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CLINICAL STUDY

Leptin and plasminogen activator inhibitor-1 levels in children on chronic dialysis

Pinar Isik Agras¹, Esra Baskin², Nurcan Cengiz², Aysegul Haberal³, and Namik Ozbek⁴

¹Ministry of Health Ankara Training and Research Hospital, Ankara, Turkey, ²Department of Pediatric Nephrology, Baskent University, Ankara, Turkey, ³Biochemistry Laboratories, Baskent University, Ankara, Turkey, and ⁴Department of Pediatric Hematology, Baskent University, Ankara, Turkey

Abstract

Purpose: In this study, it is aimed to compare the serum leptin and PAI-1 levels and evaluate their relationship in children on hemodialysis (HD) and peritoneal dialysis (PD). **Method:** Thirty-six patients on HD (mean age: 15.0 ± 2.8 years), 19 patients on PD (mean age: 13.0 ± 3.5 years) and 15 healthy subjects (mean age: 14.5 ± 2.7 years) were included in the study. Laboratory investigations included blood count, biochemical parameters, serum iron, iron binding capacity, parathormone, erythrocyte sedimentation rate, C-reactive protein (CRP), prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, serum leptin and PAI-1 levels. **Results:** Serum leptin levels were significantly higher in HD group than in control group when the effects of BMI and sex were controlled, while PD and control groups had similar leptin levels. PAI-1 levels were also significantly higher in HD group than in control group, while there was no statistically significant difference in PAI-1 levels of PD and control group. PAI-1 levels and leptin levels were significantly correlated, which was independent of the effect of BMI in both HD and PD groups when they are evaluated separately. **Conclusion:** Results of our study showed that HD patients had higher leptin and PAI-1 levels and leptin and PAI-1 levels were correlated significantly in both patient groups. The effect of elevated serum leptin and PAI-1 levels on the cardiovascular complications remains to be established.

Keywords

Children, dialysis, leptin, plasminogen activator inhibitor-1

History

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Introduction

Cardiovascular complications are among of the major causes of mortality in adults and 25% of mortality in children with end stage renal disease (ESRD).^{1,2} In recent years, the well-known relation between obesity and cardiovascular mortality has been evaluated on the basis of insulin resistance and dyslipidemia.³ Especially, definition of functions of hormone “leptin” has resulted in a variety of studies. Leptin is secreted from adipocytes and has a key role in the regulation of body weight.³ Its plasma concentration is elevated in chronic renal disease. Similarly, it is known that disorders of fibrinolytic system are important in the development of atherosclerosis and cardiovascular disease (CVD).^{4,5} Plasminogen activator inhibitor-1 (PAI-1) is the inhibitor of plasmin which is the key enzyme in fibrinolytic system. Elevation in PAI-1 has been suggested to be a risk factor for CVD.⁵

Studies on general population and other disease groups have shown that leptin and PAI-1 levels are related.^{6,7} On the basis of data summarized above, the relationship between leptin and PAI-1 levels in patients with ESRD can have a role in CVD. Review of the literature revealed no study evaluating

the leptin and PAI-1 levels together in children with ESRD. In this study, we aimed to evaluate the relationship between serum leptin and PAI-1 levels and compare their levels in hemodialysis (HD) and peritoneal dialysis (PD) groups.

Materials and methods

Thirty-six patients (19 female, 17 male) on HD, 19 patients (10 female, 9 male) on PD and 15 healthy subjects (9 female, 6 male) were included in the study. The inclusion criteria for the study were normal liver function, no recent sign of inflammation or known thrombosis, and no blood transfusion within the last month. The patients on HD underwent 4 h of treatment 3 times weekly and were dialyzed using a hemophane membrane. All these children were dialyzed via arteriovenous fistulae and with bicarbonate-buffered solution. The patients on PD were dialyzed with 1.36–3.86% glucose containing dialysate.

The age, the disease causing ESRD, the time period from the start of chronic dialysis, drugs used, dose of erythropoietin, height and weight of the subjects were recorded. The weekly erythropoietin dose, body mass index (BMI) and total cholesterol/HDL ratio of the subjects were calculated.

Blood samples were withdrawn in 08:00 am after 8 h of night-time fasting, before the dialysis session in HD patients and during routine visits in PD patients and control subjects. Peripheral venous blood samples for PAI-1 levels were

Address correspondence to Pinar Isik Agras, Ministry of Health Ankara Training and Research Hospital, Department of Pediatric Nephrology, Ulucanlar, Ankara, Turkey. Tel: +90 312 5953262; Fax: +90 312 5953116; E-mail: pinaris2001@yahoo.com

obtained without venous stasis, by using 21 G needles and put into tubes containing 0.3 mL 3.8% sodium citrate. After sampling, platelet free plasma was obtained by centrifuging at 1000rpm for 15 min and stored at -20°C until the analysis.

Laboratory investigations included blood count, biochemical parameters, serum iron, iron binding capacity, ferritin, erythrocyte sedimentation rate, C- reactive protein (CRP), prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, serum leptin and PAI-1 levels.

The study was approved by the local ethical committee (Baskent University Research Committee Project No: KA03/76, 2003. Informed consent was taken for each patient.

Leptin was measured by radioimmunoassay (RIA) using a commercially available kit (Linco Research, Inc., St. Charles, MO). PAI-1 was measured by colorimetric assay using the commercially available kit (Chemi-Con International, Inc., Cat No. ECM610, Temecula, CA).

Logarithmic transformation was performed for the data related to leptin since they were not normally distributed. One-way analysis of variance was used to compare the group findings of continuous variables. Pearson's and Sperman correlation coefficients were used to evaluate the presence and degree of correlations according to the features of variables. Analysis of co-variance was used to exclude the effect of other variables on the specific variable while

comparing the group means. The relation between one dependent variable and two independent variables was evaluated by using multiple regression analysis. All statistical analysis was performed by using the soft ware "SPSS 11.0 for Windows". Probability values less than 0.05 were considered significant.

Results

A total of 70 subjects were included in the study. The age, sex, BMI and some other findings of the groups are summarized in Table 1. The mean age was 15.0 ± 2.8 years in HD, 13.0 ± 3.5 years in PD and 14.5 ± 2.7 years in control group ($p > 0.05$). The groups were not different with respect to age and sex distribution ($p > 0.05$). The mean body weight, height and body mass index (BMI) of HD and PD group were similar ($p > 0.05$), but control group had a significantly higher mean body weight, height and BMI than HD and PD group ($p < 0.05$). There was no difference in the time period from the start of chronic dialysis between HD and PD groups ($p > 0.05$). Hematological findings of the subjects are summarized in Table 2. The mean hemoglobin, hematocrit and thrombocyte levels were lower in HD and PD group than the controls. The mean ferritin levels were higher in HD and PD patients than the controls. The mean PT and PTT levels

Table 1. Demographic and anthropometric findings of study groups.

	Hemodialysis, <i>n</i> = 36	Peritoneal dialysis, <i>n</i> = 19	Control, <i>n</i> = 15	<i>p</i> Value
Age (Years)	15.0 ± 2.8	13.0 ± 3.5	14.5 ± 2.7	>0.05
Sex (Female/Male)	19/17	10/9	9/6	>0.05
Body weight (kg)	34.6 ± 10.9	33.7 ± 11.5	50.5 ± 10.3	<0.05
Height (cm)	141.5 ± 14.4	135.5 ± 16.9	159.9 ± 13.4	<0.05
BMI (kg/m^2)	16.9 ± 3.0	17.7 ± 2.9	19.8 ± 2.9	<0.05
Time period from the start of dialysis (years)	3.5 ± 2.5	3.4 ± 2.5		>0.05
Underlying disease				
Urologic causes	16	8		
Nephronophytosis	2	2		
Chronic glomerulonephritis	9	3		
Tubulointerstitial nephritis	1	–		
Renal agenesis	1	3		
Polycystic kidney disease.	1	1		
Unknown	6	2		
Antihypertensive drug usage	16	9		>0.05
IV Iron usage	3	2		>0.05
IV Vitamin D usage	8	4		>0.05

Data are expressed mean $\pm$ standard deviation.

Table 2. Hematological findings of subjects.

	Hemodialysis, <i>n</i> = 36	Peritoneal dialysis, <i>n</i> = 19	Control, <i>n</i> = 15
Hemoglobin (g/dL)*	9.8 ± 1.8	9.9 ± 1.5	13.0 ± 0.8
Hematocrit (%)	28.8 ± 6.3	28.9 ± 4.1	38.3 ± 2.2
Thrombocytes ($10^5/\text{mm}^3$)*	225 ± 76	282 ± 94	305 ± 80
Serum iron (mg/dL)	71 ± 29	90 ± 58	69 ± 23
Serum iron binding capacity (mg/dL)	230 ± 68	235 ± 39	277 ± 42
Ferritin (ng/mL)*	387 ± 369	333 ± 542	25 ± 20
Erythropoietin/Hematocrit	7.7 ± 3.1	5.8 ± 3.2	–
Erythropoietin dose (units/kg/week)	219 ± 82	167 ± 85	
Prothrombin time (s)	13.9 ± 3.2	14.5 ± 2.1	12.9 ± 0.5
Partial thromboplastin time (s)	36.7 ± 20.9	38.5 ± 30.0	29.0 ± 2.0

* $p < 0.05$.

Table 3. Biochemical parameters and acute phase reactants of subjects.

	Hemodialysis, <i>n</i> = 36	Peritoneal dialysis, <i>n</i> = 19	Control, <i>n</i> = 15
BUN (mg/dL)	72 ± 25	67 ± 16	17 ± 3
Creatinine (mg/dL)	8.2 ± 2.1	10.7 ± 3.0	0.6 ± 0.1
Uric acid (mg/dL)	6.4 ± 2.2	6.7 ± 1.3	4.0 ± 0.9 C
Cholesterol (mg/dL)*	164 ± 39	191 ± 37	158 ± 25
HDL (mg/dL)*	41 ± 15	39 ± 10	53 ± 10
LDL (mg/dL)	94 ± 30	110 ± 32	86 ± 18
VLDL (mg/dL)*	32 ± 13	36 ± 21	17 ± 7
Cholesterol/HDL*	4.3 ± 1.3	4.9 ± 1.2	3.0 ± 0.4
Triglycerides (mg/dL)*	160 ± 73	184 ± 110	86 ± 36
Total protein (g/dL)*	7.1 ± 0.7	6.5 ± 0.9	7.5 ± 0.3
Albumin (g/dL)*	4.2 ± 0.6	3.4 ± 0.6	4.5 ± 0.3
C-Reactive protein (mg/L)*	8.1 ± 8.2	7.5 ± 7.0	2.9 ± 3.1
Erythrocyte sedimentation rate (mm/hour)*	42 ± 25	70 ± 33	12 ± 7
Fibrinogen (mg/dL)*	3.35 ± 0.95	3.48 ± 0.92	2.75 ± 0.54

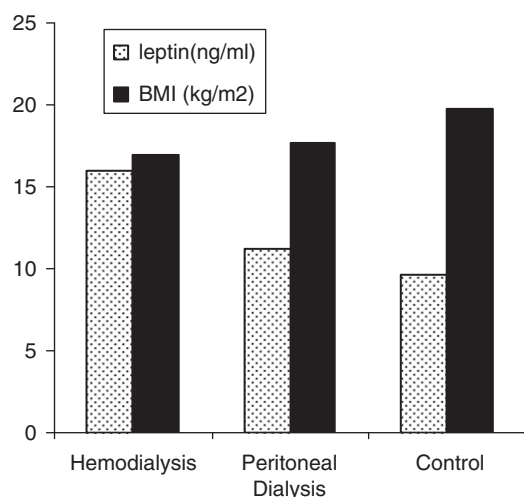
**p* < 0.05.

Figure 1. The mean serum leptin levels and BMI in study groups.

were not different among three groups ($p > 0.05$). Biochemical parameters and acute phase reactants are given in Table 3. The mean total cholesterol level was higher in HD than in PD and control group ($p < 0.05$). The mean HDL, VLDL and triglyceride levels were similar in HD and PD groups ($p > 0.05$), but they were higher than control group ($p < 0.05$). The mean total protein and albumin levels were not different in HD and control group, but they were found to be significantly lower in PD group than other groups ($p < 0.05$).

Erythrocyte sedimentation rate, CRP and fibrinogen levels were higher in HD and PD group compared to control group ($p < 0.05$).

Serum leptin and PAI-1 levels

The mean absolute levels of serum leptin in HD, PD and control groups are shown in Figure 1. Multiple regression analysis showed that the mean log leptin levels were significantly higher in HD group than in control group when the effects of BMI and sex were controlled ($r^2 = 0.523$, adjusted $r^2 = 0.491$, $p < 0.05$), while there was no statistically significant difference between the mean log leptin levels of PD and control group ($r^2 = 0.713$ and adjusted $r^2 = 0.681$, $p > 0.05$).

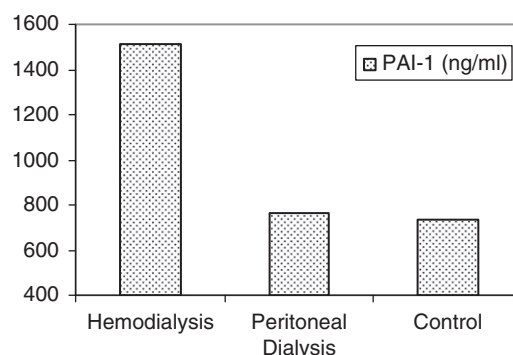


Figure 2. The mean serum PAI-1 levels in study groups.

When the patients are grouped according to total protein level (cut-off level of 6 g/dL) and albumin levels (cut-off level of 4 g/dL), the median serum leptin level was higher in both patient with total protein level higher than 6 g/dL and albumin level higher than 4 g/dL ($p < 0.05$). In analysis of co-variance, BMI was added to the model to eliminate its effect, the difference in serum leptin level according to serum albumin and total protein level persisted ($r^2: 0.471$, adjusted $r^2: 0.454$ and $r^2: 0.514$, adjusted $r^2: 0.599$, respectively, $p < 0.05$).

The mean PAI-1 levels were 1583 ± 206 , 791 ± 220 and 716 ± 253 ng/mL in HD, PD and control groups, respectively. The mean PAI-1 level of HD group was significantly higher than those of control group ($p < 0.05$), while PD and control groups had similar mean PAI-1 levels ($p > 0.05$; Figure 2).

Correlations

The correlations between serum leptin, PAI-1 levels and other parameters are summarized in Table 4.

PAI-1 levels were correlated with log leptin levels, which was independent of the effect of BMI in whole group of subjects ($r^2 = 0.353$, adjusted $r^2 = 0.321$, $p < 0.0001$). After the addition of BMI and sex to the model of linear regression analysis to control their effect, this positive correlation persisted ($r^2 = 0.353$, r^2 adjusted = 0.321, $p < 0.0001$).

The correlation between PAI-1 and log leptin was also examined in HD and PD groups separately. Both in HD and PD group, log leptin and PAI-1 were significantly correlated and the correlation persisted after the effect of BMI was

Table 4. The correlations between log leptin, PAI-1 and age, BMI, dose of erythropoietin, nutritional markers, inflammatory findings and cardiovascular risk factors in the group of patients on hemodialysis and peritoneal dialysis ($n = 55$).

	Log Leptin, (r)	<i>p</i> Value	PAI-1 (r)	<i>p</i> Value
Log leptin (ng/mL)	–	–	0.560	<0.001
PAI-1 (ng/mL)	0.560	<0.001	–	–
Age (years)	0.468	0.003	0.259	0.033
BMI (kg/m^2)	0.581	<0.001	0.296	0.013
Leptin/BMI	0.648	<0.001	0.455	<0.001
Weekly erythropoietin dose (u/kg/week)	0.057	NS	0.464	0.001
Erythropoietin/Hematocrit (u/kg/week/%)	0.081	NS	0.439	0.002
Nutritional markers				
Total protein (g/dL)	0.369	0.003	0.191	NS
Albumin (g/dL)	0.343	0.005	0.216	NS
Inflammatory markers				
ESR (mm/h)	–0.017	NS	–0.394	0.018
C-reactive protein (mg/L)	–0.276	NS	–0.091	NS
Fibrinogen (mg/dL)	0.423	0.001	0.173	NS
Ferritin (ng/mL)	0.001	NS	–0.057	NS
Lipid levels				
Triglyceride (mg/dL)	0.192	NS	0.167	NS
Cholesterol (mg/dL)	0.050	NS	0.113	NS
HDL (mg/dL)	0.006	NS	–0.038	NS
LDL (mg/dL)	0.283	0.035	0.288	0.028
VLDL (mg/dL)	–0.050	NS	0.099	NS
Cholesterol/HDL	0.260	0.049	0.305	0.018

NS, not significant; PAI-1, plasminogen activator inhibitor-1; BMI, body mass index; ESR, erythrocyte sedimentation rate; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein.

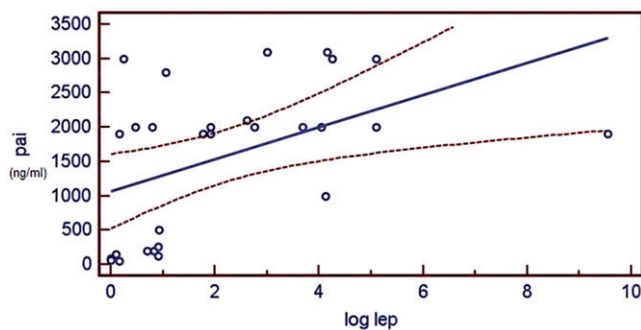


Figure 3. The regression plot of log leptin and PAI-1 in hemodialysis patients.

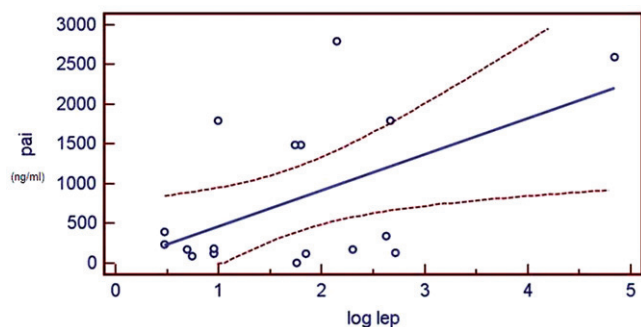


Figure 4. The regression plot of log leptin and PAI-1 in peritoneal dialysis patients.

eliminated ($r^2 = 0.650$, adjusted $r^2 = 0.621$ in HD group and $r^2 = 0.679$, adjusted $r^2 = 0.636$ in PD group, $p < 0.05$). The Figures 3 and 4 demonstrate the regression plots of log leptin and PAI-1 in HD and PD groups, respectively.

There was a significant correlation between log leptin and serum total protein and albumin levels ($r = 0.369$ vs. $r = 0.343$, respectively, $p < 0.05$). The correlation persisted after the effect of BMI was controlled ($r^2 = 0.706$, r^2 adjusted = 0.498 , $p < 0.05$).

Log leptin was significantly correlated with serum total cholesterol/HDL ratio and LDL levels ($r = 0.260$ and $r = 0.283$, respectively, $p < 0.05$). Also Serum PAI-1 level was correlated with total cholesterol/HDL ratio and LDL levels ($r = 0.259$ and $r = 0.296$, respectively, $p < 0.05$).

PAI-1 levels were correlated with weekly erythropoietin dose and erythropoietin/hematocrit ratio ($r = 0.464$ and $r = 0.439$, respectively, $p < 0.05$).

Discussion

Since the kidneys are known to play role in the clearance of many polypeptide hormones like parathyroid hormone and glucagon, leptin is expected to accumulate in renal failure. However, increased leptin level is not a constant finding in patients with ESRD and etiology of increased leptin levels in uremia has not been well understood. Serum leptin levels were higher in patients with the signs of ongoing inflammation.⁸ Daschner et al.⁹ reported that the percentage of body fat remains the main determinant of serum leptin in children with ESRD but their levels increase with declining glomerular filtration. In our study, serum leptin level was found to be higher in HD group after the effect of BMI and sex were eliminated. Review of the literature revealed some studies with a variety of results, some reporting higher leptin levels in HD, some reporting contrary results.^{10–17} In different studies, variety in BMI of patients and other factors affecting the protein binding of leptin can affect leptin levels both in HD

and PD patients. More stable and continuous clearance of free leptin in PD patients can contribute to lower serum leptin levels in PD patients.¹⁸ Also transperitoneal protein loss causing hypoalbuminemia in PD patients can contribute to lower serum leptin levels in PD patients.

Thus, nutritional condition, BMI, sex of the patients, type of filters used and transperitoneal protein loss are the factors affecting serum leptin levels of patients on dialysis. Our results showed higher serum leptin levels in HD patients suggesting that HD patients are exposed more intensively to negative effects of hyperleptinemia.

Human PAI-1 is a single chain glycoprotein with a molecular weight of 43 kDa. Its rapid interaction with tissue plasminogen activator (tPA) may function as a major control point in the regulation of fibrinolysis. High concentrations of PAI-1 have been associated with thromboembolic disease and increased cardiovascular mortality.⁵

In our study, PAI-1 levels were found to be higher in HD group than in control while PD group had similar PAI-1 levels to control group. Review of literature revealed different results. Irish et al.¹⁹ and Tamura et al.² reported lower PAI-1 levels in HD patients than PD and controls. However, many studies have recently demonstrated that endothelial cell related glycoproteins including PAI-1 are increased in HD patients.^{14,16,20–25} These findings are thought to be related to subclinical endothelial injury in ESRD patients.^{2,21} However, there are other factors contributing to higher PAI-1 levels. Chronic inflammation is one of these factors. It has been suggested that recurrent acute phase reaction as a result of cytokine activation due to contact with dialysis membranes can cause increase in PAI-1 as an acute phase reactant.^{19,20} PAI-1 has been shown to be correlated with other acute phase reactants like CRP and IL-6, supporting this hypothesis. Results of our study showed higher ESR, CRP, fibrinogen and ferritin levels in ESRD patients than the controls. However, no significant correlation was detected between PAI-1 levels and these acute reactants.

The most striking finding of our study is the positive correlation between serum PAI-1 and leptin levels. Malyszko et al.¹⁸ demonstrated that leptin was correlated with tissue factor pathway inhibitor, protein C, thrombomodulin and ristocetin induced thrombocyte aggregation. Review of the literature revealed no study evaluating the relation between leptin and PAI-1 in children. Although correlations do not necessarily mean a biological cause-result relationship, we demonstrated increase in leptin levels parallel PAI-1 levels. Leptin is almost completely synthesized in adipose tissue. PAI-1 is known to be synthesized by hepatocytes and endothelial cells but it has been also shown to be synthesized in adipose tissue.⁷ These findings may bring into mind that the parallel increase in PAI-1 and leptin levels are related to body fat mass. However, we showed that the significant correlation between PAI-1 and leptin is independent of BMI. This finding is compatible with the findings of De Mitrio et al.⁷ which showed that PAI-1 levels were correlated with leptin levels independent of BMI in premenopausal women. These findings suggest that leptin may increase the synthesis of PAI-1 by a direct and independent effect. Further study is needed to establish the hypothesis of possible direct effect of leptin on PAI-1 synthesis. The relationship between leptin and

PAI-1 levels suggest that changes in leptin level by its effect on PAI-1, may contribute to tendency to thrombosis and related complications and long-term CVD risk in ESRD patients.

Recombinant human erythropoietin is effective in correcting renal anemia. However, erythropoietin replacement therapy is associated with increased risk of thrombosis. Transient changes in protein C and thrombin-antithrombin III complex during erythropoietin treatment have been demonstrated and may represent markers of prothrombotic tendency.^{25–27} In our study, we demonstrated positive correlation between PAI-1 level and erythropoietin dose/hematocrit ratio. This finding was consistent with previous reports, indicating that erythropoietin therapy suppresses fibrinolytic capacity increasing thrombotic tendency.

In conclusion, the results of our study revealed that serum leptin and PAI-1 levels are higher in HD patients and they are correlated independent of the effect of BMI and sex in both HD and PD patients. The effect of elevated serum leptin and PAI-1 levels on the development of cardiovascular complications in children on chronic dialysis remains to be established.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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