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Original Article

Association between Low Adiponectin Level and Cardiovascular Complications in Diabetic and non Diabetic Patients with End Stage Renal Disease

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Abstract

Introduction: Adiponectin is a collagen-like protein synthesized by adipose tissue that has anti-inflammatory and anti-atherogenic properties. We aimed to evaluate adiponectin levels in end stage renal disease (ESRD) patients with and without diabetes mellitus and its relation to the presence of cardiovascular complications (CVC).

Methods: The study included 20 healthy subjects who served as controls (group I), 20 non-diabetic ESRD patients without CVC (group IIA), 20 non-diabetic ESRD patients with CVC (group IIB), 20 diabetic ESRD patients without CVC (group IIIA) and 20 diabetic ESRD patients with CVC (group IIIB). Evaluation included mean arterial blood pressure (MABP), body mass index (BMI), fasting plasma glucose, fasting plasma insulin, homeostasis model assessment for insulin resistance (HOMA-IR), lipid profile, and serum adiponectin levels.

Results: Adiponectin level in the control group was 6.4±1.2 mcg/ml, and was significantly lower than both group II and III (P<0.01). Adiponectin was also significantly lower in group III compared to group II (11±3.9 versus 13.1±4.1 mcg/ml, P<0.01). Patients in group IIB were found to have a lower adiponectin level than group IIA (11.3±2.9 versus 14.9±4.5 mcg/ml, P < 0.01). Patients in group IIIB were also found to have a lower adiponectin level than group IIIA (9.0±2.5 versus 12.9±4 mcg/ml, P < 0.01). Adiponectin level had a significant positive correlation with HDL-C and a significant negative correlation with MABP, BMI, plasma insulin, HOMA-IR, LDL-C, triglycerides and cholesterol in all subgroups.

Conclusion: Adiponectin level was higher in ESRD patients compared to controls. Adiponectin level was lower in diabetic ESRD patients compared to non-diabetic patients, and lower in ESRD patients with CVC compared to patients without CVC.

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Introduction

Atherosclerotic complications are the leading cause of high cardiovascular mortality rates among patients with end stage renal disease (ESRD) [1]. Classic risk factors partly explain the high cardiovascular risk of these patients [2]. Adiponectin is a novel collagen-like protein synthesized by white adipose tissue that circulates at relatively high (2-20 mcg/ml) serum concentrations [3]. It has gained attention for its role in glucose and lipid metabolism. There is also a strong positive relationship between adiponectin level and insulin sensitivity [4].

Adiponectin is reported to be present in human blood, with its plasma levels accounting for 0.01% of total plasma proteins [5]. Plasma adiponectin level is decreased in obesity suggesting that the dysregulation of adiponectin may be relevant to obesity-linked disorders [6]. It is also reduced in type 2 diabetes, insulin-resistant states, coronary artery disease and dyslipidemia [7, 8]. Adiponectin has anti-atherogenic properties [9]. In fact, adiponectin has been shown to suppress all processes involved in atherosclerotic vascular changes, including the expression of adhesion molecules in vascular endothelial cells and proliferation of vascular smooth muscle cells [10]. Adiponectin plays an important role in inhibition of the inflammatory response, perhaps because it suppresses the attachment of monocytes to endothelial cells [9]. This may explain why low levels of adiponectin are associated with adverse metabolic states such as diabetes [11], metabolic syndrome [12], dyslipidemia [13], lipodystrophy and atherosclerotic cardiovascular disease [14].

Plasma adiponectin levels are dependent on glomerular filtration rate, being markedly increased among patients with renal impairment [2] and also in ESRD patients on

Table 1: Comparisons of clinical and laboratory parameters between different groups of the study

Characteristics	Group I	Group II	Group III
Age (years), mean ± SD	50.6 ± 5.6	52.0 ± 6.8	51.5 ± 7.1
Male gender, %	70%	67.5%	70%
BMI (kg/m^2), mean ± SD	23.85 ± 0.99*	26.83 ± 4.2	26.24 ± 3.75
Waist hip ratio, mean ± SD	0.774 ± 0.157*	0.961 ± 0.14	0.925 ± 0.12
Mean arterial blood pressure (mmHg), mean ± SD	91.99 ± 4.5	99.9 ± 19.6	106.5 ± 16.2
Cholesterol (mg/dl), mean ± SD	165.0 ± 25*	226.3 ± 43.8†	249.9 ± 47.0
Triglycerides (mg/dl), mean ± SD	124.5 ± 16.5*	165.4 ± 40.7†	244.7 ± 69.9
High density lipoprotein (mg/dl), mean ± SD	57.3 ± 8.3*	45.3 ± 7.5†	40.1 ± 6.6
Low density lipoprotein (mg/dl), mean ± SD	132.6 ± 26.6*	214.0 ± 53.0†	238.8 ± 56.7
Glucose (mg/dl), mean ± SD	91 ± 6	93 ± 9	216 ± 36‡
Insulin (microU/ml), mean ± SD	5.54 ± 0.58	5.65 ± 0.99	17.75 ± 5.09‡
HOMA-IR, mean ± SD	1.28 ± 0.14	1.31 ± 0.29	9.65 ± 3.34‡
Creatinine (mg/dl), mean ± SD	0.85 ± 0.19*	10.96 ± 2.65	11.92 ± 2.45
Adiponectin (mcg/ml), mean ± SD	6.44 ± 1.22*	13.09 ± 4.12†	10.97 ± 3.85

* $P < 0.01$ when comparing group I with both groups II and II
† $P < 0.01$ when comparing groups II and III
‡ $P < 0.01$ when comparing group III with both groups I and II

maintenance hemodialysis (HD) and peritoneal dialysis (PD) [15]. Most of the interest in adiponectin arises from its potential protective role for the cardiovascular system [16]. Chronic renal failure is the only known disease to be associated with increased plasma adiponectin concentrations, therefore it represents a useful model for elucidation of the potential clinical implications of this substance. However, hyperinsulinemia, which is a well known metabolic complication of chronic renal failure, might down regulate plasma adiponectin levels among dialysis patients [17].

Plasma adiponectin is associated with a decreased cardiovascular risk in non-renal patients [8]. This study was planned to evaluate the levels of adiponectin in uremic patients with and without diabetes and study any relationship between adiponectin level and certain variables: insulin resistance status (HOMA-IR), body mass index (BMI), waist hip ratio (WHR), mean arterial blood pressure (MABP), lipid profile, glucose and creatinine levels. We also aimed to find out the possible association of the hormone with cardiovascular complications (CVC) in ESRD patients: angina, myocardial infarction, cerebrovascular stroke.

Methods

This study was carried out in the Internal Medicine and Clinical Biochemistry Departments, Faculty of Medicine, Zagazig University. It included 100 subjects that were classified into 3 groups: a control group (group I) comprised of 20 apparently healthy volunteers, a group of 40 ESRD patients maintained on regular HD who were not diabetic (group II), and a group of 40 ESRD patients maintained on regular HD who were also diabetic (group III). Both group II and group III contained 20 subjects without evidence of cardiovascular complications (groups IIA and IIIA) and 20 subjects with evidence of cardiovascular complications (groups IIB and IIIB).

All patients and control subjects were submitted to comprehensive history taking and complete clinical examination including blood pressure measurement and assessment of mean arterial blood pressure (MABP), body mass index (BMI) and waist to hip ratio (WHR). They were screened by resting ECG and echocardiography for evidence of left ventricular hypertrophy. Laboratory investigations included fasting and two hours post-prandial blood glucose, urine analysis, complete blood count, blood urea and serum creatinine, and lipid profile including total cholesterol, serum triglycerides (TG), high density lipoprotein cholesterol (HDL-C) and low density

Table 2: Correlation coefficient (R) between adiponectin level and some studied parameters in different subgroups*

	Group IIA		Group IIB		Group IIIA		Group IIIB	
	R	P	R	P	R	P	R	P
HOMA-IR	- 0.47	<0.05	- 0.55	<0.01	- 0.51	<0.01	- 0.48	<0.05
Creatinine (mg/dl)	- 0.20	NS	- 0.36	NS	- 0.41	NS	- 0.22	NS
Age (year)	- 0.49	<0.05	- 0.48	<0.05	- 0.75	<0.01	- 0.50	<0.05
BMI (kg/m^2)	- 0.51	<0.01	- 0.46	<0.05	- 0.55	<0.01	- 0.48	<0.05
WHR	- 0.34	NS	- 0.30	NS	- 0.55	<0.01	- 0.18	NS
MABP (mmHg)	- 0.51	<0.01	- 0.47	<0.05	- 0.47	<0.05	- 0.46	<0.05
Cholesterol (mg/dl)	- 0.44	<0.05	- 0.46	<0.05	- 0.53	<0.01	- 0.48	<0.05
Triglycerides(mg/dl)	- 0.45	<0.05	- 0.52	<0.01	- 0.48	<0.05	- 0.48	<0.05
HDL (mg/dl)	0.69	<0.01	0.47	<0.05	0.69	<0.01	0.48	<0.05
LDL (mg/dl)	- 0.52	<0.01	- 0.48	<0.05	- 0.03	NS	- 0.67	<0.01
Glucose (mmol/L)	0.47	<0.05	0.46	<0.05	0.49	<0.05	- 0.22	NS
Insulin (microU/ml)	- 0.47	<0.05	- 0.46	<0.05	- 0.46	<0.05	- 0.45	<0.05

* Group IIA: 20 non-diabetic hemodialysis patients with no evidence of CVC; group IIB: 20 non-diabetic hemodialysis patients with CVC; group IIIA: 20 diabetic hemodialysis patients with no evidence of CVC; group IIIB: 20 diabetic hemodialysis patients with CVC

HOMA-IR: homeostasis model assessment for insulin resistance; BMI: body mass index; WHR: waist hip ratio; MABP: mean arterial blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein

lipoprotein cholesterol (LDL-C). Fasting plasma insulin was also measured, and insulin resistance by homeostasis model assessment (HOMA) index was determined by the following formula:

HOMA-IR index = fasting insulin (microU/ml) x fasting plasma glucose (mmol/L) / 22.5

Subjects were categorized as insulin resistant if their HOMA-IR index was greater than 1.64. Estimation of adiponectin serum level was performed by human adiponectin ELIZA kit 96-well plate (cat.# EZHADP-61K), linco research.

Results

Table 1 shows some differences in clinical and laboratory parameters between the study groups. The three study groups had similar age and gender distribution, but healthy controls had significantly lower BMI and WHR than ESRD patients. The control group had higher cholesterol, TG and LDL-C levels and lower HDL-C levels than ESRD patients. ESRD patients with and without diabetes did not differ in mean BMI and WHR, but ESRD patients with diabetes had significantly higher serum cholesterol, TG, and LDL-C and significantly lower HDL-C.

Serum adiponectin level was significantly higher in ESRD patients compared to controls ($P < 0.01$). However, ESRD patients with diabetes had significantly lower adiponectin level than ESRD patients without diabetes ($P < 0.01$).

Adiponectin level had no significant correlation with glucose level or HOMA-IR index in any group, but showed significantly negative correlation with insulin level in the control group ($R = -0.5$, $P < 0.05$). It had no correlation to BMI in any group, but showed significant positive correlation with WHR in group III ($R = 0.5$, $P < 0.01$). Adiponectin level was negatively correlated with MABP in group II ($R = -0.3$, $P < 0.05$) and group III ($R = -0.4$, $P < 0.05$) but not in healthy volunteers. Adiponectin level was not correlated to cholesterol level in any group, but was negatively correlated to TG level in both groups II and III ($R = -0.3$, $P < 0.05$), negatively correlated to LDL-C in group II ($R = -0.4$, $P < 0.05$), and positively correlated to HDL-C in group II ($R = 0.8$, $P < 0.01$) and group III ($R = 0.8$, $P < 0.05$). Table 2 shows the correlation coefficient between adiponectin level and some studied parameters in different subgroups.

Patients with ESRD who were not diabetic (group II) included 20 patients with evidence of CVC (seven patients had history of myocardial infarction, ten patients had angina, and three patients had history of stroke).

Table 3: Comparisons of clinical and laboratory parameters of ESRD patients who are not diabetic (group II) between patients with (group IIB) or without (group IIA) cardiovascular complications

	Group IIA	Group IIB
Age (years)	51.3 ± 7.6	52.8 ± 6.1
Male gender	70%	65%
Duration on HD (years)	2-5	3-6
BMI (kg/m^2)	26.6 ± 4.2	27.1 ± 4.4
WHR	1.02 ± 0.14	0.90 ± 0.16†
MABP (mmHg)	106.2 ± 12.4	93.7 ± 23.5*
Cholesterol (mg/dl)	208.0 ± 24.5	244.8 ± 51.3†
Triglycerides (mg/dl)	136.3 ± 24.4	194.6 ± 32.0†
HDL (mg/dl)	51.0 ± 6.4	39.8 ± 3.1†
LDL (mg/dl)	184.2 ± 21.9	243.9 ± 58.5†
Glucose (mg/dl)	88 ± 7	99 ± 9†
Insulin (microU/ml)	5.4 ± 0.6	5.9 ± 1.3
HOMA-IR	1.2 ± 0.1	1.4 ± 0.4†
Creatinine (mg/dl)	10.1 ± 1.7	11.8 ± 3.2*
Adiponectin (mcg/ml)	14.9 ± 4.5	11.3 ± 2.9†

* statistically significant, $P < 0.05$
† statistically significant, $P < 0.01$

BMI: body mass index; WHR: waist hip ratio; MABP: mean arterial blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA-IR: homeostasis model assessment for insulin resistance

This subgroup of patients with CVC were found to have a significantly lower adiponectin level (11.3±2.9 versus 14.9±4.5 mcg/ml, $P < 0.01$) compared to patients without CVC (Table 3).

Patients with ESRD who were also diabetic (group III) included 20 patients with evidence of CVC (six patients had history of myocardial infarction, ten patients had angina, and four patients had history of stroke). This subgroup of patients with CVC were found to have a significantly lower adiponectin level (9.0±2.5 versus 12.9±4 mcg/ml, $P < 0.01$) compared to patients without CVC (Table 4).

Among HD patients with evidence of CVC, diabetic patients had a significantly lower adiponectin level than non-diabetics (9±2.5 versus 11.3±2.9 mcg/ml, $P<0.01$). Among HD patients without evidence of CVC, diabetic patients also had a significantly lower adiponectin level than non-diabetics (12.9±4 versus 14.9±4.5 mcg/ml, $P<0.01$).

Discussion

This study revealed a significantly higher adiponectin level in uremic patients with and without diabetes mellitus compared to control subjects. These results are consistent with those obtained by Zoccali *et al* [18], who have observed that adiponectin levels are markedly increased among patients with ESRD. The increase in adiponectin levels in our uremic patients may be due to impaired adiponectin clearance by the kidney [2].

Also, our study revealed a significantly lower serum adiponectin levels in uremic diabetic patients (group III) as compared to uremic non-diabetic patients (group II), both of which were still higher than controls. The current study confirmed the negative relation between diabetes and adiponectin level by revealing a significantly lower adiponectin levels when comparing diabetic to non-diabetic patients irrespective of the presence or absence of CVC. These results are supported by studies of both Yang *et al* [19] and Steffes *et al* [4] who have shown that adiponectin decreases in insulin resistant and diabetic patients, although they studied diabetic, non uremic, patients. The reduced levels of adiponectin in diabetic patients may be due to the inhibitory effect of adiponectin on the tumor-necrosis factor (TNF) pathway which contributes to insulin resistance [5]. However, despite the reduction in adiponectin level in diabetic uremic patients it remains higher than control group. This may be due to the presence of renal failure which reduces the clearance of adiponectin.

Our study revealed a significant negative correlation between adiponectin and each of HOMA-IR and insulin in all patient subgroups (groups IIA, IIB, IIIA and IIIB). These results are in agreement with those obtained by both Zoccali *et al* [18] and Matsubara *et al* [13] who reported that hyperinsulinemia down-regulates plasma adiponectin levels in dialysis patients (non-diabetic and diabetic). Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration was found to precede a decrease in whole-body insulin sensitivity in humans [20].

The present study demonstrated a significant negative correlation between serum adiponectin level and BMI in subgroup analysis. Our results go in harmony with those obtained by Zoccali *et al* [18] who reported that adiponectin levels are significantly reduced among obese subjects in comparison with lean, healthy control subjects. The link between BMI and adiponectin seems to be a causal one because weight loss induces a marked increase in plasma adiponectin levels among both normal individuals and type 2 diabetic patients [21]. The inverse relation between adiponectin and BMI suggests the

Table 4: Comparison of clinical and laboratory parameters of ESRD patients who are also diabetic (group III) between patients with (group IIIB) or without (group IIIA) cardiovascular complications

	Group IIIA	Group IIIB
Age (years)	51.7±7.6	51.4±6.8
Male gender	70%	70%
Duration on HD (years)	3-6	4-8
BMI (kg/m^2)	26.7±4.4	25.8±3.1
WHR	0.98±0.10	0.87±0.12†
MABP (mmHg)	107.5±17.0	105.4±15.8
Cholesterol (mg/dl)	234.1±48.6	265.9±40.5*
Triglycerides (mg/dl)	207.7±70.7	281.8±46.2†
HDL (mg/dl)	42.5±8.2	37.7±3.2*
LDL (mg/dl)	233.0±57.6	284.6±43.4†
Glucose (mg/dl)	218±34	214±38
Insulin (microU/ml)	18.5±5.5	17.0±4.6
HOMA-IR	10.2±3.5	9.1±3.2
Creatinine (mg/dl)	11.9±2.0	11.9±2.9
Adiponectin (mcg/ml)	12.9±4.0	9.0±2.5†

* statistically significant, $P < 0.05$
† statistically significant, $P < 0.01$

BMI: body mass index; WHR: waist hip ratio; MABP: mean arterial blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA-IR: homeostasis model assessment for insulin resistance

presence of a feedback inhibition process as the total body fat mass increases, perhaps by increased secretion of other adipokines, such as TNF-α which has been shown to decrease the expression of adiponectin from cultured adipocytes [22]. Another possibility is the decrease in metabolic function of aged adipocytes which became not only more insulin resistant but also had decreased gene expression of adiponectin compared to young adipocytes [23].

The current study revealed significant negative correlation between serum adiponectin level and serum cholesterol, serum TG, serum LDL in all patients subgroups, as well as significant positive correlation with serum HDL. These results are in agreement with those obtained by both Deborah *et al* [24] and Zoccali *et al* [18] who have observed a negative correlation between adiponectin and cholesterol, TG and a positive correlation between adiponectin and HDL. The present study revealed a significant negative correlation between serum adiponectin level and MABP in all uremic patients subgroups. Our results are consistent with those obtained by both Emilio *et al* [25] and Iwashima *et al* [26] who found an inverse relation between adiponectin and blood pressure and reported that adiponectin decreases with increases in blood pressure, even in young and normal weight individuals without insulin resistance. The main possible reasons for the negative association between adiponectin and blood pressure may be an increase in the sympathetic nervous activity which inhibits adiponectin gene expression via adrenergic stimulation and the induced activation of the renin angiotensin system in the adipose tissue by hypoadiponectinemia [27]. The relation between serum adiponectin level and insulin resistant status in our work is consistent collectively with those obtained by Salvado *et al* [28], who found that plasma adiponectin levels are significantly reduced in obese subjects, insulin resistant and diabetic patients, and that they increase after weight loss [20].

The present study revealed a significant decrease in serum adiponectin level when comparing non-diabetic patients with CVC (group IIB) to non-diabetic patients without CVC (group IIA), and between diabetic patients with CVC (group IIIB) when compared to diabetic patients without CVC (group IIIA). That is to say that the cardiovascular complications (angina, myocardial infarction, cerebrovascular stroke) increase with reduced serum adiponectin level. It appears that the reduced level of adiponectin in uremic patients increases the risk of cardiovascular complications irrespective to the absence or presence of diabetes. Our results go with the results of Ouchi *et al* [9] who demonstrated that adiponectin levels were reduced among patients with cardiovascular complications, although they studied non-diabetic non-uremic patients. Also, our results are consistent with the results of Hotta *et al* [5] who found that subjects with higher adiponectin levels had a significantly decreased risk of myocardial infarction even after adjustment for LDL, HDL levels, BMI, history of diabetes and hypertension at baseline. This relation between adiponectin and cardiovascular risk may be explained by binding of adiponectin to matrix proteins such as collagen I, III and V but not collagen II and IV or laminin or fibronectin [29]. This may explain why it accumulates in injured vascular tissue only, where it may be involved in the repair process. Adiponectin interferes with TNF-α induced endothelial cell NF-ƙ B signaling [30] and inhibits phagocytic activity of macrophages. The initial steps in atherogenesis comprise increased expression of adhesion molecules on endothelial cells, permitting monocyte adhesion and invasion. Adiponectin is thought to inhibit the endothelial expression of adhesion molecules VCAM-1, ICAM-1 and E-selectin, which is

triggered by inflammatory cytokines, such as TNF-α. Also, adiponectin suppresses production of cytokines for example, TNF-α in macrophages. Similar results were obtained by Zoccali *et al* [2] who have suggested that adiponectin may be a strong and independent (inverse) predictor of cardiovascular outcomes among these patients.

In our study, the directions of the relationships between adiponectin and several metabolic risk factors, such as insulin, triglycerides, cholesterol LDL and HDL, are all in agreement with the hypothesis that adiponectin may have a protective role for the cardiovascular system in ESRD (diabetic and non-diabetic) patients. Atherosclerosis is currently regarded as an inflammatory disease, and there is evidence that atherosclerosis is strongly associated with inflammation among uremic patients. If the inflammatory response detected in atherosclerotic lesions is effectively counteracted by adiponectin in vivo, then this protein may have the potential for prevention and/or retardation of atherogenesis in various diseases, including chronic renal failure.

Conclusion

Serum adiponectin level increases in uremic patients with and without diabetes in comparison to control, although diabetic uremic patients have lower levels than non-diabetic uremic patients. These high levels were negatively correlated to dyslipidemia and insulin resistance. Uremic patients with cardiovascular complications had lower level of adiponectin irrespective of the presence or absence of diabetes. Cardiovascular complications may be predicted in uremic patients who have lower levels of this unique hormone.

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