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ORIGINAL ARTICLE

Serum markers of inflammation and endothelial activation in children with obesity-related hypertension

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Abstract

OBJECTIVES: It has been suggested that a rise in blood pressure (BP) causes low-grade inflammation of the endothelium which, in turn, may be responsible for further damage of endothelium and worsening of BP control. The aim of the study was to evaluate serum levels of inflammation and endothelial activation markers in children with obesity-related hypertension and normotensive controls in relation to other traditional risk factors of arterial hypertension.
METHODS: Plasma insulin, glucose, C-reactive protein (CRP), fibrinogen (FB) interleukin-6 (IL-6), interleukin-1β (IL-1β), intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and lipids levels were determined in 50 children with obesity-related hypertension and 143 obese children with normal BP. Insulin resistance was assessed by the homeostasis model.
RESULTS: Children with hypertension had significantly higher levels of all inflammatory markers as well as endothelial activation indices compared with normotensive subjects. In the stepwise regression model significant independent correlates for systolic BP were CRP, FB, VCAM-1, HOMA IR, LDL cholesterol and fat mass, whereas CRP, IL-6, ICAM-1, FB, LDL and HDL cholesterol were the determinants of diastolic BP in children with obesity-related hypertension.
CONCLUSION: These results indicate that low-grade inflammation and endothelial dysfunction are closely involved in the pathogenesis of obesity-related hypertension relatively early in life.

Introduction

Arterial hypertension, a major health problem in adults is best predicted by the blood pressure (BP) level during childhood [10]. The Task Force on Blood Pressure [16] indicated that detection of arterial hypertension (AH) in a pediatric population and its early treatment contribute to a reduction in the high risk of morbidity in adulthood. Obesity is frequently associated with AH in adults and the same appears true in children [21]. Up to 30% of obese children suffer from hypertension [9], and among adolescents one survey found 56% of those with persistent elevated BP were also significantly overweight [19].

Insulin resistance and hypertension may be present as part of the insulin resistance syndrome (IRS) associated with obesity [2]. Other researchers, however, suggest that BP is mediated by the various bioactive substances secreted from adipose tissue such as leptin, angiotensinogen, interleukin-6 (IL-6), tumor necrosis factor–α (TNF-α) and adiponectin [4,12,24]. It has been suggested that a rise in blood pressure activates a vicious cycle, causing chronic inflammation of the endothelium, which in turn might be responsible for a further damage of endothelium and worsening of BP control. Individuals with AH have higher circulating levels of intercellular cell adhesion molecule-1 (ICAM-1), IL-6 and TNF-α than non-hypertensive persons, supporting a possible role of hypertension as a proinflammatory stimulus [3]. Moreover, it has been shown that proinflammatory cytokines such as IL-6 and interleukin-1 β (IL-1β) affect arterial BP control [8,18]. Overall, these results suggest that low-grade chronic inflammation is a common link between cardiovascular risk factors and hypertension, but this hypothesis has never been tested in obese children and adolescents.

The purpose of this study was to investigate the relationship of serum inflammation and endothelial activation markers with blood pressure in children with obesity-related hypertension, independently of other traditional cardiovascular risk factors.

Methods

The study group consisted of 50 obese children and adolescents with essential hypertension. The control group comprised 143 obese subjects with normal BP. Essential hypertension was recognized on the basis of ambulatory blood pressure monitoring when mean (24-h) systolic and/or diastolic BP values exceed 95 percentile for sex and height [16], and other reasons of AH were excluded. Obesity was recognized on the basis of body mass index (BMI) greater than 97th percentile for age and sex [17]. None of the children had any medical problem other than obesity. A positive family history of hypertension was determined by parental report of AH in a first-degree relative.

TABLE I. Clinical characteristics of the study subjects

Variable	Hypertensive (n=50)	P	Normotensive (n=143)
	X±SD		X±SD
Age (yr)	13.0±2.5	NS	13.1±2.7
BMI (kg/m^2)	30.0±5.1	NS	29.8±3.5
BMI-SD score	3.8±1.8	NS	3.8±1.4
WHR	0.98±0.06	NS	1.05±0.87
% fat	35.0±6.1	NS	35.3±6.3
Fat mass	26.8±9.9	NS	26.7±8.4
Systolic BP (mmHg)	125.7±9.1	<.001	108.7±8.0
Diastolic BP (mm Hg)	70.9±9.3	<.001	60.8±6.2
AH in family history	n(%)	P	n(%)
	27 (54.0)	NS	76 (53.1)

TABLE II. Biochemical characteristic of the study subjects

Variable	Hypertensive (n=50)	p	Normotensive (n=143)
Fasting glucose (mmol/L)	5.1±0.7	<.05	4.8±0.5
Fasting insulin (pmol/L)*	158.9 (54.3–829.8)	<.001	104.3 (2.2–463.4)
HOMA IR*	4.9 (1.5–28.8)	<.001	3.4 (0.9–15.3)
T chol (mmol/L)	5.07±0.99	<.001	4.44±0.78
LDL chol (mmol/L)	3.09±0.86	<.001	2.47±0.74
HDL chol (mmol/L)	1.25±0.35	NS	1.32±0.28
TG (mmol/L)	1.67±0.85	<.01	1.34±0.78
CRP (mg/L)	1.7±0.9	<.001	0.9±0.4
FB (mg/dL)	348.6±58.4	=.01	321.1±70.5
IL-6 (pg/mL)*	2.1 (0.7–14.8)	<.001	1.2 (0.1–3.6)
ICAM-1 (ng/mL)	331.2±138.3	<.001	230.9±109.3
VCAM-1 (ng/mL)	1258.1±368.3	<.001	872±439.1

Values are mean ±SD * Values are median and range.

TABLE III. Stepwise regression model with systolic BP as the dependent variable

Independent variable	SBP					
	Hypertensive			Normotensive		
Model 1	beta	t	*p*	beta	t	*p*
Age	0.36	2.20	0.040	–	–	–
Fat mass	0.38	2.23	0.040	0.50	2.80	0.007
CRP*	0.45	2.82	0.012	–	–	–
FB	0.39	2.01	0.031	–	–	–
LDL chol	0.44	2.91	0.010	0.36	2.53	0.015
HDL chol	–0.35	–2.00	0.056	–	–	–
Model 2	beta	t	*p*	beta	t	*p*
Age	–	–	–	0.18	1.68	0.097
WHR	–	–	–	0.30	2.74	0.007
Fat mass	0.38	2.30	0.028	–	–	–
HOMA IR*	0.32	2.10	0.045	–	–	–
LDL chol	0.40	2.79	0.009	–	–	–
VCAM-1	0.31	2.12	0.041	–	–	–

* Back log transformed.

TABLE IV. Stepwise regression model with diastolic BP as the dependent variable

Independent variable	DBP					
	Hypertensive			Normotensive		
Model 1	beta	t	*p*	beta	t	*p*
Sex	0.50	2.57	0.020	0.27	1.80	0.080
BMI	–	–	–	0.39	2.36	0.023
CRP*	0.77	3.23	0.005	0.20	1.36	0.182
FB	0.48	2.41	0.029	–	–	–
IL-6*	0.82	3.42	0.003	–	–	–
HDL chol	–0.53	–2.55	0.021	–	–	–
HOMA IR*	0.58	2.42	0.027	–	–	–
Model 2	beta	t	*p*	beta	t	*p*
Sex	0.32	2.18	0.039	–	–	–
BMI	–	–	–	0.27	2.11	0.038
Fat mass	0.49	2.98	0.006	–	–	–
ICAM/1	0.51	3.15	0.004	–	–	–
LDL chol	0.32	1.93	0.065	–	–	–

* Back log transformed.

Physical examination, body weight, height, waist and hip circumferences were performed using standardized methods and devices [17]. On the basis of anthropometric measurements the BMI and waist to hip ratio (WHR) were calculated. Since BMI changes with age, the BMI-SD score was also calculated. Measurement of body composition was performed by means of bioelectrical impedance (Bioelectrical Impedance Analyzer Tanita 131, Japan) with an applied current of 0.8 mA at a fixed frequency of 50 kHz.

Ambulatory blood pressure monitoring was performed using Mobil-O-Graph device, which uses the oscillometric method. Systolic and diastolic blood pressures were measured with an interval of 60 min between 2300 h and 0700 h, and 30 min between 0700 and 2300 h.

Blood samples were obtained in the morning after an overnight fast. Circulating IL-6, IL-1β, ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) levels were determined by ELISA with the use of the Quantikine kit (R & D Systems, Minneapolis, USA). The minimum detectable concentrations were 0.10 pg/mL for IL-6, 0.01 pg/mL for IL-1, 0.35ng/mL for ICAM-1 and 2.0 ng/mL for VCAM-1, and the interassay coefficient of variation was 7.0% for all kits. CRP was measured by high-sensitivity immunoturbidimetric method (CRP-Latex, Olympus), fibrinogen (FB) – in citrated plasma with a modified clot-rate assay by use of the Diagnostica STAGO ST4 instrument. Glucose was measured with the glucose oxidase technique (Glucose HK analyzer, Olympus). Free insulin concentrations were determined by RIA (Pharmacia RIA kit). Total cholesterol (T chol), HDL cholesterol (HDL chol) and triglyceride (TG) levels were measured in serum by automated enzymatic procedures (Olympus). LDL cholesterol (LDL chol) was measured after separating LDL fraction from fresh fasting sera by sequencial ultracentrifugation, using Olympus kit.

The homeostasis model was used to assess insulin resistance (HOMA IR). The formula for HOMA IR is as follows: HOMA IR = fasting insulin (mIU/mL) x fasting glucose (mmol/L)/ 22.5

All statistical analyses were performed with the version 9.0 of the SPSS for Windows software (SPSS Inc., Chicago, USA). Comparisons between two groups were tested with Mann-Whitney U-test. Parameters with skewed distributions were log-transformed. Multivariate linear regression analyses and stepwise regression models were used to test the independent association of clinical and biochemical parameters with mean (24-h) systolic and diastolic BP. A P-value less than 0.05 was considered statistically significant.

The study was approved by the Ethical Committee of the Pomeranian Medical University.

Results

Clinical and biochemical characteristics of the subjects in this protocol are summarized in Table I and Table II.

Fasting glucose, insulin, HOMA IR and lipids (except HDL chol) were significantly higher in children with obesity-related hypertension. Similarly, all inflammation parameters (except IL-1β) as well as soluble cell adhesion molecules were significantly higher in hypertensive children than in normotensive subjects.

In multiple regression analyses, the contribution of the independent variables such as sex, age, BMI, fat mass, WHR, log HOMA IR, LDL chol, HDL chol, triglycerides, CRP, FB, IL-6, IL-1β, ICAM-1, VCAM-1, and positive family history of AH to the variance in mean 24-h systolic and diastolic BP were investigated (data not shown). In the stepwise regression model, LDL cholesterol, CRP, FB, VCAM-1, HOMA IR, age and fat mass were independently associated with systolic BP (SBP) in children with obesity-related hypertension, whereas fat mass, WHR and LDL cholesterol were the independent predictors of SBP in obese subjects with normal BP (Table III).

With regard to diastolic BP (DBP), the serum CRP, IL-6, ICAM-1, FB, LDL and HDL cholesterol levels, fat mass and HOMA IR were independent determinants of DBP in the group of obese children with AH. In subjects with normal BP, only BMI was independently associated with DBP (Table IV).

Discussion

In this paper we found that children and adolescents with obesity-related hypertension had higher serum inflammation and endothelial activation markers than those seen in obese subjects with normal BP, in spite of similar BMI, WHR and fat mass. Our data are in agreement with those obtained in adults [3,5,18]. Dalekos and co-workers [5] found elevated serum IL-1β levels in patients with essential hypertension. Moreover, these patients had also increased TG levels and low HDL cholesterol levels. Similarly, in our study several metabolic components of insulin resistance syndrome were also higher in children with hypertension compared to normotensive controls. All these data indicate the importance of both inflammation and endothelial activation as well as dyslipidemia, obesity and insulin resistance in determining of BP. However, stepwise multiple regression models demonstrated that low-grade inflammation and endothelial activation are independently associated with BP in children with obesity and hypertension. In particular, the effect of acute-phase proteins, proinflammatory cytokines and soluble cell adhesion molecules was almost trivial on SBP, whereas it was particulary evident on DBP. In obese children with normal blood pressure classic cardiovascular risk factors i.e. BMI, fat mass, WHR and LDL cholesterol were independent determinants of BP. Our data seems to confirm the previous observation that increased BP may exert a proinflammatory effect on the arterial wall, causing subclinical inflammation of the endothelium, which in turn may be responsible for a further damage of endothelium and developing of arterial hypertension [3]. Two different possible mechanisms in which BP cause of arterial wall inflammation are suggested. First, elevated BP may promote atherogenesis by modulating the biomechanical stimuli of the pulsatile blood flow, which in turn affects endothelial cell gene expression and function [11]. Second, hypertension may cause the enhanced endothelial responsiveness to different biomechanical and metabolic factors, resulting in the adhesion of circulating monocytes and T cells, and in the formation of an inflammatory nidus. This latter hypothesis is suggested by in vitro [14] and in vivo [13] studies that found an increased ICAM-1 expression and greater monocyte adhesion in spontaneously hypertensive rats compared with normotensive animals.

On the contrary to others [1,5], we did not find a significant relationship of serum IL-1β with BP in obese children. A possible explanation for such apparent discrepancy might be that IL-1β levels were too low to exert the significant effect on BP, although this cytokine seemed to play a physiological role in human development [22]. Another possible explanation is that IL-1β can be more useful as a marker of endothelium damage but as a less powerful determinant of change in BP.

According to several previous reports [1,2], an expected finding of our study was that HOMA IR index was significant predictor of both SBP and DBP. The insulin resistance of obesity has for many years been attributed to the effects of nonesterified fatty acids (NEFAs), which impair insulin action in both liver and skeletal muscle [20]. In addition, the endothelial dysfunction demonstrated in obese persons may be a consequence of elevated NEFA levels, as a consequence of inhibitory effects on endothelial nitric oxide synthase [6]. However, it has been recently shown that adipose-generated proinflammatory cytokines may impair insulin action [15,23,24].

Insulin resistance is increasingly viewed as a chronic inflammatory disorder [7]. Therefore, we can not exclude the jointed effect of inflammation (directly and indirectly via insulin resistance) on BP in hypertensive children.

Perspectives

Results of this study indicate that low-grade inflammation and endothelial activation may be involved in the pathogenesis of obesity-induced hypertension. Further studies will be needed to confirm our findings in a longitudinal prospective and to gain insight into the pathophysiologic mechanism by which chronic inflammation affects blood pressure. In addition, well-known anti-inflammatory properties of thiazolidinediones, statins, and aspirin may have beneficial effect, apart from weight reduction, in the treatment of obesity-related hypertension.

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