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Associations of Adiponectin with Paraoxonase 1 and sE-Selectin in Hemodialyzed Patients

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Key Words
Hemodialysis · Adiponectin · Soluble E-selectin · Serum paraoxonase 1 · Insulin resistance

Abstract
Background/Aims: In hemodialyzed (HD) patients, adiponectin and sE-selectin levels are elevated, while antioxidant paraoxonase 1 activity (PON1) is decreased. We determined if the hyperadiponectinemia in HD patients has a protective effect on the decrease in PON1 and elevation in sE-selectin in kidney failure. ***Methods and Design:*** Predialysis serum adiponectin, PON1 and sE-selectin as well as other metabolic variables were measured in 70 HD patients. ***Results:*** Adiponectin had (1) no association with PON1 or sE-selectin, (2) a positive association with dialysis efficiency and HDL-C, and (3) an inverse association with BMI, waist circumference, HOMA IR, triglyceride, hsCRP, fibrinogen, and albumin. Moreover, albumin, BMI, and HOMA-IR were independent negative predictors of adiponectin. ***Conclusions:*** In kidney failure, in contrast to normal renal function, higher adiponectin levels had no correlation with PON1 activity or the sE-selectin level. However, adiponectin has an association with dialysis efficiency and, similar to individuals with preserved kidney function, traits of metabolic syndrome. In addition to BMI and HOMA-IR, the serum albumin concentration is also one of the independent negative predictors of the serum adiponectin level. Collectively, these findings may add details to the understanding of the role that adiponectin plays in chronic renal disease related to 'reverse epidemiology'.

Introduction

Adiponectin, a 29-kDa protein, is the most abundant adipose tissue-derived protein in human plasma. Adiponectin has insulin-sensitizing, anti-inflammatory, and anti-atherosclerotic properties; however, adiponectin plays a controversial role in chronic renal diseases [1]. The adiponectin level is increased in kidney failure and decreased shortly after kidney transplantation [2], suggesting that the kidneys play an important role in adiponectin biodegradation and/or elimination. Furthermore, Guebre-Egziabher et al. [3] established that adiponectin is related more to metabolic disturbances than to the decline in renal function in chronic kidney disease. Further, Zoccali et al. [4] demonstrated that adiponectin may act as a protective factor against atherosclerosis in this patient population. These data were confirmed by Takemo-

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to et al. [5] in a Japanese population. In contrast, Menon et al. [6] reported high, rather than low, adiponectin levels are associated with increased mortality in a cohort of patients with chronic kidney failure, and suggested further studies to elucidate the underlying mechanisms. Beige et al. [7] proposed a paradoxical role of adiponectin in chronic renal diseases according to a reverse epidemiology due to the uremic environment that overwhelms the vascular-protective effect of adiponectin.

High-density lipoprotein-cholesterol (HDL-C) has antioxidative characteristics in which one of its associated enzymes, paraoxonase (PON1), plays an outstanding role protecting lipoproteins from oxidative modification [8]. We and others have established that PON1 has reduced activity, among others, in kidney failure [9–11]. Earlier we also determined whether another adipokine that has an elevated level in kidney failure and shows inverse association with PON1 in individuals with preserved kidney function, leptin, is responsible for low PON1 activity [12]. However, we found that hyperleptinemia was not associated with decreased PON1 activity in hemodialyzed (HD) patients. In patients with preserved kidney function, we also demonstrated that the serum adiponectin concentration is correlated with PON1 activity, in addition to HDL-C and triglyceride levels. This relationship was independent of other factors, including HDL-C [13], a finding that may contribute to the anti-atherosclerotic effect of adiponectin.

Based on the anti-atherosclerotic effect of adiponectin, an inverse correlation has been demonstrated in various populations with one of the soluble adhesion molecules, sE-selectin, which is a marker of inflammatory activation in the endothelium [14–16]. In addition, with the high cardiovascular risk of HD patients, an elevated serum level of sE-selectin has been demonstrated in this population, probably due to both inadequate clearance, and enhanced synthesis/release [17].

Kidney failure and obesity have some overlap with respect to our investigation; specifically, in both conditions there are altered levels of adipokines and inflammatory markers, as well as decreased PON1 activity. The aim of the present study was to determine if the uremic hyperadiponectinemia has a protective effect on serum PON1 activity and/or inflammatory activation of the endothelium.

Subjects and Methods

Participants

This cross-sectional study was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association and the requirements of the Ethics Committee of School of Medicine, University of Pecs. The main characteristics of 70 HD patients are shown in table 1. Eighteen of the HD patients had polycystic kidney disease, 13 diabetes nephropathy, 12 glomerulonephritis, 11 pyelonephritis, 8 ischemic renal disease, 4 idiopathic kidney atrophy, 2 nephrotic syndrome and 2 had earlier nephrectomy. Fifty-one of the HD patients took antihypertensive medication, and 19 had diabetes. None of the patients involved in the study had evidence of liver disease, thyroid disorders, or infectious diseases for 3 months prior to study, or triglyceride levels higher than 4.5 mM. The form of hemodialysis treatment was hemodiafiltration (HDF) in every patient, except for 2 of them in whom high flux HD treatment alone could be applied. Kt/V (dialysis efficiency) was calculated by the use of $Kt/V = -\ln(R\ 0.03 - 0.075 \times UF/W)$, where R = ratio of blood urea concentration measured after and before dialysis, UF = volume of ultrafiltrate (l), W = body weight after dialysis (kg). Mean (lower/upper quartile) HD time of patients was 38 (16.7/62.7) months.

Biochemical Analyses

The blood samples were collected before the dialysis sessions. For routine automated laboratory analyses, a modular autoanalyser (Roche, Switzerland) was used. Concentrations of albumin and high sensitivity CRP were measured by turbidimetric immunoassay (Roche Cobas Integra), parathormone and insulin by electro-chemiluminescence immunoassay (Roche Elecsys), fibrinogen by Clauss Derived Fibrinogen assay (Sysmex CA 5000 Coagulation Analyzer). Low-density lipoprotein cholesterol (LDL-C) level was estimated using Friedewald's formula. The insulin resistance index calculation was based on homeostasis model assessment (HOMA-IR). Serum concentration of adiponectin, and sE-selectin were measured by commercially available sandwich enzyme immunoassays (Quantikine; R&D Systems, Minneapolis, Minn., USA).

PON1 activity was determined as described earlier [9]. The increase in the absorbance was measured in the Hewlett-Packard 8453 UV-Visible spectrophotometer at 412 nm, and at 25°C due to the formation of 4-nitrophenol after the addition of 50 µl serum to 1 ml Tris/HCl buffer (100 mmol/l, pH 8.0) containing 2 mmol/l $CaCl_2$, and 5.5 mmol/l paraoxon (*O,O*-diethyl-O-*p*-nitrophenylphosphate; Sigma). Enzymatic activity was calculated using the molar extinction coefficient of 17,100 $M^{-1} \cdot cm^{-1}$. One unit of paraoxonase activity was defined as 1 nmol of 4-nitrophenol formed per minute under the above assay conditions. The intra- and inter-assay coefficients of variation in PON1 activities were <3%.

Statistical Analysis

Statistical analyses were performed using SPSS 11.0 software (SPSS, Inc., Chicago, Ill., USA). Normality of distribution of data was tested by Kolmogorov-Smirnov test. Non-normally distributed parameters were transformed logarithmically to correct their skewed distributions. Differences across paired subgroups were tested with Student's t test. Correlations between continuous variables were assessed by Pearson's test. Backward multiple regression analyses were performed to determine which variables best predicted adiponectin as a dependent variable. Data were expressed as means ± SD in case of normal distribution, and median (lower/upper quartile) in case of non-normal distribution.

Table 1. Anthropometric and selected laboratory characteristics in the whole studied population and the two adiponectin subgroups of HD patients (adiponectin >, or ≤ compared to median 17.6 value, respectively)

	Total population	Adiponectin >17.6	Adiponectin ≤17.6
Number	70	35	35
Age, years[a]	56.2 ± 11.5	55.8 ± 12.5	56.5 ± 10.5
Female/male	37/33	19/16	18/17
BMI[a]	26.4 ± 5.7	24.1 ± 4.3	28.7 ± 6***
Waist, cm[a]	99.8 ± 15.9	93 ± 13.3	106.5 ± 15.6***
Diabetes	19	6	13
Dialysis efficiency, Kt/V[a]	1.58 ± 0.26	1.66 ± 0.22	1.51 ± 0.28*
HD time, months[b]	38 (16.7/62.7)	38 (17/65)	36 (16/55)
Systolic blood pressure, mm Hg[a]	126.9 ± 16.8	126 ± 13.5	128 ± 19.7
Diastolic blood pressure, mm Hg[b]	79 (70/91)	77 (69/86)	81 (70/93)
Creatinine, μmol/l[b]	692.5 (619.3/854.5)	688 (606/938)	697 (627/846)
Albumin, g/l[a]	39.3 ± 3.9	38.3 ± 4.1	40.3 ± 3.5*
hsCRP, mg/l[b]	7.9 (3.5/14.1)	7.5 (1.5/11.1)	8.6 (5/14.2)*
Fibrinogen, g/l[a]	4.2 ± 1.1	3.9 ± 1.2	4.4 ± 0.9
sE-Selectin, ng/ml[a]	38.7 ± 15.9	38.5 ± 17.4	38.8 ± 14.6
Plasma glucose, mM[b]	5.5 (5/6.7)	5.5 (4.8/6.4)	5.4 (5.1/7.7)
HOMA-IR, mU·M^2 [b]	3.5 (1.9/7.9)	2.5 (1.2/5.6)	5.5 (2.8/11)**
Triglyceride, mM[a]	1.9 ± 0.9	1.7 ± 0.8	2.3 ± 0.9**
Total cholesterol, mM[a]	4.6 ± 0.9	4.6 ± 0.9	4.5 ± 1.1
HDL-C, mM[b]	0.90 (0.8/1.2)	1.0 (0.9/1.2)	0.85 (0.78/1)**
LDL-C, mM[a]	3.1 ± 0.9	3.1 ± 0.8	3.2 ± 0.9
Parathormone, pM[b]	29.9 (14.5/59.3)	41.1 (16.3/66.5)	27.0 (10.3/46.6)
Adiponectin, μg/ml[b]	17.6 (13.4/27.6)	27.4 (21.0/47.2)	13.4 (11.0/15.2)***
PON1 activity, U/l[b]	51.2 (35.1/119.2)	50.4 (33.6/121.0)	52.6 (36.6/118.4)

[a] Normal distribution, data are mean ± SD.
[b] Non-normal distribution, data are median (lower/upper quartile).
Significant differences between the adiponectin subgroups: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Results

Subgroup Analyses

As compared to median values, the studied population has been divided into two subgroups: by adiponectin (table 1) as well as by HOMA-IR (table 2). The following investigated characteristics were significantly higher in the lower adiponectin subgroup: BMI, waist, albumin, CRP, HOMA-IR, and triglyceride; while dialysis efficiency and HDL-C were significantly lower. In the more insulin-resistant group, BMI, waist circumference, CRP, glucose, and triglyceride were significantly higher, while dialysis efficiency, HDL-C, and adiponectin were significantly lower. Among the diabetic patients (n = 19), dialysis efficiency and HD time were lower as compared to the non-diabetic groups (n = 51): Kt/V: 1.44 ± 0.22 vs. 1.64 ± 0.25, $p < 0.01$, and 32 (7/40) vs. 39 (19/69) months, $p < 0.05$, respectively.

Univariate Correlations

The following parameters had to be transformed logarithmically to approximate normal distributions: HD time, diastolic blood pressure, creatinine, CRP, plasma glucose, HOMA-IR, HDL-C, parathormone, adiponectin, and PON1 activity.

Pearson correlations between selected variables with special interest are demonstrated in table 3. Adiponectin level was correlated positively with dialysis efficiency, and HDL-C, while negatively with BMI, waist, albumin, CRP, fibrinogen, HOMA-IR, and triglyceride levels. PON1 activity did not have any significant association with the investigated parameters. The correlation pattern of dialysis efficiency was very similar: positive with HDL-C ($R = 0.46$, $p < 0.001$), while negative with BMI ($R = -0.51$, $p < 0.001$), waist ($R = -0.49$, $p < 0.001$), CRP ($R = -0.32$, $p < 0.01$), fibrinogen ($R = -0.30$, $p < 0.05$), and HOMA-IR ($R = -0.33$, $p < 0.01$), but did not show asso-

Table 2. Anthropometric and laboratory characteristics of two HOMA-IR subgroups in HD patients (HOMA-IR ≤, or > compared to median 3.6 value, respectively)

	HOMA-IR ≤3.6	HOMA-IR >3.6
Number	35	35
Age, years[a]	54.5 ± 11.4	57.7 ± 11.6
Female/male	21/14	16/19
BMI[a]	24.3 ± 3.9**	28.4 ± 6.5
Waist, cm[a]	93.4 ± 12.3***	105.9 ± 16.8
Diabetes	4**	15
Dialysis efficiency, Kt/V[a]	1.67 ± 0.21**	1.51 ± 0.27
HD time, months[b]	38 (12/69)	37 (16.7/51.2)
Systolic blood pressure mm Hg[a]	127.7 ± 16.5	126.2 ± 17.6
Diastolic blood pressure mm Hg[b]	76 (68/85)	82 (71/95)
Creatinine, μmol/l[b]	673 (614/811)	758 (617/913)
Albumin, g/l[a]	39.9 ± 4	38.6 ± 3.7
hsCRP, mg/l[b]	5.2 (1.7/9.9)**	9.4 (5.1/22)
Fibrinogen, g/l[a]	4.2 ± 0.9	4.1 ± 1.2
sE-Selectin, ng/ml[a]	39.9 ± 19.8	37.5 ± 11.3
Plasma glucose, mM[b]	5.1 (4.8/5.5)***	6.7 (5.6/8)
HOMA-IR, mU·M^{2}, [b]	1.9 (1.1/2.8)***	7.9 (5.6/11)
Triglyceride, mM[a]	1.7 ± 0.8**	2.2 ± 0.9
Total cholesterol, mM[a]	4.7 ± 0.9	4.4 ± 1.1
HDL-C, mM[b]	1.0 (0.8/1.3)***	0.8 (0.7/0.9)
LDL-C, mM[a]	3.2 ± 0.8	3.0 ± 0.9
Parathormone, pM[b]	28.9 (19.0/65.5)	31.4 (9.6/59.5)
Adiponectin, μg/ml[b]	20.6 (16.2/30.4)**	14.8 (11.0/22.2)
PON1 activity, U/l[b]	55.6 (35.1/117)	46.8 (34.3/127.2)

[a] Normal distribution, data are mean ± SD.
[b] Non-normal distribution, data are median (lower/upper quartile).
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 3. Pearson correlation coefficients of adiponectin and PON1 with selected variables in HD patients

	Adiponectin	PON1
Age	0.021	0.044
BMI	−0.439***	−0.074
Waist, cm	−0.471***	−0.003
Dialysis efficiency	0.351**	0.111
HD time[1]	−0.047	0.067
Systolic blood pressure	−0.059	0.226
Diastolic blood pressure[1]	−0.106	0.125
Creatinine[1]	−0.183	0.096
Albumin	−0.338**	0.027
hsCRP[1]	−0.278*	−0.076
Fibrinogen	−0.290*	−0.031
sE-selectin	−0.060	0.126
Plasma glucose[1]	−0.109	0.084
HOMA-IR[1]	−0.375***	−0.050
Triglyceride	−0.359**	−0.006
Total cholesterol	0.180	−0.045
HDL-C[1]	0.501***	0.055
LDL-C	0.090	−0.077
Parathormone[1]	0.036	0.082
Adiponectin[1]	-	0.011

[1] Log-transformed statistics.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

ciation with albumin ($R = 0.02$, $p = 0.88$) (data not shown in table 3). Trends of correlations were similar in both diabetic and nondiabetic subgroups.

Multivariate Correlations

The independent predictors of adiponectin level were tested in multiple regression models (table 4). At first, two less-adjusted models (models 1 and 2) were constructed in which, beside the albumin, the impact of age, sex, and BMI were tested. In model 3, CRP was also included, while in the more fully adjusted model, model 4, HOMA-IR, as a parameter of metabolic syndrome, was included too. Additionally, we tried to avoid the inclusion of too closely linked variables (e.g. waist along with BMI, or HDL-C along with HOMA-IR) that might have neutralized each others' effects. Of the selected anthropometric and laboratory variables, the correlations of BMI, albumin concentration and HOMA-IR were independent with adiponectin level, while with CRP was not. In other models we also investigated the dialysis efficiency as a variable, but this was not an independent predictor of adiponectin when BMI was also included in the model, beside age and gender (data not shown).

Discussion

In individuals with normal renal function, adiponectin has a positive and independent correlation with the antioxidant, PON1, an enzyme protecting lipoproteins from lipid peroxidation [13], yet an inverse relationship with sE-selectin, a marker of inflammatory activation of the endothelium [14–16]. To the best of our knowledge, this is the first study that has investigated the possible relationship between adiponectin with PON1 and sE-selectin in kidney failure. We found no correlation between PON1 activity and the adiponectin level compared to patients with preserved renal function. This finding may

Table 4. Multiple regression analysis for adiponectin as a dependent variable

Variable	Model 1 ($R^2 = 0.222$)			Model 2 ($R^2 = 0.325$)			Model 3 ($R^2 = 0.354$)			Model 4 ($R^2 = 0.396$)		
	β	t	p	β	t	p	β	t	p	β	t	p
Age	0.149	1.323	0.19	0.075	0.694	0.49	0.068	0.635	0.528	0.095	0.897	0.373
Sex	−0.104	−0.953	0.344	−0.061	−0.59	0.557	−0.073	−0.718	0.476	−0.044	−0.437	0.664
BMI	**−0.476**	**−4.242**	**0.001**	**−0.468**	**−4.448**	**0.001**	**−0.421**	**−3.917**	**0.001**	**−0.358**	**−3.281**	**0.002**
Albumin	–	–	–	**−0.331**	**−3.149**	**0.002**	**−0.331**	**−3.194**	**0.002**	**−0.333**	**−3.271**	**0.002**
hsCRP	–	–	–	–	–	–	−0.179	−1.716	0.091	−0.122	−1.152	0.254
HOMA-IR	–	–	–	–	–	–	–	–	–	**−0.238**	**−2.163**	**0.034**

Significant values indicated in bold; β = standardized regression coefficient.

suggest that the uremia-related elevated adiponectin level has no protective effect on the PON1 activity, which is typically decreased in these patients [9–11]. Furthermore, according to prior investigations [18, 20, 21], while adiponectin has a clear inverse correlation with acute phase proteins (CRP and fibrinogen) produced primarily or exclusively by the liver, we found no association between adiponectin and sE-selectin.

The following slight, but statistically significant differences could be demonstrated in the higher as compared to the lower adiponectin subgroup; the albumin level was slightly lower, while dialysis efficiency was higher. The latter finding existed in the less insulin-resistant subgroup as well. The adiponectin concentration also had an inverse relationship with the serum albumin level.

Many known pathophysiologic pathways of metabolic syndrome can be demonstrated in kidney failure; the abdominal obesity, atherogenic dyslipidemia, and elevation of acute phase proteins are more pronounced in the lower adiponectin and the more insulin-resistant subgroups of HD patients compared to the respective counterparts. Furthermore, the adiponectin level was lower in the more insulin-resistant subgroup and the lower adiponectin subgroup was more insulin resistant. Moreover, similar to previous studies carried out in renal failure [5, 18, 19], the adiponectin concentration was correlated negatively with the measures of adiposity, dyslipidemia, and insulin resistance. Multiple regression analyses showed that not only BMI and HOMA-IR were independent negative predictors of serum adiponectin level, but also the albumin level that is a marker of nutrition. Although by itself the lower insulin resistance in patients with higher adiponectin levels might be beneficial, even in kidney failure, the condition related to uremic malnutrition marked by the lower serum albumin concentration may be more detrimental. Therefore, the inverse relationship between adiponectin and albumin may be an aspect of the pathomechanism existing in the background of chronic renal disease related to the 'reverse epidemiology' of adiponectin [7].

Dialysis efficiency has also shown associations with the metabolic syndrome (a positive association with adiponectin, and a negative association with the measures of adiposity, dyslipidemia, insulin resistance, and acute phase proteins), but not with the serum albumin level. The association between adiponectin and dialysis efficiency has been also shown by Chen et al. [22] in chronic peritoneal dialysis patients. However, in hemodialysis patients, Huang et al. [18] did not find a correlation between dialysis efficiency and the adiponectin level. This discrepancy may be related to the small number of investigated populations (n = 28 vs. n = 70 of our study). The possible relationship between the serum adiponectin concentration and dialysis efficiency is not simply due to the enhanced clearance of adiponectin during HD sessions, since the large molecular weight of adiponectin is minimally removed by dialysis [7, 18]. However, this association between the adiponectin level and dialysis efficiency was not an independent one in a simple regression model that also included BMI.

The limitations of our study were that the investigated population was not large and no healthy control group was included. However, the clinically significant correlations were clearly established, even at this sample size. Moreover, we did not consider it essential to recheck the previously well-documented kidney failure-related alterations of variables, e.g. adiponectin, PON1, and sE-selectin. Furthermore, to reliably demonstrate correlations between PON1 and adiponectin, a larger population with a wide

range of adiponectin (enabled by a wide range of BMI) is needed. Another potential shortcoming of our study was that the various isoforms of adiponectin were not investigated, so it cannot be excluded that a high molecular weight form of adiponectin might be correlated with PON1.

Conclusions

Our findings raise the possibility that the uremic environment, despite the kidney failure-related hyperadiponectinemia, may overwhelm the protective effect of adiponectin against endothelial dysfunction and low PON1 activity. Furthermore, adiponectin has associations with dialysis efficiency and, similar to individuals with preserved kidney function, traits of metabolic syndrome. In addition to BMI and HOMA-IR, the serum albumin concentration is one of the independent negative predictors of the serum adiponectin level. These findings collectively may add to the understanding of the role that adiponectin plays in the chronic renal disease-related 'reverse epidemiology.'

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