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Book Name	Paraoxonases in Inflammation, Infection, and Toxicology	
Corresponding Author	Family Name	**Seres**
	Particle	
	Given Name	**Ildikó**
	Suffix	
	Division	Department of Internal Medicine
	Organization	Medical and Health Science Centre, University of Debrecen
	Address	Debrecen, Hungary
	Email	seres@internal.med.unideb.hu
Author	Family Name	**Bajnok**
	Particle	
	Given Name	**László**
	Suffix	
	Division	Department of Medicine
	Organization	School of Medicine, University of Pécs
	Address	Pécs, Hungary
	Email	
Author	Family Name	**Harangi**
	Particle	
	Given Name	**Mariann**
	Suffix	
	Division	Department of Internal Medicine
	Organization	Medical and Health Science Centre, University of Debrecen
	Address	Debrecen, Hungary
	Email	
Author	Family Name	**Sztanek**
	Particle	
	Given Name	**Ferenc**
	Suffix	
	Division	Department of Internal Medicine
	Organization	Medical and Health Science Centre, University of Debrecen
	Address	Debrecen, Hungary
	Email	
Author	Family Name	**Koncsos**
	Particle	
	Given Name	**Peter**
	Suffix	
	Division	Department of Internal Medicine
	Organization	Medical and Health Science Centre, University of Debrecen
	Address	Debrecen, Hungary

	Email	
Author	Family Name	**Paragh**
	Particle	
	Given Name	**György**
	Suffix	
	Division	Department of Internal Medicine
	Organization	Medical and Health Science Centre, University of Debrecen
	Address	Debrecen, Hungary
	Email	

Abstract

Obesity as a pathogenic disorder is a predisposing factor for cardiovascular diseases and shows an increasing incidence in the industrialized countries. Adipokines such as leptin, adiponectin and resistin have a great impact on the development of atherosclerosis in obesity. Elevated levels of leptin have been found to be atherogenic whereas decreased levels of adiponectin have been proved to be anti-atherogenic in recent studies. The exact role of resistin in the process of atherosclerosis has so far remained uncertain and controversial. In our recent work, we studied the alteration in human paraoxonase-1 (PON1) activity and adipokine levels; furthermore, we also aimed at identifying the potential correlation between these parameters in this metabolic disorder. We investigated the above-mentioned parameters both in adults and in children, with regard to the emerging role of childhood obesity and to get a clearer view of these factors during a whole lifetime. Investigating the adult population with a broad range of body mass index (BMI) we found significantly increased leptin and significantly decreased adiponectin and resistin levels and PON1 activity in the obese group compared to the lean controls. Adiponectin and resistin levels showed significantly positive correlation, while leptin and BMI showed significantly negative correlation with PON1 activity.Our findings were similar in childhood obesity: leptin showed significantly negative correlation, while adiponectin showed significantly positive correlation with PON1 activity. We found gender differences in the univariate correlations of leptin and adiponectin levels with PON1 activity in the adult population. In multiple regression analysis, adiponectin proved to be an independent factor of PON1 activity both in childhood and adult obesity, furthermore thiobarbituric acid-reactive substances (TBARS) also proved to be an independent predictor of the enzyme in adults, reflecting the important role of oxidative stress in obesity. Investigating PON 192 Q/R polymorphism by phenotypic distribution (A/B isoenzyme) in obese children, we found a significant correlation of PON1 arylesterase activity with leptin and adiponectin levels, and of body fat percentage with PON1 192 B isoenzyme.According to our studies, these metabolic changes in obesity predispose to the early development of atherosclerosis throughout our whole lifetime. Decreased activity of PON1 and alterations in adipokine levels in childhood obesity could contribute to an early commencement of this process, detected only later in adulthood by increased cardiovascular morbidity and mortality. Changed levels of leptin, adiponectin, resistin and PON1 activity at all ages, just like 192 Q/R polymorphism determined by phenotypic distribution, may be useful markers beside the general risk factors.

Keywords (separated by '-') Adipokines - Leptin - Adiponectin - Resistin - Obesity - Paraoxonase-1 - Childhood

Alteration of PON1 Activity in Adult and Childhood Obesity and Its Relation to Adipokine Levels

Ildikó Seres, László Bajnok, Mariann Harangi, Ferenc Sztanek, Peter Koncsos, and György Paragh

Abstract Obesity as a pathogenic disorder is a predisposing factor for cardiovascular diseases and shows an increasing incidence in the industrialized countries. Adipokines such as leptin, adiponectin and resistin have a great impact on the development of atherosclerosis in obesity. Elevated levels of leptin have been found to be atherogenic whereas decreased levels of adiponectin have been proved to be anti-atherogenic in recent studies. The exact role of resistin in the process of atherosclerosis has so far remained uncertain and controversial. In our recent work, we studied the alteration in human paraoxonase-1 (PON1) activity and adipokine levels; furthermore, we also aimed at identifying the potential correlation between these parameters in this metabolic disorder. We investigated the above-mentioned parameters both in adults and in children, with regard to the emerging role of childhood obesity and to get a clearer view of these factors during a whole lifetime. Investigating the adult population with a broad range of body mass index (BMI) we found significantly increased leptin and significantly decreased adiponectin and resistin levels and PON1 activity in the obese group compared to the lean controls. Adiponectin and resistin levels showed significantly positive correlation, while leptin and BMI showed significantly negative correlation with PON1 activity.

Our findings were similar in childhood obesity: leptin showed significantly negative correlation, while adiponectin showed significantly positive correlation with PON1 activity. We found gender differences in the univariate correlations of leptin and adiponectin levels with PON1 activity in the adult population. In multiple regression analysis, adiponectin proved to be an independent factor of PON1 activity both in childhood and adult obesity, furthermore thiobarbituric acid-reactive substances (TBARS) also proved to be an independent predictor of the enzyme in adults, reflecting the important role of oxidative stress in obesity. Investigating PON 192 Q/R polymorphism by phenotypic distribution (A/B isoenzyme) in obese

I. Seres (✉)
Department of Internal Medicine, Medical and Health Science Centre, University of Debrecen, Debrecen, Hungary
e-mail: seres@internal.med.unideb.hu

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children, we found a significant correlation of PON1 arylesterase activity with leptin and adiponectin levels, and of body fat percentage with PON1 192 B isoenzyme.

According to our studies, these metabolic changes in obesity predispose to the early development of atherosclerosis throughout our whole lifetime. Decreased activity of PON1 and alterations in adipokine levels in childhood obesity could contribute to an early commencement of this process, detected only later in adulthood by increased cardiovascular morbidity and mortality. Changed levels of leptin, adiponectin, resistin and PON1 activity at all ages, just like 192 Q/R polymorphism determined by phenotypic distribution, may be useful markers beside the general risk factors.

Keywords Adipokines · Leptin · Adiponectin · Resistin · Obesity · Paraoxonase-1 · Childhood

1 Introduction

1.1 Obesity and Atherosclerosis: The Role of Adipokines in Atherogenesis and Lipid Peroxidation

Obesity has been identified as a major health concern, and as its level continues to grow steadily the condition threatens to rank among the biggest causes of premature death in both the industrialized and emerging economies. Obesity is an important determinant of atherosclerosis, but the mechanisms behind it are only partially understood. Intra-abdominal or visceral adiposity plays a fundamental role in the stimulation of hyperglycemia, dyslipidemia and hypertension, collectively termed metabolic syndrome, which is one of the most significant risk factors of cardiovascular diseases (Ford, 2005).

Previously, a direct relation was found between general obesity and markers of *oxidative stress* (Mutlu-Turkoglu et al. 2003). In humans the susceptibility of lipids to oxidative modification is an independent risk factor of coronary heart disease (Holvoet et al. 2001). Furthermore, it was also shown that body mass index (BMI) is one of the strongest predictors of circulating ox-LDLconcentrations (Holvoet, 2006; Ho et al. 2002). In addition, previous studies have demonstrated significant correlations of urinary isoprostanes and ox-LDL/LDL ratio with BMI (Sjogren et al. 2005). Collectively, these findings indicate that weight is an important determinant of oxidative stress. However, the mechanisms by which obesity per se could induce increased oxidative stress are not well defined. According to one hypothesis, oxidative stress is induced by low-grade systemic inflammation. Other factors that have been discussed in relation to increased oxidative stress in obesity are insulin resistance and lipoprotein abnormalities (Weinbrenner and Schroder, 2006).

Previous studies have revealed that humoral factors secreted by adipose tissue contribute to the metabolic syndrome and cardiovascular diseases (Bełtowski et al. 2008). Adipocytes are more than passive fuel storage sites; they release numerous biologically active peptides. Obesity alters adipocytokine secretion profiles, and

some obesity-related disorders, including cardiovascular diseases, are associated with dysfunction of adipose tissue (Katagiri et al. 2007).

Leptin, the product of *ob* gene, is a 16 kDa peptide hormone produced mainly by differentiated adipocytes, although leptin expression has been demonstrated in other tissues such as liver, skeletal muscle and placenta. Leptin acts on the central nervous system suppressing food intake and stimulating energy expenditure. Leptin receptors have been found ubiquitously in the body, indicating a general role of leptin. The concentration of leptin is directly proportional to total body fat, and thus obese subjects have usually higher leptin concentrations than non-obese subjects. However, not only the rare human leptin deficiency, but also resistance to the effect of leptin, which is common in obesity, is associated with weight gain. Numerous observations indicate a correlation between serum leptin and cardiovascular diseases (Wannamethee et al. 2007; Patel et al. 2008).

Leptin contributes to the pathogenesis of atherosclerosis by several mechanisms including the enhancement of oxidative stress. Leptin increases the generation of reactive oxygen species by activating c-Jun amino-terminal kinase, AP-1 and nuclear factor kappa B pathways (Bouloumie et al. 1999). Hyperleptinaemia promotes vascular inflammation, stiffness, calcification and proliferation by increasing oxidative stress. ROS enhances the expression of adhesion molecules, which promote the chemotaxis of monocytes in the vessel wall (Curat et al. 2004). By increasing oxidative stress and activating protein kinase C, leptin also increases the production of proatherogenic lipoprotein lipase (LPL) in macrophages. LPL promotes the retention of lipoproteins in the subendothelial space, favors monocyte adhesion and stimulates the transformation of macrophages into foam cells (Dubey and Hersong, 2006). In rats, leptin administration decreased the activity of paraoxonase, and increased plasma and urinary concentrations of isoprostanes reflecting increased oxidative stress (Beltowski et al. 2003; Beltowski, 2006).

Adiponectin is an adipocyte-specific protein with roles in glucose and lipid homeostasis. A negative correlation between obesity and circulating adiponectin has been shown, and decreased adiponectin concentrations are associated with insulin resistance and hyperinsulinemia (Szmitko et al. 2007). Adiponectin also plays antiatherogenic and anti-inflammatory roles. Accordingly, adiponectin concentrations are decreased in patients with coronary artery disease. The mechanisms underlying the role of adiponectin in lipid peroxidation may involve the regulation of proteins associated with triglyceride metabolism, including CD36, acyl CoA oxidase, 5′-AMP-activated protein kinase and peroxisome proliferator-activated receptor γ (Meier and Gressner, 2004).

Resistin is another adipocyte-specific protein with unknown physiologic roles. Data obtained from animal models suggest that resistin induces insulin resistance. Human studies demonstrated conflicting results in obesity (Rabe et al. 2008). Some of them found a positive correlation between resistin and BMI. Furthermore, resistin may be involved in the regulation of cell proliferation and in the differentiation of fat cells, and in chronic inflammatory reactions associated with obesity (Meier and Gressner, 2004). The role of resistin in the development of obesity-related vascular diseases in humans is still uncertain (Katagiri et al. 2007).

Obesity is associated with derangements in lipid profile, called atherogenic lipid profile, consisting of elevated ApoB and triglyceride levels and low HDL cholesterol. HDL is able to intervene at different stages of the atherosclerotic process (Rosenson, 2006). The antioxidant effect of HDL is mainly provided by the human paraoxonase enzyme 1 (PON1). PON1 has been shown to protect LDL from oxidative modification by hydrolyzing lipid hydroperoxides and cholesterol ester hydroperoxides (esterase activity), with peroxidase activity that reducing peroxides to their respective hydroxides and thiolactonase activity hydrolyzing homocysteine thiolactone, thus protecting proteins from homocysteinylation (Beltowski, 2005).

Serum PON1 activity has been shown to be decreased in several diseases with disturbed lipid metabolism that are associated with accelerated atherogenesis, e.g., in diabetes mellitus (Mackness and Durrington, 1995), hypercholesterolemia (Tomás et al. 2000), coronary heart disease (Mackness et al. 2004), and in hemodialysis patients (Paragh et al. 1998), and with aging (Seres et al. 2004).

1.2 Relationship of Leptin to PON1

There are only a few studies that have examined the effects of leptin on PON1 activity and none has investigated the correlation between adiponectin, resistin and PON1 activity.

1.2.1 Animal Studies

It was demonstrated that leptin administered for 7 days decreased plasma PON1 activity and induced oxidative stress in rats (Beltowski, 2005). In addition, leptin reduced PON1 activity in the aorta, renal cortex and medulla but not in the heart, lung or liver. Interestingly, leptin decreased PON1 activity only in tissues in which it stimulated oxidative stress. These data suggest that leptin-induced decrease in PON1 in tissues results from excessive ROS production, consistent with a well-known inactivation of the enzyme by oxidative processes which may be involved in atherogenesis in hyperleptinemic obese individuals.

1.2.2 Human Studies

An inverse relation of PON1 with obesity and serum leptin levels has been demonstrated. Ferretti et al. demonstrated that the increase in oxidative stress in HDL and LDL of obese subjects (monitored by the levels of lipid hydroperoxides in HDL and LDL) was associated with a decrease of PON1 activity in isolated HDL (Ferretti et al. 2005). Uzun et al have also shown an inverse correlation between serum leptin levels and PON1 activity in morbid obesity after gastric banding (Uzun et al. 2004). These data suggest that hyperleptinemia could lead to reduced PON1 activity in humans. However, in our previous work we have showed that hyperleptinemia occurring in chronic renal failure was not responsible for decreased paraoxonase activity (Varga et al. 2006). Moreover, we found a positive correlation between leptin and PON1 activity in hemodialysis (HD) patients. This relationship might be explained by the elevated PON1 activity in HD patients with BMI > 25 kg/m^2

compared to the group with BMI < 25 kg/m^2. However, the reason for enhanced PON1 activity in the high BMI group of HD patients remains unknown.

The above-mentioned studies were performed on animal models, on isolated HDL or in HD patients with special metabolic conditions. However, the relation of these adipokines – leptin, adiponectin and resistin – to PON1 has not been clarified in obesity.

The goal of our study was to examine the relationship between adipokines and PON1 activity in obese adults and obese children (when the cardiovascular complications are not yet manifested).

In order to magnify the impact of obesity on the investigated parameters, we selected the adult study population with a broad range of BMI ranging from 19 to 53 with a mean of 34.2 (± 7.11) kg/m^2. Patients were divided into three groups according to BMI values, and were age- and sex-matched (Bajnok et al. 2007). Obese (BMI = 28–39.9 kg/m^2) and morbidly obese (BMI > 40 kg/m^2) patients had significantly higher blood pressures and plasma glucose levels and had atherogenic lipid profiles compared to lean subjects (BMI = 20–24.9 kg/m^2).

We found a significant negative correlation between PON1 activity and BMI ($r = -0.503$, $p < 0.001$). According to BMI categories, we found that obese and morbidly obese patients had significantly lower PON1 activity compared to lean subjects (Fig. 1a). Serum leptin concentration was significantly higher in both obese groups compared to the lean group (Fig 1b). Examining the correlation

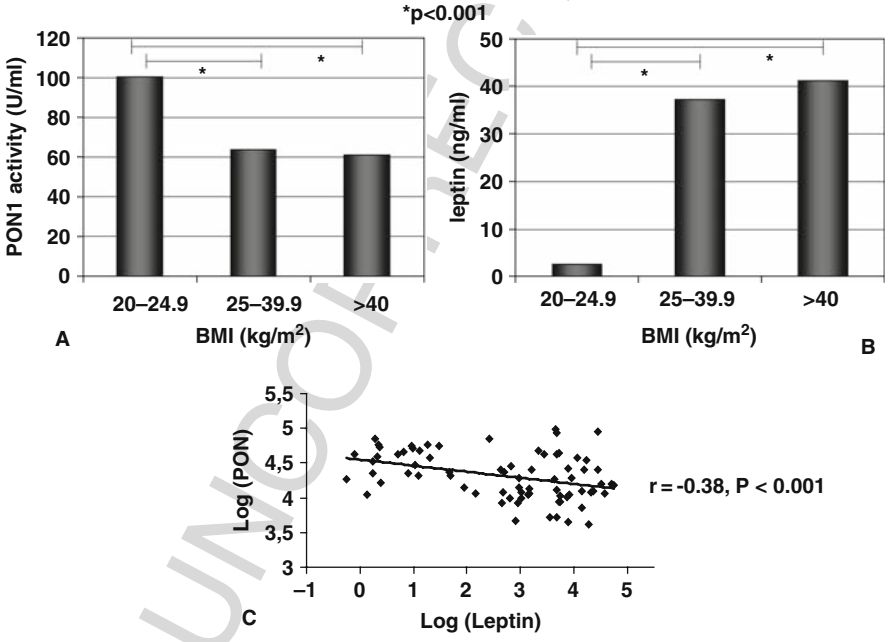

Fig. 1 PON1 paraoxonase activities (**a**) and serum leptin concentrations (**b**) in the different BMI categories, and correlation between PON1 activity and leptin levels (**c**) in adult obesity

between PON1 activity and leptin levels, we found a significant negative correlation between these two parameters, similar to animal studies ($r = –0.38$, $p < 0.001$, Fig 1c). The relationship between leptin and PON1 was also evaluated in male and female subjects separately, and a stronger correlation was found among men ($r = –0.50$, $p < 0.01$) than among women ($r = –0.28$, $p = 0.06$) (Bajnok et al. 2007).

2 Relationship of Adipokines to PON1 in Adult Obesity

2.1 Relationship of Adiponectin to PON1

It was previously demonstrated that adiponectin levels in obese patients were significantly decreased and inversely correlated with both body weight and fat mass (Díez and Iglesias, 2003). In confirming this well-known fact, we also demonstrated that the obese and morbidly obese patient groups had significantly lower adiponectin levels compared to the lean group (Fig. 2a). Our results show a negative and significant correlation between adiponectin levels and BMI ($r = –0.38$, $p < 0.001$) (Fig. 2b). Since several in vivo and in vitro studies have reported that adiponectin has direct anti-atherogenic effects on the arterial wall (Matsuda et al.

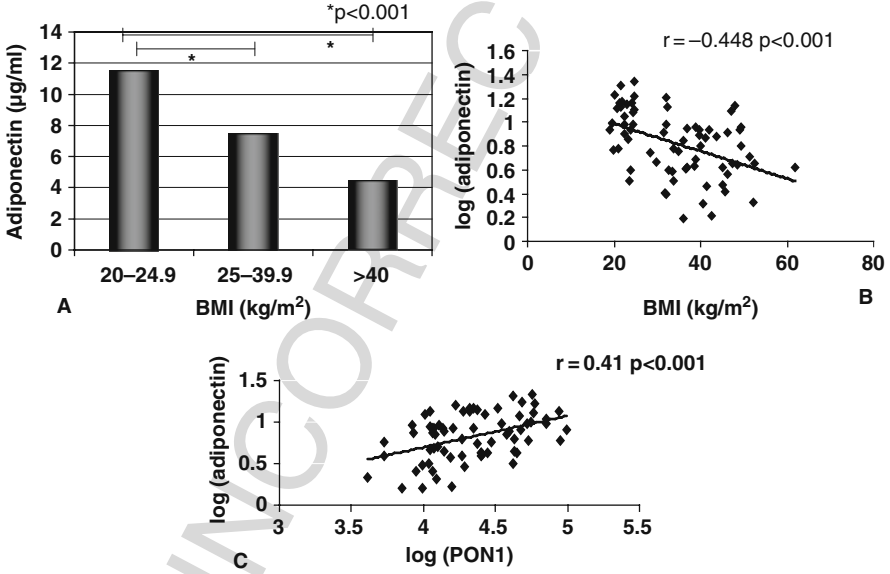

Fig. 2 Adiponectin levels in the different BMI categories (**a**), and correlations between adiponectin level and BMI (**b**) and between adiponectin level and PON1 activity (**c**) in adult obesity

2002) and that hypoadiponectinemia was associated with endothelial dysfunction (Shimabukuro et al. 2003), cardiovascular disease (Kumada et al. 2003) and diabetes mellitus (Hotta et al. 2000), we hypothesized that there might be correlations between antioxidant PON1 activities and adiponectin levels. We analyzed the relationship of adiponectin concentration to PON1 activity (Bajnok et al. 2008a). To the best of our knowledge this was the first study to investigate the relationship between PON1 activity and adiponectin levels. We found a strong positive correlation between these two anti-atherogenic factors ($r = 0.41$; $p < 0.001$) (Fig. 2c). There was a stronger correlation between adiponectin and PON1 among males ($r = 0.49$, $p < 0.01$) than among females ($r = 0.37$, $p < 0.05$).

To test if the association between adiponectin and PON1 was independent of anthropometric and other laboratory parameters, we carried out a multiple regression analysis. During this test only adiponectin turned out to be an independent predictor of serum PON1, but none of the other variables that were included in the model (Table 1). The association between adiponectin and PON1 was independent of anthropometric and other parameters, i.e. age, gender, BMI, systolic blood pressure, insulin resistance index by homeostasis model assessment (HOMA-IR), LDL-C, HDL-C and lipid peroxidation (measured by thiobarbituric acid-reactive substances [TBARS]).

Table 1 Multiple regression analysis for PON1 activity as a dependent variable

Variable	β	P
Intercept	4.289	< 0.001
Age	−0.002	0.724
Gender	−0.052	0.629
BMI	0.003	0.746
Systolic BP	0.001	0.928
HOMA-IR	−0.120	0.186
LDL-C	−0.061	0.658
HDL-C	−0.079	0.574
TBARS	−0.032	0.698
Adiponectin	0.252	0.011

BMI: Body mass index; BP: blood pressure; HDL-C: high-density lipoprotein-cholesterol; HOMA-IR: insulin resistance index by homeostasis model assessment; LDL-C: low-density lipoprotein-cholesterol; TBARS: thiobarbituric acid-reactive substances

2.2 Relationship of Resistin to PON1

Resistin levels were higher in the controls than among the obese subjects, with no differences between the obese subgroups (Fig. 3a). The concentrations of resistin were similar in the three groups of PON1 phenotypes, and there were no significant differences in the distribution of PON1 phenotypes among the three BMI groups of

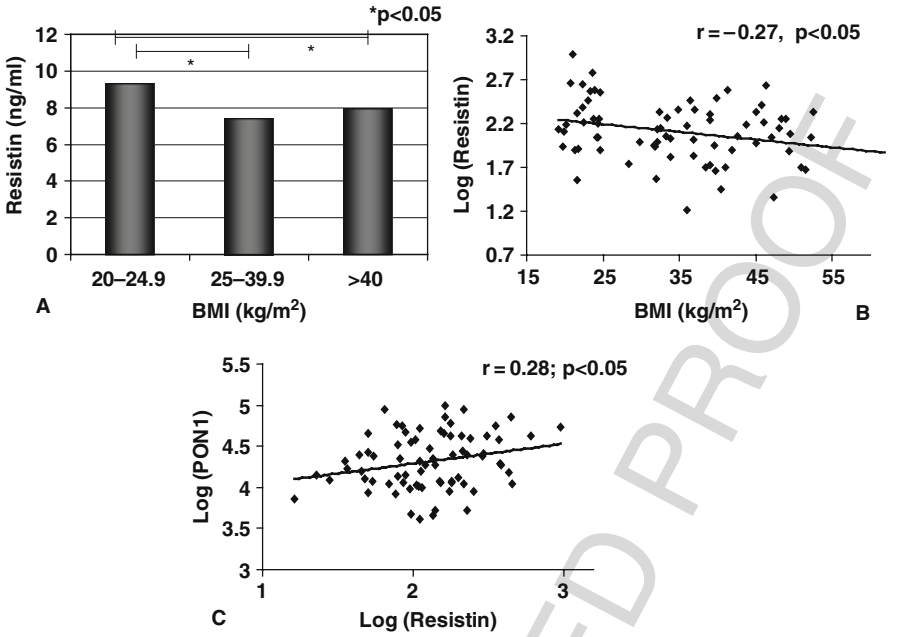

Fig. 3 Resistin levels in the different BMI categories (**a**), and correlations between resistin level and BMI (**b**) and between resistin level and PON1 activity (**c**) in adult obesity

subjects. Impact of BMI categories on the resistin level remained significant even after adjustments for age and gender (Bajnok et al. 2008b).

Univariate correlation analysis showed that in the whole population, serum levels of resistin were correlated negatively with BMI and correlated positively with PON1 activity (Fig. 3b,c).To test if the association of resistin with PON1 existing in the univariate analysis was independent of anthropometric and other laboratory parameters, we carried out multiple regression analyses with PON1 as the dependent variable.

At first, two less well adjusted models (Model *A* and *B*) were constructed in which, beside resistin, the impact of age, sex and BMI were tested (Table 2). In Model *B* HDL-C was also included, since PON1 is associated with a subfraction of HDL. In these models only BMI turned out to be an independent predictor of PON1, explaining the 12.6% of the variance of PON1. We also constructed a more fully adjusted model (Model *C*), applying parameters that are related either to metabolic syndrome (systolic blood pressure, HDL-C, HOMA-IR) and/or lipid peroxidation (LDL-C and TBARS). The reason for including these latter two parameters was that higher levels of cholesterol concentration and lipid peroxidation are associated with enhanced inactivation of PON1 in an interaction between lipid peroxides and the sulfhydryl groups of the enzyme.

In the extended model (Model *C*), BMI ceased to be a significant independent variable of PON1, and of the investigated parameters only TBARS proved to be a

Table 2 Multiple regression analysis for PON1 paraoxonase activity as a dependent variable

	Model A ($R^2 = 0.20$)			Model B ($R^2 = 0.21$)			Model C ($R^2 = 0.22$)		
Variable	B	t	P	β	t	P	β	t	P
Age	0.08	0.67	0.50	0.04	0.34	0.73	0.05	0.37	.071
Gender	−0.09	−0.79	0.44	−0.14	−1.22	0.23	−0.04	−0.27	0.79
BMI	−0.42	−3.87	< 0.001	−0.42	−3.87	< 0.001	0.11	0.39	0.70
Resistin	0.14	1.22	0.23	0.14	1.22	0.23	0.11	0.78	0.44
HDL-C	–	–	0.11	0.82	0.42	0.06	0.34	0.74	
LDL-C	–	–	–	–	–	−0.06	−0.42	0.68	
TBARs	–	–	–	–	–	−0.41	−3.2	0.002	
Systolic BP	–	–	–	–	–	−0.07	−0.35	0.73	
HOMA-IR	–	–	–	–	–	−0.23	−1.54	0.13	

BMI: Body mass index; BP: blood pressure; HDL-C: high-density lipoprotein-cholesterol; HOMA-IR: insulin resistance index by homeostasis model assessment; LDL-C: low-density lipoprotein-cholesterol; TBARS: thiobarbituric acid-reactive substances

predictor of PON1, showing that of the partially related variables, TBARS and BMI, the variance of PON1 was explained better by TBARS than by BMI (Table 2).

To the best of our knowledge, this is the first report of the relationship between resistin and PON1. However, when we tested if the association between resistin and PON1 was independent of anthropometric and other parameters in multiple regression analysis, resistin was not an independent predictor of PON1. In fact, during this multivariate analysis only the negative correlation between PON1 and lipid peroxidation (measured by TBARS) remained significant, and neither the BMI, nor the age, gender, systolic BP, HOMA-IR, LDL-C or HDL-C were significant predictors of PON1 activity.

3 Relationship of Adipokines to PON1 in Childhood Obesity

3.1 Association of Adipokines and PON1 Activity in Childhood Obesity

Genetic polymorphisms in the promoter and coding regions of the *PON1* gene are the main determinants of the enzyme activity, but serum PON1 activity can be modulated by several other factors. Aging and pathologic states such as renal disease, diabetes mellitus, cardiovascular disease, and liver cirrhosis are associated with decreased PON1 activity, and various dietary and lifestyle factors have been reported to influence serum PON1 activity (Seres et al. 2004; Paragh et al. 1998, 1999; Mackness and Durrington, 1995; Ferré et al. 2006). Smoking has been associated with reduced PON1 activity and concentrations in patients with coronary artery disease. On the other hand, lipid-lowering therapy with statins (Tomás et al. 2000;

Paragh et al. 2004), and hormone replacement therapy (Sutherland et al. 2001), have been demonstrated to increase serum PON1 activity.

Since other factors influencing PON1 activity (smoking, concomitant diseases like DM2, CRF, CVD) can be present in obese adults, we decided to investigate PON1 activity in obese children, where the incidence of these factors are markedly lower. Similar to the results in adult patients, obese children (age: 11.95 ± 1.61 years, BMI: 28.23 ± 4.33 kg/m^2) had significantly higher serum leptin levels (43.61 ± 26.64 vs. 11.69 ± 14.63 ng/ml; $p < 0.001$) that correlated positively with their body fat percentage ($r = 0.52$; $p < 0.001$). (Body fat percentage (BFP) is a better characterizing parameter for obesity in childhood than BMI.) We found gender differences in leptin levels both in the obese and the age- and gender-matched normal-weight groups, and similarly to other studies girls had significantly higher leptin levels than boys ($p < 0.05$). Adiponectin levels were significantly lower in the obese children group compared to the control group (8.59 ± 4.39 vs.12.24 ± 4.86 μg/ml, p <0.001), as was expected. Obese children had significantly lower PON1 activity (97.31 ± 21.24 vs. 111.44 ± 23.52 U/L; $p < 0.01$). Similar to adult obese individuals, we demonstrated an inverse relation between PON1 activity and leptin levels ($r = –0.29$, $p < 0.05$) and a positive relation between PON1 activity and adiponectin concentrations ($r = 0.39$; $p < 0.01$). In order to test whether the associations of PON1 with leptin and adiponectin existing in the univariate analysis were independent of other parameters, we carried out a multiple regression analysis. Adiponectin level also proved to be an independent predictor of PON1 activity after adjusting for age, sex, BFP, leptin and HDL-C in the model (Table 3).

Table 3 Multiple regression analysis for PON1 arylesterase as a dependent variable (model $R^2 = 0.442$, $p < 0.05$)

Independent variable	Regression coefficient	SE of regression coefficient	Standardized coefficient (β)	t	p
Age	1.039	2.513	0.068	0.413	0.68
Sex	13.356	7.168	0.326	1.863	0.08
Leptin	−0.312	0.180	−0.349	−1.734	0.10
Adiponectin	2.151	0.841	0.453	2.557	0.02
HDL-cholesterol	−20.480	15.920	−0.236	−1.286	0.21
Body fat percentage	−0.192	0.526	−0.073	−0.365	0.72

3.2 Correlations Between Adipokine Levels and PON1 Phenotypes

Investigating the phenotypic distribution of PON1 in the obese group, we found differences in the correlations of PON1 activity in the subgroups (Figs. 4 and 5). We could divide the obese children into two groups: 40 children belonging to the group with AA phenotype and 19 children to the group with AB phenotype; none

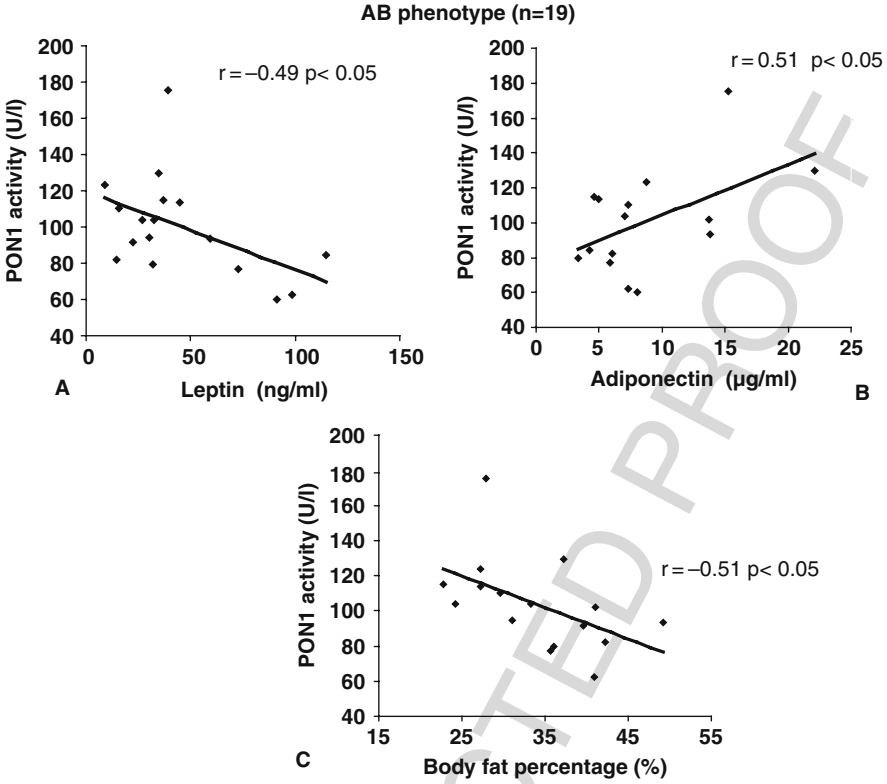

Fig. 4 Correlations between PON1 activity and serum leptin levels (**a**), serum adiponectin levels (**b**) and body fat percentage (BFP) (**c**) in obese children with AB phenotype

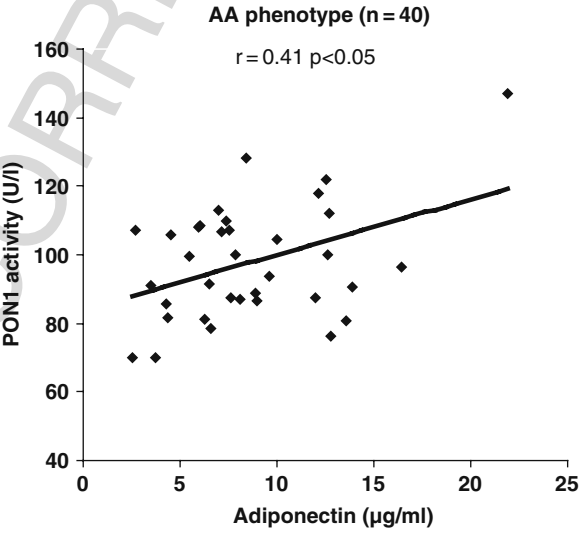

Fig. 5 Correlation between PON1 activity and serum adiponectin level in obese children with AA phenotype

of the obese children had BB phenotype. We did not find any significant differences in anthropometric and clinical data between the two groups. Obese children with AB phenotype had a significant correlation between PON1 activity (Fig. 4a,b,c) and serum leptin ($r = –0.49$, $p < 0.05$), adiponectin levels ($r = 0.51$, $p < 0.05$) and BFP ($r = –0.51$, $p < 0.05$) whereas children with AA phenotype had a significant correlation between PON1 arylesterase activity and adiponectin levels ($r = 0.41$, $p < 0.05$; Fig. 5) but with no significant correlation observed between PON1 activity and the other investigated parameters.

4 Conclusions

Taken together, in a population with a broad range of BMI that could be divided into three equal groups, we found a significant negative correlation between PON1 activity and BMI ($r = –0.503$ $p < 0.001$) that was independent of age, sex and HDL-C; BMI explained 12.6% of the variance of PON1. Compared to lean subjects, obese patients had significantly higher leptin and lower adiponectin and resistin levels and PON1 activity. Serum PON1 activity showed a negative correlation with leptin ($r = –0.38$, $p < 0.001$), while a positive correlation was shown with adiponectin ($r = 0.41$; $p < 0.001$) and resistin. However, only adiponectin turned out to be an independent predictor of PON1 activity in a multiple regression model in which other factors, such age, gender, BMI, systolic blood pressure, HOMA-IR, LDL-C, HDL-C and a marker of lipid peroxidation were also included, beside the adipokines.

These results were confirmed among children, except resistin that was not investigated.

The low PON1 activity in obese children is a novel and alarming result. Previously we had found that serum PON1 activity significantly decreased with age (Seres et al. 2004). It may mean that the initially higher cardiovascular risk of obese children caused by lower PON1 activity will be even higher with aging. Therefore, screening and treatment of these children is especially important to prevent early manifestations of atherosclerosis.

Our studies suggest that obesity predisposes to accelerated progression of atherosclerosis throughout our whole lifetime. Childhood obesity also demonstrates the importance of this pathologic metabolic state, the consequences of which can be detected only in later adulthood, and that is why the investigation of this population has become so important. Changed levels of leptin, adiponectin, resistin and PON1 activity, just like 192 Q/R polymorphism determined by phenotypic distribution, may be useful markers beside the general risk factors in both adult and childhood obesity.

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Chapter

Q. No.	Query
AQ1	please check BMI = body mass index
AQ2	please define 'ox-LDL'
AQ3	please define these abbreviations