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ORIGINAL PAPERS

PROGNOSTIC VALUE OF PLASMA ADIPONECTIN IN TYPE 2 DIABETIC DIALYSIS PATIENTS

Ina Maria Kacso[1], Alina Lenghel[1], I. M. Patiu[2], Simona Racasan[2], R. Orasan[2], Crina Claudia Rusu[1], Diana Moldovan[1], Cosmina Ioana Bondor[3], Cristina Nita[4], N. D. Hancu[4], Mirela Gherman Caprioara[1]

[1.] Nephrology Department "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj Napoca
[2.] Nefromed Dialysis Center Cluj
[3.] Biostatistics Department "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj Napoca
[4.] Diabetology Department "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj Napoca

Abstract. Background: Adiponectin, an insulin-sensitizing, anti-inflammatory and antiatherogenic adipokine, seems to conserve its protective effect against cardiovascular complications in dialysis patients. In diabetic dialysis patients however results are less consistent, higher adiponectin levels being associated with mortality. We intend to study the prognostic value of plasma adiponectin for atherosclerotic complications and all-cause mortality in type 2 diabetic patients on hemodialysis in a multicenter trial; we hereby present our pilot study. Material and methods: All (28) diabetic patients on maintenance hemodialysis in our center were included in the study. History, clinical data, routine laboratory assessment and total plasma adiponectin were obtained. Patients were compared to a control group of 20 nondiabetic hemodialysis patients. During 1 year of follow-up, new occurrence of cardiovascular complications due to atherosclerosis (myocardial infarction and revascularization, amputation or revascularization due to arteriosclerosis obliterans, stroke) and all-cause mortality were recorded. Results: Type 2 diabetic dialysis patients had lower adiponectin levels than dialysis controls (21.08±3.17/ml versus 39.00±10.11μg/ml, p=0.03). In simple regression, adiponectin was correlated to body mass index (r=-0.43, p=0.01) and serum triglycerides (r=-0.62, p=0.0003); in multiple stepwise regression, triglycerides remained the only predictor of plasma adiponectin (p=0.01). Adiponectin levels were higher in women than in men (28.73±5.76 μg/ml versus 15.33±2.88 μg/ml, p=0.03). There was a statistically significant difference in plasma adiponectin levels between patients with proliferative retinopathy and patients without this condition (27.22±4.87 μg/ml versus 16.46±3.91 μg/ml, p=0.02). Patients with new onset of cardiovascular events had lower adiponectin levels than controls (12.76±3.52 μg/ml versus 23.34±3.81 μg/ml but the difference did not reach statistical significance, probably due to the small number of patients. Baseline adiponectin was higher in deceased patients than in survivors (29.87±10.32 μg/ml versus 19.61±3.29 μg/ml); again, statistical significance was not reached due to the small cohort. The number of patients to be included in the multicenter trial in order to attain statistical significance for each arm of the above mentioned comparisons was calculated. Conclusions: In diabetic patients treated with hemodialysis, lower adiponectin levels were found in patients with new onset of complications of atherosclerosis, while increased adiponectin might predict all-cause mortality. Further large-scale prospective studies are required to confirm these findings.
Keywords: adipokines, hemodialysis, atherosclerosis, diabetes, inflammation, mortality

Introduction

Body fat is not merely a storage tissue, but also has an active endocrine function, as products of adipocytes and infiltrating inflammatory cells secrete adipokines with various metabolic

Ina Maria Kacso
Spitalul Clinic Judeţean de Urgenţă Cluj
3-5 Clinicilor Str., Cluj-Napoca, Romania
email: inakacso@yahoo.com

functions. Adiponectin is an anti-inflammatory, antiatherogenic and insulin-sensitizing adipokine, with lower levels characterizing disease states like obesity, metabolic syndrome and type 2 diabetes [1]. Increase of plasma adiponectin in renal patients parallels decrease in glomerular filtration rate (GFR) [2], dialysis patients having higher adiponectin levels compared to the general population or to predialysis chronic kidney disease patients. Whereas in nondiabetic patients on dialysis adiponectin seems to conserve its known protective effects against cardiovascular morbidity [3-10], it is unclear if in diabetic patients on dialysis elevated adiponectin levels maintain the above-mentioned favorable prognostic significance, an increase in mortality in patients with higher adiponectin being reported [11]. The aim of our research is to determine whether plasma adiponectin levels predict cardiovascular morbidity due to atherosclerosis or overall mortality in type 2 diabetic hemodialysis patients in a multicenter trial setting; we hereby present a pilot study.

Material and methods

All patients with type 2 diabetes mellitus on maintenance hemodialysis in our center were included in the study. 20 nondiabetic patients on hemodialysis served as controls. All patients signed an informed consent. All patients were undergoing standard three-times weekly hemodialysis using high flux synthetic membranes. History (including presence of retinopathy and neuropathy), clinical examination, current medication, routine laboratory analysis (automated analyzer), blood glycated hemoglobin (HbA1c – chromatography), serum C-reactive protein (CRP) and total plasma adiponectin (CYBER- ELISA total adiponectin) were obtained. A cardiovascular score was calculated by assigning 1 point for each preexisting cardiovascular event (myocardial infarction or revascularization, stroke, revascularization or amputation due to lower limb arteriosclerosis obliterans).

Statistic analysis was performed using SPSS 13.0, StatView 7.0 and Microsoft EXCEL programs.

For identifying correlations between two normally distributed continuous variables, Pearson's correlation coefficient (r) was used; for non-normally distributed continuous variables Spearman's (r) coefficient was employed. This was followed by linear univariate and multivariate regression using enter and stepwise methods to estimate correlation between two or more quantitative variables. Coefficients, confidence intervals and statistical significance of each parameter are presented.

For comparison of means of normally distributed continuous variables, the t test was used. If distribution of variables was not normal, the Wilcoxon test was employed. For testing normal distribution, the Kolmogorov-Smirnov test was applied. Statistic significance threshold was considered $\alpha=0.05$. Values are expressed as mean ± standard error of the mean.

The study was approved by the ethical committee of our university.

Results

28 type 2 diabetic patients currently on hemodialysis in the Nefromed Dialysis Center Cluj were included; 20 nondiabetic age and sex-matched patients on dialysis served as controls. General characteristics of patients and comparison to controls are presented in table I.

In nondiabetic patients on dialysis, adiponectin levels were significantly higher than in diabetic patient (39.00±10.11 versus 21.08±3.17, p=0.03); diabetic patients displayed an unfavorable lipid profile and a significantly higher inflammatory state (as quantified by CRP) when compared to nondiabetic dialysis controls.

Adiponectin was higher in female than in male patients (28.73±5.76 versus 15.33±2.88, p=0.03).

In simple regression, plasma adiponectin levels were correlated to BMI (r=-0.43, p=0.01) and serum triglycerides (r=-0.62, p=0.0003), the latter remaining significant in stepwise multiple regression (p=0.003 for the model) (table II).

Baseline cardiovascular score, presence or absence of treatment with conversion enzyme inhibitors or angiotensin receptor blockers (used in 43% of patients), statins (used in 39% of patients) or presence of neuropathy (present in 21% of patients) did not correlate to total baseline plasma adiponectin levels. However, patients with proliferative retinopathy (43% of patients) had higher adiponectin levels (27.22±4.87 μg/ml) than patients without proliferative diabetic nephropathy (16.46±3.91 μg/ml), the difference being statistically significant (p=0.02).

All patients were followed-up for one year. During this timeframe no complications of atherosclerosis or deaths occurred in the control group. Out of the diabetic patients, 6 patients developed new atherosclerotic cardiovascular events (1/patient)

	Diabetic dialysis patients (n=28)	Nondiabetic dialysis patients (n=20)	
Age (years)	62.29±1.34	62.80±3.20	NS
Gender (% male)	58	70	NS
SBP (mmHg)	135±2	126±7	NS
DBP (mmHg)	77±1	77±3	NS
BMI	31.41±8.38	27.92±1.98	NS
HDL cholesterol (mg/dl)	36.72±3.26	53.45±4.22	0.01
LDL cholesterol (mg/dl)	157±35	112±62	0.03
Triglycerides (mg/dl)	235±36	139±26	NS
Albumin (g/dl)	3.76±0.06	3.86±0.06	NS
CRP (mg/dl)	2.27±0.61	0.49±0.15	0.0007
Hb (g/dl)	11.20±0.32	11.95±0.35	NS
HbA1C %	6.79±1.38	ND	
Adiponectin (μg/ml)	21.08±3.17	39.00±10.11	0.03

Table I. General characteristics of patients and comparison to controls
Legend: SBP – systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index, HDL – high density lipoproteins, LDL – low density lipoproteins, CRP – C-reactive protein, Hb – hemoglobin, HbA1C – glycated hemoglobin

	Unstandardized Coefficients B	Std. Error	Standardized Coefficients beta	p	95% Confidence Interval for B	
					Lower Bound	Upper Bound
(Constant)	42.22	12.52	3.37	0.003	16.10	68.35
BMI	-0.69	0.35	-1.99	0.060	-1.42	0.03
HDL chol.	0.32	0.16	1.96	0.064	-0.02	0.67
TG	-0.04	0.01	-2.73	0.013	-0.07	-0.01

Table II. Multiple stepwise regression with adiponectin as dependent variable
Legend: BMI – body mass index, HDL – high density lipoproteins, LDL – low density lipoproteins, TG – triglycerides

as follows: one patient died of acute myocardial infarction, 2 patients needed coronary stenting for unstable angina, 3 patients needed surgical interventions for aggravation of lower limb arteriosclerosis obliterans (two amputations and one aorto-femural by-pass).

4 diabetic patients died (one of acute myocardial infarction, 2 of sepsis and one of massive gastrointestinal bleeding).

When patients were divided according to occurrence of new atherosclerotic events, almost twofold lower levels of adiponectin were found in the patients with new onset of atherosclerotic complications (12.76±3.52) than in those without such events (23.34±3.81), although statistical significance was not reached. A comparison of these subgroups of patients is presented in table III and a comparison of their adiponectin levels is presented in figure 1.

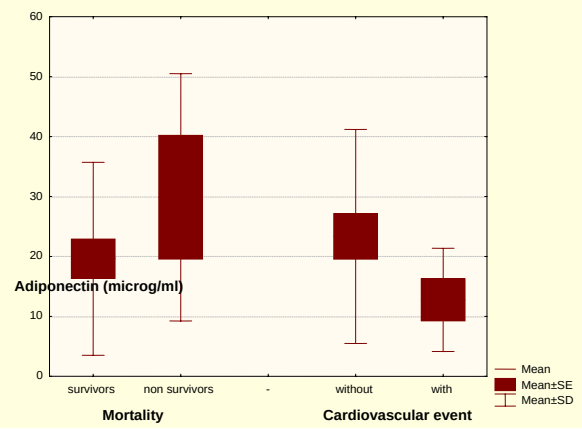

Figure 1. Comparison of adiponectin levels in subgroups according to atherosclerotic cardiovascular events and mortality

Parameter	Complication of atherosclerosis		P
	Present (n=6)	Absent (n=22)	
Age (years)	62.50±1.54	62.23±1.66	NS
SBP (mmHg)	130±3	136±3	NS
DBP (mmHg)	73±2	78±1	NS
BMI (kg/m^2)	32.15±2.24	31.22±1.94	NS
HDL cholesterol (mg/dl)	39.22±9.03	36.15±3.55	NS
LDL cholesterol (mg/dl)	150±30	160±13	NS
Triglycerides (mg/dl)	239±82	235±40	NS
Hb A1C (%)	6.78±0.88	6.80±0.25	NS
Albumin (g/dl)	3.75±0.14	3.76±0.07	NS
Hb (g/dl)	11.53±0.58	11.10±0.38	NS
CRP (mg/dl)	2.49±0.71	2.20±0.78	NS
Adiponectin (μg/ml)	12.76±3.52	23.34±3.81	NS

Table III. Comparison between patients according to the occurrence of new atherosclerotic cardiovascular events during follow-up

Legend: SBP – systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index, HDL – high density lipoproteins, LDL – low density lipoproteins, HbA1C – glycated hemoglobin, Hb – hemoglobin, CRP – C-reactive protein

Parameter	Survivors (n=24)	Nonsurvivors (n=4)	p
Age (years)	62.75±1.41	52.50±4.21	NS
SBP (mmHg)	135±3	132±3	NS
DBP (mmHg)	77±1	75±3	NS
BMI (kg/m^2)	32.16±1.78	26.97±2.04	NS
HDL cholesterol (mg/dl)	35.98±3.46	42.63±11.19	NS
LDL cholesterol (mg/dl)	165±13	115±27	NS
Triglycerides (mg/dl)	260±39	92±19	NS
Hb A1C (%)	6.96±0.28	5.83±0.60	NS
Albumin (g/dl)	3.81±0.06	3.46±0.22	0.05
Hb (g/dl)	11.12±0.34	11.68±1.02	NS
CRP (mg/dl)	2.22±0.70	2.53±1.17	NS
Adiponectin (μg/ml)	19.61±3.29	29.87±10.32	NS

Table IV. Comparison of survivors with deceased patients according to presence or absence of atherosclerotic cardiovascular events during follow-up

Legend: SBP – systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index, HDL – high density lipoproteins, LDL – low density lipoproteins, HbA1C – glycated hemoglobin, Hb – hemoglobin, CRP – C reactive protein

When patients were divided according to mortality, patients who died during follow-up had higher adiponectin levels compared to survivors. A comparison of these subgroups is shown in table IV and a depiction of their adiponectin levels, in figure 1.

Discussion

It is known that type 2 diabetic patients have lower adiponectin levels than those in the general population, hypoadiponectinemia being implicated in the pathogenesis of diabetes, obesity and insulin

resistance [1]. This difference in adiponectinemia was conserved in our dialysis patients: type 2 diabetes mellitus patients had statistically significant lower adiponectin levels than nondiabetic ones. It is noteworthy that adiponectin levels of both diabetic (21.08±3.17 μg/ml) and nondiabetic (39.00±10.11 μg/ml) dialysis patients were substantially higher than those found by us in a previous study in healthy controls (14.57±3.56 μg/ml – not published) and type 2 diabetic patients with normoalbuminuria (6.98±0.82 μg/ml) or albuminuria (10.87±2.09 μg/ml) [12].

In our patients, adiponectin levels correlated inversely with BMI and triglycerides, the latter remaining the only significant predictor of adiponectin in multiple regression analysis, data in line with the literature [3, 13, 14, 15]. The fact that the correlation of adiponectin to BMI disappeared in multiple regression reflects previous findings showing that dependency of plasma adiponectin to body mass and composition is attenuated in dialysis patients [16]. We also found that gender dependency of adiponectin was maintained in dialysis patients, higher adiponectin levels being found in female rather than in male patients, as it has previously been reported [3].

In nonrenal patients it is currently accepted that higher adiponectin levels are protective for cardiovascular morbidity due to atherosclerosis [17]. On the other hand adiponectin levels increase as the GFR falls, reaching the highest levels in dialysis patients, as already mentioned. It seems therefore paradoxical that these patients exhibit an extremely high prevalence of atherosclerosis and hence a morbi-mortality due to this condition. There are numerous confounding factors that can be implicated in this apparent contradiction: first - modification of the ratio between different circulating forms of adiponectin with lower ratio of high molecular weight form /total adiponectin and thus modification of biological activity [18]; second - wasting and inflammation within the malnutrition-inflammation-atherosclerosis syndrome - the microinflammatory state accompanying this condition triggers an increase in adiponectin on one hand and accelerates atherogenesis on the other hand [19]; third - interference of cardiac function and fluid overload, via pro BNP (brain natriuretic peptide) with adiponectin levels [11]. Other potential mechanisms may also intervene. Thus, the proinflammatory and atherogenic milieu of uremia may overwhelm the protective effects of adiponectin and this may be one of the reasons of conflicting results reported in the literature with regard to the predictive role of adiponectin. In nondiabetic dialysis patients several prospective multicenter trials seem to confirm the protective effects of adiponectin either on mortality, or on occurrence of cardiovascular events related to atherosclerosis [3-10], although association of high adiponectin with mortality has also been reported [20]. Data on the prognostic value of adiponectin in diabetic patients on dialysis are scarce; one large study, relying on patient population of the 4D study showed that low adiponectin levels predict worse overall mortality [11].

In order to try and contribute to the clarification of this matter, we designed a prospective multicenter trial aiming to ascertain the prognostic value of adiponectin as a predictor of future cardiovascular events or of mortality in diabetic dialysis patients; we present here our pilot study, including all type 2 diabetic patients in our dialysis center.

Patients with new onset of atherosclerotic complication had *lower* values of adiponectin than patients without such events, the difference was not however statistically significant. This is probably due to the small number of patients; at least 10 patients in each group would have been required in order to obtain a significant difference with alpha error 5% and beta error 50% and at least 17 in each arm for an alpha error 5% beta error 30% respectively. Considering the relative frequency of events between the two subgroups, at least 46 patients would be required in the first case, and 80 in the second case.

In contrast to this finding, patients who died during the follow-up period had *higher* adiponectin levels than survivors. Again, the difference failed to be statistically significant; at least 11 patients in each group would have been required in order to obtain a significant difference with alpha error 5% and beta error 50% respectively, and at least 19 in each arm for an alpha error 5% beta error 30%. Considering the relative frequency of deaths between the two subgroups, at least 51 patients are required in the first case and 88 in the second case.

Explanation of these apparently conflicting results is difficult, but it might well be that adiponectin retains its antiatherogenic properties in type 2 diabetic patients on dialysis as well, lower levels being associated with development and complication of plaques. On the other hand, adiponectin being an anti-inflammatory molecule, it may increase reactively in states of severely exacerbated inflammation

like sepsis or wasting, conditions leading in some instances to death. In these situations, adiponectin levels cannot efficiently counteract inflammation and therefore become merely a marker of severity of the inflammatory state. Indeed, in our patients, 2 out of 4 deaths were due to sepsis. Our results are in line with the fact that high adiponectin levels predict combined cardiovascular endpoints, sudden death and stroke, but not myocardial infarction in diabetic patients on dialysis [11]; also overall mortality is predicted by high plasma adiponectin but coronary artery disease is not in nondiabetic dialysis patients [20].

We did not find a statistically significant correlation of CRP to adiponectin and data in the literature are also conflicting [3, 4, 7, 10, 15, 21], it is possible that not the absolute value of adiponectin but its rise or decrease in relation to triggering events could be of clinical significance [11].

It is noteworthy that 3 of 6 patients with atherosclerotic events had complications due to lower limb arteriosclerosis obliterans; association of low adiponectin levels to this condition has previously been documented. [22, 23].

A very interesting finding concerns higher levels of adiponectin in patients with proliferative diabetic retinopathy. This is in line with previous data in the literature reflecting association of high levels of adiponectin to severity of retinopathy in different subjects [24-27] although adiponectin itself has been shown to reduce microvascular neovascularization [28]. Again, reactively increased adiponectin levels seem to reflect the severity of underlying inflammation. To our knowledge this is the first report of association of high adiponectin to retinopathy in type 2 diabetic patients on hemodialysis.

Conclusion

In diabetic patients treated with hemodialysis, lower adiponectin levels are found in patients with new onset of complications of atherosclerosis, while increased adiponectin may predict all-cause mortality. Large-scale prospective studies are required to confirm these findings.

Conflict of interest:

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