and diastolic blood pressures (SBP/DBP) were calculated and recorded. The evaluation was undertaken according to the report published by the American Pediatrics Academy 'National High Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents' and 'The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents'. According to age, gender and height, SBP and/or DBP under 90th percentile was defined as normal, between 90–95th percentile as pre-hypertension, between 95th and 99th percentile as hypertension, and greater than 99th percentile as malignant hypertension[20]. BPs of students in the hypertension and malignant hypertension groups were measured after two weeks with the same method and average SBP and DBP were calculated. The second measurement was applied to all students who were diagnosed

with hypertension and malignant hypertension on the first measurement. According to those measurements, SBP and/or DBP between 95th and 99th percentile was accepted as hypertension and greater than 99th percentile as malignant hypertension. Those averages were taken into account while calculating hypertension and malignant hypertension prevalence. Weight of students was measured sensitive to 0.1 kg after removing shoes and school uniforms, and height sensitive to 0.1 cm with a height-weight measurer. Body mass index (BMI) was calculated by using weight (kg)/height^2 (m). Evaluation of BMIs was undertaken according to the percentage tables and graphs published in 2000 by the American Centers for Disease Prevention and Control (CDC): BMI <85th percentile: normal, 85–94th percentile: risk of overweight, and ≥95th percentile: overweight[21].

At the end of this study, 147 hypertensive cases were found. The cases and the parents of these cases were informed about the case–control study. The study was conducted on 118 (80.3%) cases because 29 families did not give their permission for the blood test. As a control group, 118 students with normal BP who attended the same school and were matched for age and sex were selected by a random sample method.

The study was explained to the students and written permission was obtained from the parents and children.

Biochemical Measurements

Approximately 5 ml venous blood samples were obtained from the antecubital veins of students after 12–14 h fasting. Serum triglyceride (TG), total cholesterol (TC) and HDL-cholesterol (HDL-C) were measured the same day that the blood was collected. Serum aliquots for PON measurements were kept at -80°C and analyzed within two months.

Serum levels of TC, HDL-C and TG were determined using enzymatic assays on an Aeroset autoanalyzer (Abbott Laboratories; Irving, TX, USA). LDL-cholesterol (LDL-C) concentrations were calculated according to Friedewald's formula[22].

Paraoxonase activity was determined as described by Eckerson et al.[13]. The rate of hydrolysis of paraoxon was measured by monitoring the increase in absorbance at 412 nm at 25°C in the absence (basal activity) and presence of 1 M NaCl (salt-stimulated activity) for three minutes. The basal assay mixture included 1.0 mM paraoxon and 1.0 mM calcium chloride in 0.05 M glycine-natrium hydroxide buffer, pH 10.5. The amount of p-nitrophenol generated was calculated from the molar extinction coefficient at pH 10.5, which was 18 290 M^{-1} cm^{-1}. PON activity is expressed in U/L serum. One unit of PON activity is defined as 1 µmol p-nitrophenol generated per minute under the above conditions.

Arylesterase activity was determined by using phenylacetate as the substrate. The reaction mixture (incubated for 1 minute at 25°C) contained 1.0 mM phenylacetate and 0.9 mM calcium chloride in 9.0 mM Tris-HCl buffer, pH 8.0. Enzymatic activity was calculated from the molar extinction coefficient 1 310 M^{-1} cm^{-1}. One unit of arylesterase activity is defined as 1 µmol phenol generated per minute under the above conditions and expressed as kU/L serum[23].

The phenotype distribution of PON was determined by the double substrate method, which calculates the ratio of salt-stimulated PON activity and arylesterase activity[13]. The distribution of the ratio of salt-stimulated PON activity and arylesterase activity is trimodal, and a tentative assignment of individuals within three possible phenotypes was made by dividing the population at antimodes (2.0 and 7.6).

Our within-run precision (n=20) and between-run precision (n=40) values were below 10% for basal- and salt-stimulated PON and arylesterase activities in this study.

High levels of TC and LDL-C were defined as those >200 mg/dl and ≥130 mg/dl, respectively[24]. TG level ≥130 mg/dl was considered high[25] and HDL-C level <35 mg/dl was considered low[24].

Statistical Analyses

All of the statistical analyses were carried out using SPSS v11.0 for Windows statistical package (SPSS Inc.; Chicago, IL, USA). In this study, all quantitative variables are expressed as mean (standard deviation) or median (interquartile range, 25–75th percentiles) and qualitative variables are all expressed in terms of frequency and percentage (n, %). After the assessment of normality assumption, Student's t-test and when necessary Mann–

Whitney U test were used for the comparison of the means between the normotensive and hypertensive groups. The Pearson's chi-square test was employed to make comparisons of categorical variables between the groups. The determination of the association between HT and CVD risk factors was estimated by multivariate logistic regression analysis (Forward LR) with hierarchical models. All statistical analysis was applied according to two-sided hypothesis tests, and a p value of less than 0.05 was regarded as statistically significant.

Results

A total of 236 subjects were included in the study: 118 hypertensives and 118 non-hypertensive controls. There were 42 (35.6%) boys and 76 (64.4%) girls in each group.

The average SBP was 132.1 ± 8.4 mmHg in hypertensives and 111.6 ± 8.0 mmHg in normotensives (p<0.001; mean difference: 20.5 [95% confidence interval (CI) 18.3–22.5]). The average DBP was 76.8 ± 6.8 mmHg for hypertensives and 66.4 ± 6.3 mmHg for normotensives (p<0.001; mean difference: 10.3 [95% CI 8.6–12.3]).

Body mass index, basal PON-1 and arylesterase activities were significantly higher in hypertensives than in the control group (Table I). From the perspective of categorical variables, some of the cardiovascular risk factors were significantly higher among the cases. Risk of overweight/overweight was more frequently found in cases (45.7%) than in controls (12.7%). In the hypertensives, overweight was the most frequent risk factor (21.2%) followed by high LDL-C (6.3%).

Two of the hypertensive students were smokers. There were no smokers in the control group.

Table II presents the prevalence of combinations of the risk factors in cases and controls. Hypertension was included as a cardiovascular risk factor in the analysis for cases and controls. Among controls, 64.4% had no risk factor. Among cases, 34.8% had no risk factor other than hypertension and 65.2% had two or more risk factors. The proportion of subjects

Table I. Clinical and Biological Data in Normotensive and Hypertensive Subjects

Quantitative	Normotensives (N=118) Median (25^{th}-75^{th})	Hypertensives (N=118) Median (25^{th}-75^{th})	p
Triglyceride (mg/dl)	58 (47-79.2)	76 (52.7-105.2)	NS
Paraoxonase-1 (U/L)	173.3 (131.2-243.6)	190.3 (150.2-275.7)	0.047
Salt-stimulated Paraoxonase-1 (U/L)	243.6 (141.0-521.9)	21.4 (143.7-595.6)	NS
Arylesterase (U/L)	89.7 (72.7-108.2)	96.9 (75.9-120.3)	0.02
LDL-cholesterol (mg/dl)	75.5 (59-94)	79(65-93.3)	NS
	Mean±SD	Mean±SD	
Body mass index (kg/m^2)	19.5±3.10	22.4±4.6	<0.001
Total cholesterol (mg/dl)	140.3±27.4	148.4±35.5	NS
HDL-cholesterol (mg/dl)	47.0±9.3	46.4±9.4	NS
Qualitative	Number (%)	Number (%)	
Physical inactivity	9 (7.6)	18 (15.3)	NS
Positive family history	5 (4.2)	10 (8.5)	NS
Smoking	–	2 (1.7)	–
BMI ≥85^{th} percentile	15 (12.7)	54 (45.7)	0.001
BMI ≥95^{th} percentile	8 (4.2)	25 (21.2)	0.001
Choleseterolemia >200 mg/dl	3 (2.5)	7 (5.9)	NS
Triglyceridemia ≥130 mg/dl	10 (8.4)	13 (11.0)	NS
Low HDL-cholesterol <35 mg/dl	9 (7.6)	10 (7.9)	NS
High LDL-cholesterol ≥130 mg/dl	1 (0.8)	8 (6.3)	0.036
Dyslipidemia‡	21 (17.8)	30 (25.4)	NS

NS: Not significant. SD: Standard deviation. LDL: Low density lipoprotein. HDL: High density lipoprotein. BMI: Body mass index.

‡: dyslipidemia (cholesterolemia ≥200 mg/dl, or triglyceridemia ≥130 mg/dl, or LDL-cholesterol ≥130 mg/dl, or HDL-cholesterol <35 mg/dl).

Table II. Prevalence of Other CVD Risk Factors* in Hypertensive and Normotensive Subjects

	Normotensives		Hypertensives	
Risk factors (number)	n	%	n	%
None	76	64.4	–	–
1	35	29.7	41	34.8
2	7	5.9	49	41.5
3	–	–	25	21.2
4	–	–	3	2.5

*: Risk factors in this table: hypertension; body mass index ≥85th; dyslipidemia (cholesterolemia ≥200 mg/dl, or triglyceridemia ≥130 mg/dl, or low density lipoprotein-cholesterol ≥130 mg/dl, or high density lipoprotein-cholesterol <35 mg/dl); positive family history; and physical inactivity.

with multiple risk factors (≥2) was higher in hypertensives than in controls (65.2% vs. 5.9%, p<0.001).

If hypertension was not taken into account, prevalence of the subjects having at least one of the risk factors was still higher in the hypertensives than in the normotensive controls (65.2% vs. 35.6%, p=0.001).

Phenotype distributions of PON-1 in normotensive and hypertensive children are shown in Figure 1. Of the hypertensives, 52.5% were low activity phenotype, 39.8% were medium activity phenotype and 7.7% were high activity phenotype. These values were 55.6%, 40.2% and 4.2%, respectively, in the control group. There was no significant difference in the phenotype distributions of PON-1 between cases and controls (p>0.05).

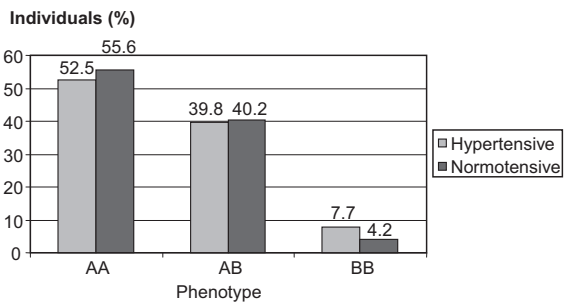

Fig. 1. The phenotypic distribution of the hypertension and normotensive groups [AA (low activity), AB (medium activity), BB (high activity)].

$$\text{Ratio} = \frac{\text{Paraoxonase activity with 1 M NaCl}}{\text{Arylesterase activity}}$$

Table III presents the odds ratios (ORs) of hypertension in logistic regression. The outcome variable was the presence or absence of hypertension. In the univariate analysis, the variables significantly associated with high BP were PON-1 and risk of overweight/overweight.

After including all the variables of univariate analysis in the multivariate logistic regression analysis, the adjusted OR (95% CI) of risk of overweight/overweight for hypertension was 5.65 (2.88-11.09).

Discussion

We found a significant relation between hypertension and risk of overweight/overweight. The ratio of the non-hypertensives who had no other risk factor was only 34.8%. The rest of the cases had one or more accompanying risk factors. The ratio of the cases with two or more cardiovascular risk factors was significantly higher in hypertensives compared to normotensives.

There are epidemiological studies that indicate obesity in children and adolescents as an important risk factor for hypertension, and some authors showed a positive association between BMI and BP[26,27]. Among obese/overweight children, hypertension prevalence is significantly higher than in children and adolescents with normal weight[1,6]. In the FRICELA study[6], it was indicated that hypertension risk in adolescents with BMI between 25 kg/m^2 and 30 kg/m^2 is 2.9 times higher compared to adolescents with BMI <25 kg/m^2. The risk is 4.9 times higher for those with BMI >30 kg/m^2 compared to those with BMI <25 kg/m^2. The multivariate OR of hypertension for risk of overweight/overweight was 5.65, the highest, in our study.

Previous studies have also shown that, in addition to the risk of hypertension, obesity further enhances total cardiovascular risk by increasing LDL-C levels, reducing HDL-C levels, diminishing glucose tolerance, and predisposing to the development of left ventricular hypertrophy[28,29].

In our study, dyslipidemia prevalence, though not significant, was higher in hypertensives compared to normotensives.

Table III. Logistic Regression Analysis (Crude and Adjusted ORs of Hypertension)

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	AOR	95% CI	p
PON-1	1.004	1.001-1.007	<0.05	1.006	0.99-1.007	NS
Risk of overweight/overweight	5.79	3.02-11.11	<0.001	5.65	2.88-11.09	<0.001
Dyslipidemia	1.57	0.84-2.95	NS	1.15	0.57-2.33	NS
Phenotype ‖	1.12	0.676-1.88	NS	1.98	0.95-4.12	NS

OR: Odds ratio. CI: Confidence interval. AOR: Adjusted odds ratio. PON: Paraoxonase. NS: Not significant.
‖: Reference category: High and medium activity phenotype; Risk category: Low activity phenotype.

Serum PON activity was found to be significantly higher in hypertensives compared to normotensives in our study. A significant relation between PON-1 activity and hypertension was also observed in univariate analysis. However, the significance vanished after multivariate logistic regression analysis. Phenotype distribution was not significantly different between cases and controls. There are limited data on serum PON activity in patients with hypertension, and there is only one recent study that investigated serum PON activity in hypertensive adolescents[30]. In that study, compared with the controls, the investigators did not find any significant difference in the enzyme activity in adolescent patients with essential or obesity-induced hypertension. In line with our findings, those authors did not find any significant difference in the phenotype distributions between the hypertensive and control groups[30]. However, in a study that was carried out with adult hypertensive patients, Uzun et al.[31] reported decreased serum PON-1 activity in white-coat and sustained hypertension. Those authors also found increased plasma malondialdehyde (MDA) levels, an indicator of oxidative stress, and suggested that decreased serum PON-1 activity might be a contributing factor and/or a result of increased oxidative stress in hypertensive subjects, since lipid peroxidation products are both substrates and inhibitors of PON-1[31]. However, Barath et al.[30] did not find any difference in plasma MDA levels between the patients with essential or obesity-induced hypertension and the control group. We cannot find an explanation for the increased serum PON activity in hypertensive adolescents observed in the present study. One of the limitations of the present study is the lack of oxidative stress parameters. Furthermore, there might be several factors contributing to the discrepancies between the studies, such as age, diet, smoking, and exercise, etc.

In our study, the CVD risk factor rate was higher among hypertensives. The percentage of cases who had only hypertension was 34.7%. One or more of the risk factors such as dyslipidemia, positive family history, physical inactivity, and risk of overweight/overweight accompanied hypertension in the other cases. In parallel with our findings, Foucan and colleagues[3] reported that other CVD risk factors were more often observed in hypertensives compared to normotensives, and furthermore, the results did not change when hypertension was excluded.

In conclusion, the fact that we did not differentiate between primary and secondary hypertension can be considered a limitation of the study. Nevertheless, CVD risk factors were observed at a higher rate in hypertensives compared to normotensives. In particular, risk of overweight/overweight is the most important risk factor in hypertensives. BP and weight measurements should be routinely conducted in schools. We conclude that it would be useful to routinely evaluate blood pressure and body weight in schools and, additionally, considering that hypertension is rarely encountered alone, it would be appropriate to evaluate the hypertensive students for other risk factors.

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