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Human Paraoxonase-1 Activity in Childhood Obesity and Its Relation to Leptin and Adiponectin Levels

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ABSTRACT: Childhood obesity is a predisposing factor for adult cardiovascular diseases. Human serum paraoxonase (PON1) may protect against atherosclerosis by hydrolyzing lipid peroxides in oxidized LDL. Alterations and potential correlations of PON1 activities, leptin and adiponectin levels in childhood obesity were studied. We measured PON1 paraoxonase and arylesterase activities, anthropometric parameters, leptin and adiponectin levels in 59 white, obese (obese group-OB: BMI corrected for age: 95.1 ± 3.5 percentile, age: 11.9 ± 1.6 y) and 51 normal-weight children (control group-C: BMI corrected for age: 64.1 ± 8.4 percentile, age: 12.0 ± 3.9 y). Obese children had significantly lower PON1 paraoxonase (OB: 84.80 (64.33/144.74) U/L *versus*. C: 99.42 (83.33/152.05) U/L; $p < 0.05$) and arylesterase activities (OB: 94.40 (82.20/108.70) U/L *versus*. C: 115.20 (93.70/126.00) U/L; $p < 0.01$), higher leptin (OB: 37.05 (24.33/53.87) ng/mL *versus*. C: 4.62 (2.52/17.6) ng/mL; $p < 0.0001$) and lower adiponectin levels (OB: 7.56 (5.69/12.06) μg/mL *versus*. C: 11.51 (8.84/14.49) μg/mL; $p < 0.001$) compared with the normal-weight group. PON1 arylesterase activity showed inverse univariate correlation with leptin ($r = -0.29$; $p < 0.05$) and positive correlation with adiponectin levels ($r = 0.39$; $p < 0.01$). In multiple regression analysis adiponectin was strongly associated with PON1 arylesterase activity in obese children ($\beta = 0.45$, $p < 0.02$). Our results emphasize the importance of the investigated metabolic alterations which may have further effects on cardiovascular morbidity and mortality in later adulthood. Altered levels of leptin, adiponectin and PON1 activities may be useful markers beside the general risk factors in childhood obesity. **(*Pediatr Res* 67: 309–313, 2010)**

Childhood obesity is an increasing epidemiologic problem that can be considered as a risk factor for adult cardiovascular diseases (1). Both genetic and environmental factors play role in the development of obesity (2). Increased adipose tissue volume promotes the development of glucose metabolism disturbances and insulin resistance, factors known to strongly correlate with the accelerated progression of atherosclerosis (1).

Human paraoxonase-1 (PON1) is a HDL-associated enzyme, which plays significant role in inhibiting the oxidation of LDL and HDL particles, and therefore is thought to protect against the development of atherosclerosis (3). PON1 activity has been found to be decreased in patients with increased risk of atherosclerosis: diabetes mellitus, patients with cardiovascular complications (4) and in kidney diseases (5). In obese adults not only enzyme levels are diminished but the enzyme activity of PON1 is also decreased correlating with low levels of the HDL-C (6). Orlistat treatment in obesity increases PON1 paraoxonase activity besides alterating the lipid profile (7). The antioxidant effect of HDL can be influenced not only by PON1 activity but also the abundance of the enzyme (8). As previous studies have demonstrated the arylesterase activity of the enzyme shows linear correlation with the enzyme levels (8,9).

Leptin is circulating hormone, expressed almost exclusively in the adipose tissue, which provides information about the energy-stores of the body to the hypothalamus *via* the neuroendocrine system (10,11). Several studies have shown that elevated leptin levels are present in obese adults (12) and children (13). Serum leptin levels strongly correlate with adipose tissue mass and other factors of the metabolic syndrome (12). Elevated leptin levels, as the cause of the obesity-related leptin resistance, have atherogenic effects (14) and lead to decreased PON1 activity in adults (15).

Adiponectin belongs also to the family of adipokines and is also synthesized by the adipose tissue. Adiponectin increases fatty acid oxidation and reduces the synthesis of glucose in the liver and other tissues (10,11). Therefore adiponectin may be a potent antiatherogenic factor (14). Previous studies have found decreased adiponectin levels in obese children (13), adults and patients with type 2 diabetes mellitus (16).

It has been already shown that adiponectin and leptin levels are altered in childhood obesity. It is also known that in childhood obesity the total serum antioxidant capacity is decreased (17). Moreover decreased PON1 acivity have been found in obese adults (6). However, PON1 activities in obese children have not yet been investigated.

Correlations between leptin levels (15) as well as adiponectin levels and PON1 activity have been previously proven in obese adults (18). There are several mechanisms how these adipokines may influence PON1 activity. Beltowski found that

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Abbreviations: BFP, body fat percentage; **HOMA,** homeostasis model assessment; **PON1,** human serum paraoxonase - 1 (E.C. number: 3.1.8.1.)

rats treated with leptin had decreased PON1 activity (19). These mechanisms may be the followings: leptin as a hydrophobic peptide can bind to HDL (20) and inhibit directly the PON1 enzyme; however, it has not been proven *in vitro* studies. On the other hand, leptin enhances oxidative stress (21,22) through the generation of ROS (19), stimulates the secretion of inflammatory cytokines (23) and other acute phase proteins which have diminishing effect on PON1 enzyme activity by the inhibitory effect on hepatic PON1 synthesis (24). Leptin also enhances the production of serum amyloid A protein (25) which can replace apolipoprotein-AI in HDL. Apolipoprotein-AI plays main role in stabilizing the structure of PON1. Leptin may have modulatory effect through the alteration of the lipid content in HDL particles (26); inverse correlation has been observed between leptin, HDL and apo-AI in human subjects (27). Adiponectin might have the ability to accelerate the reverse cholesterol transport and increase apoA-I-mediated cholesterol efflux through enhancing HDL assembly in the liver (28,29).

Based on these previous observations we hypothesized that PON1 activity would be lower in obese children and we also assumed that there might be significant correlations between PON1 activities and adipokine levels childhood obesity.

METHODS

Study population. Our study was performed on 59 obese and overweight children (obese group: OB; age: 11.95 ± 1.61 y; 25 girls, 34 boys) and 51 normal-weight children (control group, C; age: 12.00 ± 3.91 y; 22 girls, 29 boys). To determine the degree of obesity of the participants, we used the Hungarian percentile curves; children, whose BMI corrected for age exceeded the 90th percentile (OB: 95.08 ± 3.53% *versus*. C: 64.10 ± 8.36%), were considered overweight (23 children) and obese above the 97th percentile (36 children). None had other chronic diseases (diabetes mellitus, endocrinological disorders, hereditary diseases or systemic inflammation) or was taking any medications.

A detailed medical and family history was obtained from all subjects and a complete physical examination was performed, including anthropometric parameters (height, weight). Participants of the study belonged to the Tanner stage I–IV, defined on the basis of breast development in girls and genital development in boys. Fatness indices as BMI, waist circumference, body fat percentage (BFP) were also determined. BFP was measured with bioelectrical impedance analysis (BIA, Biodynamics, Model 310, Seattle, WA).

Systolic and diastolic blood pressures were measured twice with the subject in sitting position after resting for at least 5 min using a quality-approved automatic electronic sphygmomanometer.

The research protocol was approved by the Ethics Committee of the University of Debrecen, Hungary, Medical and Health Science Centre. Informed written consent was obtained from all parents and oral consent from all children.

Blood sampling. After overnight fasting, 10 mL of venous blood was drawn between 08:00 h and 10:00 h.

Hb, hematocrit, white blood cell count, sedimentation rate, liver enzymes, urea, creatinine, creatine kinase, bilirubin, serum glucose, total cholesterol, HDL-C, LDL-C, triglyceride, insulin were determined from fresh serum. The sera for leptin, adiponectin levels, PON1 paraoxonase and arylesterase activity measurements were kept at −70°C before analysis.

Evaluation of adipokines, PON1 paraoxonase and arylesterase activity, insulin levels and lipid parameters. Serum leptin levels were measured by sandwich enzyme immunoassays (BioVendor Laboratory Medicine, Inc.; Czech Republic) with intra-assay CVs ranging from 2.2% to 5.2% and inter-assay CVs ranging from 6.2% to 8.6%. The detection limit was 0.5 ng/mL.

Serum adiponectin levels were measured by sandwich enzyme immunoassays (R&D Systems, Inc.; USA) with intra-assay CVs ranging from 2.5% to 4.7% and inter-assay CVs ranging from 5.8 to 6.9%. The detection limit was 0.246 ng/mL.

PON1 activity was determined using paraoxon (O,O-diethyl-O-p-nitrophenylphosphate; Sigma Chemical Co.) as substrate and measured by the increase in the absorbance at 412 nm due to the formation of 4-nitrophenol as previously described (8). Briefly: the activity was measured at 25°C, by adding 50 μL of serum to 1 mL Tris/HCl buffer (100 mM, pH 8.0) containing 2 mM $CaCl_2$ and 5.5 mM paraoxon. The rate of generation of 4-nitrophenol was determined at 412 nm by the use a Hewlett–Packard 8453 UV–Visible spectrophotometer. Enzymatic activity was calculated from the molar extinction coefficient 17.100 M^{-1} cm^{-1}. One unit of paraoxonase activity is defined as 1 nmol of 4-nitrophenol formed per minute under the above described assay conditions. The intra- and interassay coefficients of variation were <3% in the tests.

Arylesterase activity was measured spectrophotometrically. The assay contained 1 mM phenylacetate in 20 mM Tris/HCl pH 8.0. The reaction was started by the addition of the serum and the absorbance increase was determined at 270 nm as previously described (30). Blanks were included to correct the spontaneous hydrolysis of phenylacetate. Enzyme activity was calculated using a molar extinction coefficient of 1310 $M^{-1}cm^{-1}$. 1 unit (U) is defined as 1 mmol phenylacetate hydrolyzed per minute. The intra- and interassay coefficients of variation were <3% in the tests.

Serum cholesterol and triglyceride levels were measured by using enzymatic colorimetric tests (GPO-PAP, Modular P-800 Analyzer, Roche/Hitachi), while HDL-C was assessed by a homogenous enzymatic colorimetric assay (Roche HDL-C plus 3rd generation). The LDL-C fraction was calculated indirectly using the Friedewald equation (31) (triglyceride level <4.5 mM).

The serum concentration of insulin was measured by a commercially available RIA kit (MP Biomedicas, Orangeburg, NY) with intra- and interassay coefficients of variance (CVs) ranging from 4.2% to 8.2% and from 6.4% to 8.8%. HOMA (homeostasis model assessment) scores were calculated using the formula: fasting insulin (μU/mL)* fasting glucose (mmol/L) / 22.5, assuming that normal young subjects have an insulin resistance of 1 (32).

Statistical methods. The statistical analysis was performed by SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented by descriptive analysis (case number, in case of normal distribution mean, SD; in case of non-normal distribution median, lower and upper quartile). Comparisons between groups were performed by Student *t* test. Distributions of data were tested with Kolmogorov-Smirnov test. Non-normally distributed parameters as leptin, adiponectin levels, PON1 paraoxonase and arylesterase activities were transformed logarithmically to correct their skewed distributions. Relationships between parameters were assessed by Pearson correlation analysis. We carried out multiple regression analysis using the stepwise method to determine the variables best predicted PON1 arylesterase activities adjusting for age, sex, BFP, HDL-C, leptin, adiponectin in the model. At first (Model 1), a less adjusted model was constructed in which, beside the two adipokines that showed significant univariate correlation with PON1 arylesterase activity, the impact of sex and age were tested, since our previous investigation showed significant decrease in PON1 activity with age through the whole lifetime (33). Although HDL-C and BFP did not show significant univariate correlation with PON1 arylesterase activity, we investigated their impact in Model 2 adjusting them to the previous parameters in Model 1, since PON1 is associated to a subfraction of HDL and BFP reflects well the degree of obesity in adolescent children (34). We used two sided *p*-values; $p < 0.05$ probability was accepted as the level of significance.

RESULTS

The clinical and anthropometric data of the obese and control children are shown in Table 1. There was no difference in age, sex ratio and Tanner stage between the two groups. HDL-C levels (OB: 1.12 ± 0.26 mM *versus*. C: 1.27 ± 0.28 mM, $p < 0.05$) were significantly lower in obese children and they had higher total and LDL-C, triglyceride (TG) and fasting glucose levels but none of these differences were significant compared with the control group. Regarding the insulin-resistance status, obese children had significantly higher HOMA-IR (OB: 8.40 ± 3.64 *versus*. C: 1.17 ± 0.44, $p < 0.0001$) and fasting plasma insulin levels (OB: 38.09 ± 16.67 mU/L *versus*. C: 5.98 ± 2.36 mU/L, $p < 0.0001$).

PON1 enzymatic activities were determined by two substrates as paraoxon and phenylacetate. We measured significantly lower values in both activities in the obese group compared with the normal-weight children (PON1 arylesterase activity OB: 94.40 (82.20/108.70) U/L *versus*. C: 115.20 (93.70/126.00) U/L, $p < 0.01$; PON1 paraoxonase activity

Table 1. *Clinical and anthropometric data of the obese and control group*

	Controls (n = 51)	Obese group (n = 59)	p
Boy/girl	29/22	34/25	
Age (y)	12.00 ± 3.91	11.95 ± 1.61	Nonsignificant (n.s.)
Height (cm)	151.98 ± 11.90	155.09 ± 11.63	n.s.
Weight (kg)	43.24 ± 6.53	68.75 ± 17.23	<0.0001
Body fat percentage	18.02 ± 1.98	34.78 ± 9.05	<0.0001
BMI (kg/m^2)	20.65 ± 1.97	28.23 ± 4.33	<0.0001
BMIA (percentile)	64.10 ± 8.36	95.08 ± 3.53	<0.0001
Waist circumference (cm)	64.57 ± 6.48	90.83 ± 10.94	<0.0001
Leptin (ng/mL)*	4.62 (2.52/17.6)	37.05 (24.33/53.87)	<0.0001
Adiponectin (μg/mL)*	11.51 (8.84/14.49)	7.56 (5.69/12.06)	<0.001
PON1 paraoxonase activity (U/L)*	99.42 (83.33/152.05)	84.80 (64.33/144.74)	<0.05
PON1 arylesterase activity (U/L)*	115.20 (93.70/126.00)	94.40 (82.20/108.70)	<0.01
Fasting plasma glucose (mmol/L)	4.78 ± 0.65	4.89 ± 0.40	n.s.
Fasting plasma insulin (mU/L)	5.98 ± 2.36	38.09 ± 16.67	<0.0001
HOMA-IR	1.17 ± 0.44	8.40 ± 3.64	<0.0001
Triglyceride (mmol/L)	1.06 ± 0.61	1.30 ± 0.56	n.s.
Cholesterol (mmol/L)	4.07 ± 0.52	4.30 ± 0.88	n.s.
LDL-cholesterol (mmol/L)	2.50 ± 0.68	2.61 ± 0.78	n.s.
HDL-cholesterol (mmol/L)	1.27 ± 0.28	1.12 ± 0.26	<0.05
Systolic BP (mm Hg)	110.84 ± 8.96	114.63 ± 16.88	n.s.
Diastolic BP (mm Hg)	76.02 ± 8.62	80.57 ± 15.75	n.s.

In case of normal distribution data are means ± SD.
* In case of non-normal distribution, data are median (lower/upper quartiles).

Table 2. *Pearson correlations of serum leptin and adiponectin levels*

	Leptin*, r	Adiponectin*, r
Leptin*		
Adiponectin*	−0.32†	
PON1 arylesterase*	−0.29†	0.39‡
PON1 paraoxonase*	0.05	−0.04
HOMA-IR	0.42‡	−0.47‡
LDL-cholesterol	0.19	0.18
HDL-cholesterol	−0.24	0.33†
Triglyceride	−0.47‡	−0.23
Body mass index	0.53§	−0.10
Body fat percentage	0.52§	−0.08
Waist circumference	0.42‡	−0.14
Systolic BP	0.34†	−0.26
Diastolic BP	0.34†	−0.29

* Log-transformed statistics.
† $p < 0.05$.
‡ $p < 0.01$.
§ $p < 0.001$.

OB: 84.80 (64.33/144.74) U/L *versus*. C: 99.42 (83.33/152.05) U/L, $p < 0.05$).

Obese children had significantly lower adiponectin (OB: 7.56 (5.69/12.06) μg/mL *versus*. C: 11.51 (8.84/14.49) μg/mL, $p < 0.001$) and higher leptin levels (OB: 37.05 (24.33/53.87) ng/mL *versus*. C: 4.62 (2.52/17.6) ng/mL, $p < 0.0001$). To examine their relation to other parameters, we carried out Pearson correlation analysis, which is shown in Table 2. Surprisingly, we could not find any significant correlation between PON1 paraoxonase activity and the two investigated adipokines. However, PON1 arylesterase activity showed significant positive correlation with adiponectin levels (r = 0.39, $p < 0.01$) and significant negative correlation with leptin levels (r = −0.29, $p < 0.05$) (Fig. 1*A*, *B*).

To test whether the associations of PON1 arylesterase with leptin and adiponectin seen in the univariate analysis were independent of other parameters, we carried out multiple regression analysis using the stepwise method. In Model 1, we investigated the two adipokines, which showed significant univariate correlation with PON1 arylesterase activity, and the impact of age and

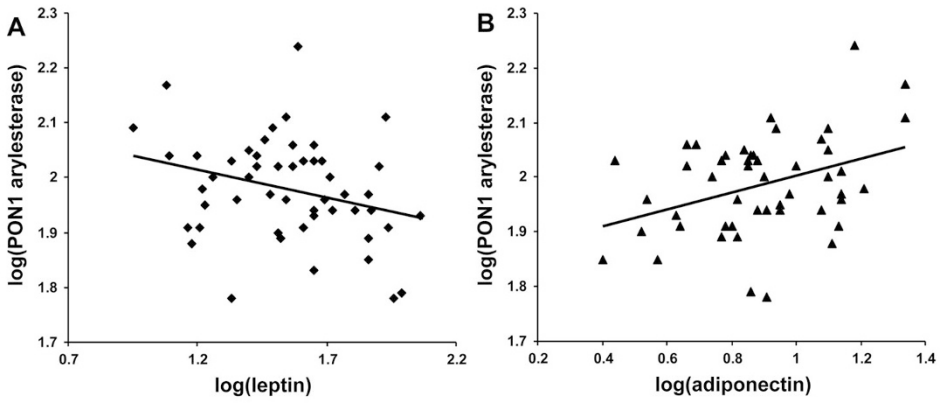

Figure 1. Pearson's correlations of PON1 arylesterase activity with leptin (*A*; r = −0.29, $p < 0.05$) and adiponectin levels (*B*; r = 0.39, $p < 0.01$) in the obese group (n = 59); PON1 arylesterase activity, leptin and adiponectin levels were log transformed.

Table 3. *Multiple regression analyses for PON1 arylesterase activity as a dependent variable*

Variables	Model 1 (R^2 = 0.289)			Model 2 (R^2 = 0.442)		
	β	t	p	β	t	p
Age	0.11	0.76	0.45	0.07	0.41	0.68
Sex	0.10	0.73	0.47	0.33	1.86	0.08
Leptin	−0.20	−1.43	0.16	−0.35	−1.73	0.10
Adiponectin	**0.45**	**3.17**	**<0.004**	**0.45**	**2.56**	**<0.02**
HDL-cholesterol	—	—	—	−0.24	−1.29	0.21
Body fat percentage	—	—	—	−0.07	−0.37	0.72

β is standardized regression coefficient. Significant values are indicated in bold.

sex. In this model adiponectin showed strong association with PON1 arylesterase activity ($\beta = 0.45$, $p < 0.004$; Table 3); however, leptin was not proven to be a strong predictor. After adjusting HDL-C and BFP to investigate their impact in Model 2, adiponectin was also strongly associated with PON1 arylesterase activity ($\beta = 0.45$, $p < 0.02$; Table 3). In Model 1 the unstandardized coefficient of adiponectin was 2.11 and in Model 2, in which we added HDL-C and BFP to the model, it was 2.15. Investigating this strong connection of PON1 arylesterase activity alone with adiponectin levels in regression analysis, the unstandardized regression coefficient was 2.12 in the model. In this way we could conclude that according to this analysis one unit increase of adiponectin was associated with 2.12 U/L increase of PON1 arylesterase activity; however further investigations are needed to determine the exact relation between these strongly associated parameters.

DISCUSSION

Previous studies found decreased PON1 activity in obese subjects; however, the association between PON1 activity and BMI has only been studied in adult populations (6,35). Bajnok *et al.* investigated a population with a broad range of BMI and found that BMI was an independent predictor of PON1 arylesterase activity (35). Our results support the initial hypothesis that obese children show decreased PON1 paraoxonase and arylesterase activity compared with their normal-weight peers. Moreover, there was a statistically significant negative correlation between leptin level and arylesterase activity and a significant positive correlation between adiponectin level and arylesterase activity. To the best of our knowledge, this is the first study, which investigated the variation of PON1 activities and their correlations with serum leptin and adiponectin levels in childhood obesity.

Several studies (12,13,16) have shown hyperleptinemia and decreased adiponectin levels in obese young and adult populations. We also found that obese children have significantly lower adiponectin and higher leptin levels. The association between PON1 paraoxonase or arylesterase activity, and these two adipokines have been already described in adults (15,18). However, in children we could not find any simple correlation between paraoxonase activity and the adipokine levels and significant correlations were only seen between arylesterase activity, serum leptin and adiponectin levels. Although, it must be noted that PON1 paraoxonase activity presents a great inter-individual variability (36).

We found significantly lower PON1 arylesterase and paraoxonase activities in obese children compared with the normal-weight group. PON1 arylesterase activity showed significant relationships with the investigated adipokines. PON1 arylesterase is directly proportional to concentration of the enzyme (9); therefore, these results may suggest that mostly the production of the PON1 enzyme protein might be affected by leptin and adiponectin. Adiponectin may have an ability to accelerate the reverse cholesterol transport and increase apoA-I-mediated cholesterol efflux through enhancing HDL assembly in the liver, which was also reflected in the association of HDL-C with adiponectin (28), but it may have such effect on the hepatic expression of PON1, too.

According to the multiple regression analysis we used in this population, adiponectin was the factor that was most strongly associated with arylesterase activity. Previously, our group found the same result in adult population (18); however, it raises several other issues which would need explanation in other further studies considering the complexity of metabolic alterations in obesity.

Leptin had also significant correlation with PON1 arylesterase activity which may be the result of the leptin induced ROS (21) generation by the inactivation of the enzyme, as well as by the inhibitory effect on the hepatic expression of PON1 through the enhancement of the acute phase response (24,25). Moreover, we found significant correlation of leptin levels with BMI, BFP, waist circumference, TG, HOMA-IR, diastolic and systolic BP that have been already demonstrated in young subjects (13). Although previous studies reported correlations between adiponectin and anthropometric parameters (13,16,37), we did not find any significant correlation between adiponectin and anthropometric data. Adiponectin correlated significantly with leptin levels, HOMA-IR, HDL-C and near-significantly with both the systolic and diastolic blood pressures in the obese group.

Our recent study showed that PON1 activities show decreasing tendency with ageing (33) highlighting the importance of our current results and the burden put on human vasculature by decreased activity already early in life. Our findings provide evidence to the complex deregulation of normal homeostatic functions in childhood obesity, which may have cardiovascular effects in the later adulthood; however, it requires further investigations.

Limitations. Limitations of our study were relatively small sample size, which clearly reduces the power of the study. We did not investigate the direct markers of lipid peroxidation. The measurement of early signs of atherosclerosis such as carotid intima-media thickness would improve the signifi-

cance of low PON1 activity in obese children. In conclusion, leptin, adiponectin levels and PON1 activities may be useful markers beside the general risk factors in childhood obesity. Our results emphasize the importance of the investigated metabolic changes which might have further effects on cardiovascular morbidity and mortality in later adulthood. PON1 activities and adipokine levels might be markers for screening and for further follow-up in childhood obesity.

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