Adiponectin and Cardiovascular Outcomes among Hemodialysis Patients

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Key Words

Adiponectin • Cardiovascular disease • End-stage renal disease • Hemodialysis

Abstract

Background: Adiponectin (ADPN) levels are consistently elevated among patients with advanced chronic kidney disease, but its relationship with cardiovascular outcomes in this population remains controversial. The aim of our study was to measure the plasma levels of ADPN in patients with end-stage renal disease on maintenance hemodialysis (HD) and we studied its correlates to cardiovascular outcomes and mortality. **Methods:** Our study included 133 HD patients (79 male and 54 female patients) with a mean age of 54.6 ± 17.3 years who had been receiving regular HD for at least 6 months in the nephrology units of Theodor Bilharz Research Institute, Cairo, Egypt. The clinical and biochemical correlates of plasma ADPN levels were investigated and the predictive power of ADPN levels with respect to cardiovascular events and mortality was prospectively tested in HD patients, who were monitored for 24 ± 9 months. Plasma ADPN levels were measured by using a sensitive enzyme-linked immunosorbent assay. **Results:** Plasma ADPN levels were 3 times higher ($p < 0.0001$) among HD patients ($18.1 \pm 6.8 \mu\text{g/ml}$) than among healthy subjects ($6.2 \pm 1.8 \mu\text{g/ml}$). Plasma ADPN levels were lower ($p < 0.007$) among patients who experienced new cardiovascular events ($13.9 \pm 6.4 \mu\text{g/ml}$) than among event-free patients ($18.6 \pm 8.4 \mu\text{g/ml}$). The relative risk of cardiovascular events was 1.96 times (95%

confidence interval 1.290–2.977, $p = 0.0016$) higher among patients in group 1 (ADPN $< 15.1 \mu\text{g/ml}$), compared with those in group 2 (ADPN $\geq 15.1 \mu\text{g/ml}$). Plasma ADPN levels were inversely related to BMI, insulin levels, homeostatic model assessment index values, triglyceride and LDL-C, CRP and left ventricular mass index. Furthermore, plasma ADPN levels were directly related to HDL-C. **Conclusion:** Plasma ADPN is an independent (inverse) predictor of cardiovascular events and mortality among HD patients. The directions of the relationships between ADPN and several metabolic risk factors indicate that ADPN has a protective role in prevention of CVD.

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Introduction

Adiponectin (ADPN), an anti-inflammatory, antiatherogenic and insulin-sensitizing adipokine exists in several isoforms in the circulation. In patients with chronic kidney disease (CKD), circulating levels of total as well as high-molecular-weight ADPN are elevated [1]. ADPN levels have been shown to be lower in males, obesity, insulin resistance, in patients with type 2 diabetes mellitus, coronary artery disease and essential hypertension [2–6]. In contrast, ADPN is elevated in kidney disease including nephrotic syndrome [7], and particularly in end-stage renal disease (ESRD), with levels up to 3 times higher compared to the normal population [8].

Table 1. Demographic, clinical, and biochemical characteristics of the studied groups

Variables	Control group	All HD patients	p*	HD patients with cardiovascular events	Event-free patients	p**
Number	20	133		53	80	
Age, years	52.4 ± 16.3	54.6 ± 17.3	0.59	56.8 ± 14.6	51.4 ± 13.1	0.027
Gender, male/female	11/9	79/54		31/22	48/32	
Duration of dialysis, months		60.4 ± 18.6		62.3 ± 12.5	58.2 ± 13.4	0.07
BMI	24.5 ± 2.3	23.8 ± 3.6	0.4	22.9 ± 2.6	24.1 ± 2.9	0.016
Systolic blood pressure, mm Hg	118.2 ± 19.4	134.6 ± 24.3	0.004	136.6 ± 23.2	129.21 ± 18.7	0.04
Diastolic blood pressure, mm Hg	74.3 ± 18.4	76.2 ± 19.3	0.68	78.7 ± 16.5	74.2 ± 13.6	0.08
Smokers		34		28	6	
Diabetic patients	–	28		19	9	
Previous cardiovascular events						
Angina pectoris	–	9		8	1	
Myocardial infarction	–	7		5	2	
Stroke	–	4		3	1	
Hemoglobin level, g/dl	13.8 ± 2.3	11.2 ± 1.6	<0.001	10.8 ± 1.3	11.2 ± 1.4	0.09
S. albumin, g/dl	4.2 ± 1.1	3.7 ± 0.9	0.026	36.3 ± 0.8	3.8 ± 0.7	0.13
S. calcium, mg/dl	9.4 ± 1.3	8.5 ± 1.2	0.002	8.3 ± 1.3	8.6 ± 1.4	0.21
S. phosphorus, mg/dl	4.3 ± 0.9	5.6 ± 1.3	<0.001	4.8 ± 1.6	5.7 ± 1.4	0.0008
S. total cholesterol, mg/dl	160.4 ± 37.2	206 ± 48.2	<0.0001	214.3 ± 46.7	198.2 ± 42.3	0.04
LDL-C, mg/dl	112.3 ± 27.2	133.7 ± 38.2	0.017	141.5 ± 36.4	125.7 ± 37.2	0.01
HDL-C, mg/dl	44.8 ± 13.4	38 ± 12.1	0.02	36.7 ± 9.4	43.2 ± 10.3	<0.0003
Triglycerides, mg/dl	137.6 ± 62.3	173.6 ± 71.3	0.03	174.4 ± 63.2	149.5 ± 68.9	0.036
S. glucose, mg/dl	84.6 ± 18.4	120.4 ± 20.6	<0.0001	123.2 ± 18.3	117.6 ± 17.8	0.08
Plasma insulin level, μU/ml	13.6 ± 4.3	18.4 ± 3.7	<0.0001	20.2 ± 2.8	16.3 ± 3.2	<0.0001
HOMA-R index, mM · μU/ml	3.1 ± 1.2	4.8 ± 1.4	<0.0001	5.7 ± 1.6	3.9 ± 1.3	<0.0001
C-reactive protein, mg/dl	1.3 ± 0.1	8.3 ± 2.1	<0.0001	9.4 ± 1.8	7.6 ± 0.9	<0.0001
LVMI, g/m ²	46.2 ± 16.3	108.4 ± 37.5	<0.0001	114.3 ± 32.6	101.5 ± 35.2	0.036
Plasma ADPN, μg/ml	6.2 ± 1.8	18.1 ± 6.8	<0.0001	13.9 ± 6.4	18.6 ± 8.4	<0.0007

* p value between all HD patients and control. ** p value between patients with cardiovascular events and event-free patients.

The rise in ADPN with declining glomerular filtration rate (GFR) is hypothesized to be secondary to diminished renal elimination, though the exact role of the kidney in the biodegradation and excretion of ADPN remains unclear. Recent observational studies have shown ADPN to be a novel risk marker of CVD in patients with stage 1–5 CKD. CVD remains a major cause of premature death in patients with CKD [2]. These prospective studies have revealed that low ADPN levels to be predictive of the development of new cardiovascular events in patients with CKD, including the hemodialysis (HD) population [8–10], while ADPN has been shown to predict the development of type 2 diabetes in renal transplant recipients [11].

Aim of Our Study

We measured the plasma levels of ADPN in patients with ESRD on maintenance HD and studied its correlates to cardiovascular outcomes and mortality.

Patients and Methods

Study Design

Our study included 133 patients with ESRD on maintenance HD (79 male and 54 female patients) with a mean age of 54.6 ± 17.3 years who had been receiving regular HD for at least 6 months, in the nephrology units of Theodor Bilharz Research Institute, Cairo, Egypt. The clinical and biochemical correlates of plasma ADPN levels were investigated and the predictive power of ADPN levels with respect to cardiovascular events and mortality was prospectively tested in our HD patients, who were monitored for 24 ± 9 months (range 1–36). Patients with evidence of circulatory congestion (defined as dyspnea, increased jugular pressure, crackles, interstitial edema in chest X-rays, requiring hospitalization or extra ultrafiltration), malignancy and major infections were excluded from the study. This study protocol was approved by the Human Investigation Review Committee and informed consent was obtained from each participant.

The demographic, clinical, and biochemical characteristics of our patients are detailed in table 1. The control group consisted of 20 healthy subjects matched to dialysis patients with respect to gender and BMI.

Methods

Laboratory Investigations

Heparinized blood samples (15–20 ml) were immediately placed on ice, plasma separated within 30 min of sample collection, aliquoted and stored at -80°C . Total cholesterol, LDL-C, HDL-C, TGs, albumin, hemoglobin, calcium, phosphate, and glucose levels were analyzed using standard methods.

ADPN levels were measured using a commercially available enzyme immunoassay kit (R&D Systems, Minneapolis, Minn., USA). The coefficients of variation for intra- and interassay precision were <5 and $<7\%$, respectively [12, 13]. CRP levels were measured using a high-sensitivity immunoassay (Hemagen Diagnostics Inc., Columbia, Md., USA).

Serum insulin levels were measured by using a RIA kit (Sorin Saluggia, Vercelli, Italy). Insulin sensitivity was estimated by using the homeostatic model assessment (HOMA-R) index (i.e. plasma glucose level $\times$ (plasma insulin level/22.5)), which was validated with the euglycemic-hyperinsulinemic clamp method [14].

An electrocardiogram was done for our patients at the start of the study and during follow-up. Echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography [15]. Left ventricular mass (LVM) was calculated according to the formula described by Devereux et al. [15] and was indexed to height^{2.7} (LVM index, LVMI). Left ventricular hypertrophy was defined as a LVMI of $>47\text{ g/m}^{2.7}$ for women or $>50\text{ g/m}^{2.7}$ for men [16].

Follow-Up of Our Patients

Our patients were monitored for 24 ± 9 months (range 1–36). During the follow-up period, cardiovascular events (anginal episodes or myocardial infarctions, heart failure, arrhythmia, transient ischemic attacks, strokes, peripheral vascular disease, arterial or venous thrombotic episodes) were accurately recorded. Each death was reviewed and an underlying cause was recorded.

Statistical Analyses

Data were expressed as mean $\pm$ SD or percentage. Between groups, comparisons were made with the t test. Relationships between plasma ADPN levels and other covariates were analyzed by using Spearman rank coefficients or the least-squares method. Cox proportional hazards regression was used to evaluate the effect of plasma ADPN on cardiovascular and mortality outcomes. Variables with independent effects on survival rates were identified by constructing hierarchical models. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated with the use of the estimated regression coefficients and their standard errors in the Cox regression analysis. Time-to-event analysis of cardiovascular outcomes was done by using the Kaplan-Meier survival curve. p values <0.05 were considered significant.

Results

Plasma ADPN Levels

The main clinical and biochemical characteristics of the studied groups are summarized in table 1. Plasma ADPN levels among HD patients ($18.1 \pm 6.8\text{ }\mu\text{g/ml}$) were approximately 3 times higher ($p < 0.0001$) than the

Fig. 1. Kaplan-Meier survival curves for analysis of time (months) to cardiovascular events. Patients were divided into two groups according to plasma ADPN levels (group 1, ADPN $<15.1\text{ }\mu\text{g/ml}$; group 2, ADPN $\geq 15.1\text{ }\mu\text{g/ml}$). HR 0.579, 95% CI 0.3352–1.0012, $p = 0.0412$.

average value for healthy subjects ($6.2 \pm 1.8\text{ }\mu\text{g/ml}$) (table 1) and exceeded the upper limit of the normal range for the majority of HD patients (84 of 133 patients, i.e. 63.16%).

Among HD patients, plasma ADPN levels were higher ($p < 0.0059$) for women ($18.6 \pm 8.1\text{ }\mu\text{g/ml}$) than for men ($15.1 \pm 6.3\text{ }\mu\text{g/ml}$), and this difference remained significant after data adjustment for BMI ($p = 0.02$). The gender difference in plasma ADPN levels among HD patients was similar to that observed for healthy control subjects (men $5.3 \pm 1.6\text{ }\mu\text{g/ml}$, women $7.4 \pm 1.7\text{ }\mu\text{g/ml}$).

Plasma ADPN levels were lower ($p < 0.0007$) among patients who experienced new cardiovascular events ($13.9 \pm 6.4\text{ }\mu\text{g/ml}$) than among event-free patients ($18.6 \pm 8.4\text{ }\mu\text{g/ml}$) (table 1). The relative risk of cardiovascular events was 1.96 times (95% CI 1.290–2.977, $p = 0.0016$) higher among patients in group 1 (ADPN $<15.1\text{ }\mu\text{g/ml}$), compared with those in group 2 (ADPN $\geq 15.1\text{ }\mu\text{g/ml}$) (fig. 1).

Biochemical and Clinical Correlates of Plasma ADPN Levels among HD Patients

Plasma ADPN levels were inversely related to BMI ($r = -0.295$, $p = 0.0006$) as well as to insulin levels ($r = -0.2786$, $p = 0.0012$) (fig. 2a) and HOMA-R indices and serum glucose levels among both men and women ($r = -0.406$, $p = 0.003$).

Fig. 2. **a** Correlation between plasma ADPN and plasma insulin levels in HD patients ($r = -0.2786$, 95% CI -0.4285 to -0.1138 , $p = 0.0012$). **b** Correlation between plasma ADPN and HDL-C in HD patients ($r = 0.4232$, 95% CI 0.2726 – 0.5536 , $p < 0.0001$). **c** Correlation between plasma ADPN and CRP in HD patients ($r = -0.4732$, 95% CI -0.5955 to 0.3296 , $p < 0.0001$). **d** Correlation between plasma ADPN and LVMI in HD patients ($r = -0.6211$, 95% CI -0.7157 to -0.5042 , $p < 0.0001$).

Plasma ADPN levels were also inversely related to serum LDL-C ($r = -0.412$, $p = 0.03$) and TGs levels for both genders ($r = -0.526$, $p < 0.0001$). Plasma ADPN levels were directly related to plasma HDL-C ($r = 0.423$, $p < 0.0001$) (fig. 2b).

Plasma ADPN levels were inversely related to CRP ($r = -0.473$, $p < 0.0001$) (fig. 2c), and also inversely related to LVMI ($r = -0.621$, $p < 0.0001$) (fig. 2d).

Plasma ADPN levels were lower ($p < 0.04$) among diabetic patients ($12.9 \pm 1.7 \mu\text{g/ml}$) than among nondiabetic patients ($17.1 \pm 1.6 \mu\text{g/ml}$).

Plasma ADPN levels were unrelated to age ($p = 0.16$), smoking ($p = 0.23$), duration of dialysis ($p = 0.18$), mean arterial pressure ($p = 0.56$), and serum albumin levels ($p = 0.14$).

Cardiovascular Events and Mortality during Follow-Up

Fifty-three cardiovascular events (fatal or nonfatal) occurred during the follow-up period. Using univariate and multivariate analysis, plasma ADPN seem to predict cardiovascular events in unadjusted analysis ($p = 0.05$) and the strength of the association is increased after adjustment for patient-related variables ($p < 0.01$) (table 2).

A total of 36 patients died, 77.8% (28/36) of all deaths were due to cardiovascular causes. Plasma ADPN levels seem to predict overall cardiovascular mortality ($p < 0.01$), using univariate and multivariate analysis after adjustment for patient-related variables. Although the relationship between ADPN and all-cause mortality did not

Table 2. Univariate and multivariate Cox regression models for the relationship between ADPN levels and outcomes

Variables	All-cause mortality			Cardiovascular events/mortality		
	HR	95% CI	p	HR	95% CI	p
Unadjusted analysis						
ADPN	1.10	0.74–1.19	0.06	0.98	0.95–0.99	0.05
Age	1.02	1.00–1.04	<0.01	1.04	1.02–1.06	<0.01
Male gender	0.86	0.60–1.40	0.31	0.86	0.59–1.24	0.36
Smoking	1.46	1.00–2.12	0.05	1.52	1.03–2.25	0.03
Mean BLP	0.99	0.96–1.70	0.72	0.98	0.96–1.10	0.42
Cholesterol	0.99	0.94–1.10	0.13	0.98	0.92–1.02	0.24
HDL-C	0.87	0.69–1.25	0.30	1.00	0.99–1.01	0.21
Diabetes	1.16	0.80–1.68	0.34	0.89	0.59–1.32	0.55
LVH	1.16	1.00–1.35	0.05	1.75	1.13–2.71	0.01
Previous CVD	1.56	1.02–2.38	0.04	1.64	1.60–2.62	0.03
Duration of HD	1.20	1.03–1.41	0.13	1.05	0.88–1.23	0.52
Albumin	0.74	0.42–1.27	0.26	1.03	0.59–1.77	0.94
CRP	1.16	1.00–1.35	0.05	1.14	0.98–1.31	0.06
Final adjusted analysis						
ADPN	1.17	1.08–1.28	<0.01	1.23	1.11–1.32	<0.01
Age	1.03	1.01–1.06	<0.01	1.14	1.12–1.18	<0.01
Smoking	1.70	1.13–2.61	0.01	1.94	1.26–3.00	<0.01
LVH	2.86	1.37–6.88	0.02	2.47	1.02–6.76	0.04
Previous CVD	2.46	1.47–3.03	0.002	2.38	1.32–4.31	0.002
Duration of HD	1.37	1.16–1.64	<0.01	1.28	1.06–1.55	0.02
CRP	1.20	1.02–1.41	0.03	1.01	1.00–1.02	0.01

reach significance in the unadjusted Cox regression model ($p = 0.06$), progressive adjustment for patient-related variables increased the strength of the association ($p < 0.01$) (table 2).

Discussion

The present study demonstrates that, independently of diabetes mellitus, plasma ADPN levels are markedly increased among HD patients and seem to be related to metabolic risk factors such as insulin levels and insulin sensitivity (HOMA-R index), TGs, LDL-C and HDL-C. Furthermore, our data demonstrate that the gender dependence of plasma ADPN levels is maintained in advanced renal failure. ADPN levels are inversely related to BMI, which is again in line with data for healthy subjects and diabetic patients [4].

In our study, ADPN levels have been shown to vary inversely with CVD and mortality and all-cause mortality suggesting a potential protective role for ADPN against the development of cardiovascular events in patients with kidney disease.

This association is consistent with several studies. Zoccali et al. [8] showed that each 1 $\mu\text{g/ml}$ increase in ADPN concentration was associated with a 3% risk reduction in new cardiovascular events in HD patients. Analogous results have been observed in nondiabetic patients with stage 3–4 CKD [9], where patients who developed new cardiovascular events had significantly lower ADPN levels (odds ratio 0.72, 95% CI 0.58–0.89, $p = 0.002$). In a recent study, Iwashima et al. [10] showed that ADPN levels were significantly higher in patients with more severe kidney impairment as assessed by CKD stage. After dividing the patients into a high and low group based upon gender-specific median values of ADPN, the low ADPN group had a significantly shorter event-free survival compared to the higher group ($<4.39 \mu\text{g/ml}$ in men, $<6.84 \mu\text{g/ml}$ in women, $p < 0.03$). Low plasma levels of ADPN were associated with inflammation and preexisting CVD; ADPN levels predicted cardiovascular and mortality outcomes, the relationship being extensively confounded by multiple patient-related factors [17].

In contrast to our study and the above findings, Me-non et al. [18], in their analysis of 820 patients with a GFR

range of between 13 and 55 ml/min from the MDRD (Modified Renal Diet) database, revealed a direct correlation between ADPN and the relative risk of cardiovascular mortality. In multivariable adjusted Cox models, a 1 µg/ml increase in ADPN was associated with a 3% (HR 1.03, 95% CI 1.01–1.05, $p = 0.02$) elevated risk for all-cause and 6% (HR 1.06, 95% CI 1.03–1.09, $p = 0.001$) higher risk for cardiovascular mortality. The direct correlation between ADPN and CVD in the MDRD study may be due to a residual confounding effect of reduced renal function or processes accompanying CKD, but unadjusted for reduced GFR. For example, the mean GFR and ADPN in the MDRD was 32 ml/min and 6 µmol/l respectively, in comparison to 63 ml/min and 12 µmol/l corresponding in the study by Becker et al. [9], highlighting the strong association between ADPN and GFR.

In contrast to initial studies, several recent and large studies on outcomes do not support a protective effect of high ADPN on CVD and overall mortality in CKD patients. Paradoxically, high ADPN predicts increased overall and cardiovascular mortality in CKD patients. This effect seems unrelated to direct effect of ADPN, but rather due to a process of protein-energy wasting [1].

In our study, the directions of the relationships between ADPN and several metabolic risk factors, such as insulin, TGs, and HDL-C, are all in agreement with the hypothesis that ADPN may have a protective role for the cardiovascular system among HD patients. Relatively higher ADPN levels were associated with better cardiovascular outcomes among HD patients. However, ADPN levels were increased, in comparison with healthy subjects, not only among patients without CVD, but also among those who developed cardiovascular complications in large proportions.

Low serum concentrations of HDL-C are associated with increased CVD risk in the general population, as well as in patients with chronic renal failure [19]. Our study demonstrated that HD patients with cardiovascular events had lower HDL levels than event-free patients, but not statistically significant.

We also demonstrated that ADPN varied inversely with CRP ($p < 0.0001$). In multiple studies, ADPN has been shown to be inversely associated with markers of inflammation including CRP [20, 21]. ADPN has also been shown to exhibit anti-inflammatory activity in atherosclerotic experimental models [22, 23]. In addition, ADPN ameliorates vascular VSMC proliferation by inhibition of mitogen-activated protein kinase, increases production of nitric oxide and tissue inhibitor of metalloproteinase-1, resulting in vasodilatation and decrease in plaque rupture, respectively [24].

It can be hypothesized that in ESRD the biologic phenomena underlying the cardiovascular protective role of ADPN must be downregulated, perhaps at the receptor level, thus resetting at a higher plasma concentration the relationship between this protein and cardiovascular damage and clinical complications.

Hyperinsulinemia and in cultured endothelial cells, high concentrations of cystatin C abolish the vasculoprotective effect of ADPN [25]. This hypothesis must be fully tested in *in vitro* and *in vivo* experiments, to better elucidate the role of this most interesting cytokine in human diseases. Limitation to this study that we did not evaluate nutritional status in our study and protein-energy wasting is very important for cardiovascular events and mortality and we need to follow-up ADPN levels measurements in relation to cardiovascular events and mortality.

Conclusion

We found a significant inverse relationship between plasma ADPN and CVD and mortality outcomes in HD patients. The directions of the relationships between ADPN and several metabolic risk factors, such as insulin, TGs, and HDL-C, indicate that ADPN has a protective role in prevention of CVD.

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