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Adiponectin Plasma Levels and Albuminuria in Patients with Type 2 Diabetes and Different Stages of Diabetic Kidney Disease

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Abstract

Adiponectin is an inflammatory cytokine produced by adipose tissue and its protective role has been recognized in the pathogenesis of obesity. A lower concentration in obesity patients is noted, in conditions of resistance to insulin, diabetes mellitus, and CKD. Patients with type 2 diabetes mellitus have a potential risk of atherosclerosis, while low concentrations of adiponectin are considered as predictor for the occurrence of complications in patients with type 2 diabetes. The aim of this study was to investigate in patients with type 2 diabetes mellitus with and without diabetic nephropathy the correlation of adiponectin levels and CKD stage or degree of albuminuria. We studied 119 patients with type 2 diabetes mellitus with different stage of renal function, the levels of plasma adiponectin, and the BMI. A statistically significant difference of plasma adiponectin levels was noted between the initial and end stages of CKD, the highest levels seen in ESKD patients. Also, the levels of adiponectin were elevated in patients with greater albuminuria (statistically significant difference between groups 1 and 3, $p=0.05$). The levels of adiponectin were found to decrease with increasing the stage of obesity (ANOVA, $p<0.05$). Finally, the group of patients receiving glitazones had higher plasma adiponectin levels compared to those not receiving. It concluded that the levels of adiponectin increase with the deterioration of renal function and with enhancement of albuminuria, while decreasing as the stage of obesity worsens. The administration of glitazones was associated with increased plasma levels of adiponectin.

Keywords: Adiponectin; Body mass index; Chronic kidney disease; Proteinuria; Obesity; Diabetes mellitus type 2

Introduction

Adipose tissue is an endocrine organ producing a plurality of biologically active peptides, which are involved in the pathogenesis of disorders associated with obesity, glucose homeostasis, inflammation and cardiovascular disease (CVD). It was discovered in 1995, and belongs to a novel class of anti-inflammatory cytokines [1,2]. Initially it was not considered particularly important, but its protective role in the pathogenesis of the different disorders was identified and its association with obesity was later recognized. Indeed, since 2001, several studies have been published showing the antidiabetic, anti-atherosclerotic and anti-inflammatory properties of this protein complex [3-5].

Adiponectin is produced solely by mature adipocytes. However, its concentrations are reduced in obesity, in conditions with resistance to insulin, in diabetes mellitus (DM) and in CVD [6]. Reduced adiponectin appears to precede the mentioned diseases [7], while low concentrations are associated with type 2 diabetes mellitus and CVD appearance [8].

Several factors in uremia, such as inflammation, oxidative stress and sympathetic over activity, reduce the expression of adiponectin, while others such as chronic kidney disease (CKD) and albuminuria have been associated with increased levels of adiponectin [9]. However, there is a controversy concerning CKD and the increased levels of adiponectin [10]. It has been found that in patients with established diabetic nephropathy, high levels of adiponectin possibly indicate a normal response of the body, which will prevent the further progression of damage with its anti-inflammatory effects [11]. Thus, low concentrations of adiponectin are considered as a prognostic factor for patients with complications of type 2 diabetes mellitus, who actually have a potential risk of atherosclerosis.

The aim of this study was to investigate the correlation between serum adiponectin levels in the stage of CKD, the degree of albuminuria in patients with type 2 diabetes mellitus (with and without diabetic nephropathy) and the relation of plasma adiponectin levels with body mass index (BMI) and the glitazones taken.

Patients and Methods

Subjects

A total of 119 unrelated patients of Caucasian origin were included in the study. The criteria for determining subjects with type 2 diabetes mellitus for inclusion in the study have been described before [12]. All eligible patients who consented to participate in the study had to have a documented history of type 2 diabetes for at least 10 years. Established diabetic nephropathy was defined by microalbuminuria

(3-30 mg/mmol creatinine) or persistent albuminuria (>30 mg/mmol creatinine) in two out of three consecutive measurements in sterile spot urine sample during a 6-month period, presence of diabetic retinopathy (DR) and absence of other kidney or urinary tract disease [13,14].

DR was included in the eligibility criteria for this study, since it is frequent in the presence of diabetic nephropathy and is a clue for its diagnosis. DR was assessed by fundoscopy, after pupillary dilatation. The ophthalmologic exam result was classified as normal, nonproliferative and proliferative retinopathy. Patients were considered to have DR if they showed nonproliferative or proliferative stage. Alternatively, the patients might have had a history of retinal laser surgery (photocoagulation) for DR. The diagnosis and classification of CKD stages were established according to the criteria from the Clinical Practice Guidelines for Chronic Kidney Disease from the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative [15]. Absence of diabetic nephropathy (controls) was defined as absence of diabetic retinopathy, eGFR above 60 ml/min/1.73 m^2, and persistent normoalbuminuria (0-3 mg/mmol creatinine) after at least 10 years of type 2 diabetes. Patients with clinical or laboratory evidence of nondiabetic nephropathy or urinary tract disease were excluded from the study. All stage 5 CKD patients had been under regular hemodialysis, for at least 6 months, and were dialyzed thrice weekly for 4 hours per session (CKD-5). Patients with clinical or laboratory evidence of non-diabetic nephropathy or other disease of the urinary excluded from the study.

All diabetics were regular patients at the Diabetes Clinic and Nephrology Clinic of the University General Hospital of Alexandroupolis, Greece and gave a written informed consent. The study was approved by the Ethics Committee of the Scientific Council of the University General Hospital of Alexandroupolis and was in accordance with the Helsinki Declaration of Human Rights.

Methods

Fasting blood sample was obtained from all patients and plasma was stored at -20ºC until analysis. Blood samples were collected from hemodialysis patients after an overnight fasting of 8 h, immediately before the start of a routine 4 h hemodialysis session, as described in previous studies [16,17]. Blood was drawn from all patients into EDTA-containing tubes and into tubes without anticoagulant in order to obtain plasma, whole blood, and serum. For adiponectin, the samples were centrifuged immediately and plasma was stored at -20ºC until analysis.

According to guidelines of American clinical practice (K/DOQI), the five stages of renal insufficiency based on eGFR are as follows: I ≥ 90, II=60-89, III=30-59, IV=15-29, and V<15 ml/min/1.73 m^2 [18,19]. The glomerular filtration rate (GFR) was estimated (eGFR) using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation, which is more accurate and less biased than the MDRD Study equation, especially in patients with higher GFR, resulting in reduced misclassification of CKD [20].

Plasma concentrations of total adiponectin were quantitated by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (humanadiponectin ELISA kit, Buhlmann, Switzerland). According to the manufacturers, the detection limits for adiponectin assay were 0.08 ng/ml. Intra- and interassay coefficients of variation were <15 for adiponectin. The albuminuria was tested by the ratio of protein/creatinine random urine sample.

Statistics

To check the regularity of variables and parameters, the Kolmogorov-Smirnov test and the dot distribution diagrams were used. Control of the possible association between the variables and parameters was carried out with the Pearson and Spearman correlation coefficients, depending on the regularity of their distribution. To investigate for differences among the various groups, such as for patients with different stage of CKD, the analysis of variance for more than two groups (ANOVA with Bonferroni correction standard) and the Kruskal-Wallis method were used, depending on the normality of the distribution of control variables and parameters. Given the homogeneity observed in the standard deviation of the average values of the samples and the pair wise comparison, for individual comparisons (post hoc) the Tukey method was used in order to analyze the relationship of adiponectin levels and albuminuria as well as albuminuria with BMI.

To compare the differences between two groups, depending on the distribution of variables and parameters, the methods t-test and Mann-Whitney U-test (MWT) were used. We considered statistically significant values, results of p less than or equal to 0.05.

Results

Patients' characteristics are shown in Table 1. The mean GFR of the 119 CKD patients studied was 47.8 (± 32.47, SD) and the mean plasma adiponectin levels were 8.33 (± 7.32 SD) (Table 2). Table 3 shows the mean values and SD of plasma adiponectin levels in patients, in different stages of CKD. A statistically significant difference was found in the serum adiponectin levels between the initial and final stages of CKD (Kruskal-Wallis Test, p=0.002).

	Controls	Stage 1 and 2	Stage 3 and 4	Stage 5	p*
n	25	22	42	30	
Age (years)	64 ± 7.1	67.5 ± 8.8	69.4 ± 8.2	69.1 ± 9.71	0.07
Sex (M/F)	8/17	3/13	25/17	13/17	0.14
BMI (kg/m^2)	31.9 ± 6.6	30.5 ± 4.1	32.3 ± 4.8	29.4 ± 5,2	0.10
Duration od DM	10.8 ± 5.8	13.7 ± 7	16.9 ± 9	16 ± 6.6	0.01
Fasting glucose	151.8 ± 38.1	148.8 ± 43.9	159 ± 49.2	189.4 ± 99.7	0.07

HbA1C	7.4 ± 1	7.1 ± 0.8	7.8 ± 1.4	7.3 ± 0.9	0.10

Table 1: Patients characteristics.

	n	mean	Std. deviation
GFR	119	47.8	32.47
Adiponectin	119	8.33	7.32

Table 2: Number of patients, averages and standard deviations GFR and adiponectin.

Comparing the plasma levels of adiponectin between the control group, patients with type 2 diabetes without renal failure (Stage 0) and diabetic patients in different CKD stages, controls had significantly higher values of adiponectin compared to CKD-1 (MWT, p=0.018), while they have no significantly statistical difference in adiponectin values compared to more advanced stage; to CKD-2 (p=0.637), with CKD-3 (p=0.673) or to CKD-4 (p=0.181). However, patients with CKD-5 had significantly higher values of adiponectin compared to controls (MWT, p=0.005) (Table 3).

Adiponectin			
Stage of CRF	**n patients**	**Mean**	**Std. Deviation**
0	26	6.06	2.832
1	4	3.07	0.75
2	17	7.21	7.92
3	32	8.53	7.95
4	11	7.53	3.15
5	29	11.82	9.31
Total	119	8.33	7.31

Table 3: The serum of adiponectin levels according the stage of renal failure (where 1,2,3,4,5 the stage of CRF).

Adiponectin levels among CKD-2 were found to show significantly higher values of adiponectin compared to CKD-1 (MWT, p=0.024), while there was no significantly statistical difference compared to CKD-3 (p=0.462) and CKD-4 (p=0.066). Similarly, the CKD-3 patients had significantly higher values of adiponectin compared to CKD-1 (MWT, p=0.012), while they had no significant statistical difference in values compared to CKD-4 (p=0.288). Also, patients with CKD-4 had significantly higher values of adiponectin compared to CKD-1 (MWT, p=0.012), while had no significant differences compared to the CKD-5 (p=0.254). Finally, the CKD-5 patients had significantly higher values adiponectin compared to CKD-1 (MWT, p=0.0001), to CKD-2 (p=0.007), and the CKD-3 (p=0.026).

The evaluation of possible differences between the plasma adiponectin levels and the different levels of albuminuria by using the cluster unidirectional analysis (One way, ANOVA), revealed that the adiponectin levels increased per those values of albuminuria, as shown in Table 4 and Figure 1. There was statistically significant difference between group 1 and 3, p=0.05 (Figure 2).

Adiponectin			
Stage of proteinuria	**n**	**Mean**	**Std. Deviation**
1	27	6.13	2.80
2	47	7.87	8.08
3	44	10.29	8.01

Table 4: Adiponectin serum levels in relation to the proteinuria (where 1, proteinuria <3 mg/mmol, 2, proteinuria=3-30 mg/mmol and 3, proteinuria ≥ 30 mg/mmol) (p=0.05 between group 1 and 3, all the other correlations p=NS).

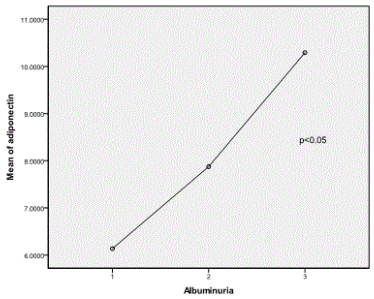

Figure 1: Graphical representation of the relationship and albuminuria levels of adiponectin.

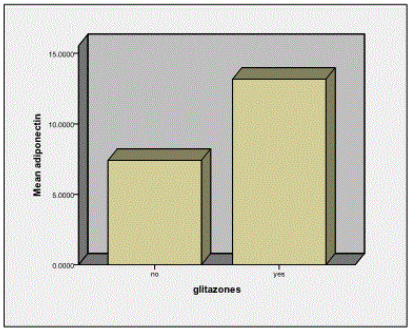

Figure 2: Correlation BMI class and adiponectin levels.

Furthermore, in order to investigate the possible differences between adiponectin plasma levels and different BMI values, unidirectional analysis of variance (One way ANOVA) was used. As shown in Table 5 and in Figure 3, the levels of adiponectin are reduced by increasing the class of obesity (ANOVA, p<0.05). A statistically significant difference between Group 1 and 4 was also observed (Figure 3).

Adiponectin			
Class of obesity	**n**	**Mean**	**Std. Deviation**
1	17	11.82	10.12
2	38	8.14	7.34
3	33	9.39	7.93
4	26	5.46	2.47
5	5	5.76	2.54

Table 5: Adiponectin serum levels (mean and std deviation) in the 5 groups of patients according the BMI (where 1=normal weight, 2=Overweight, 3=Class 1 obesity, 4=Class 2 obesity, 5=Class 3 obesity ($p<0.05$ between group 1 and 4).

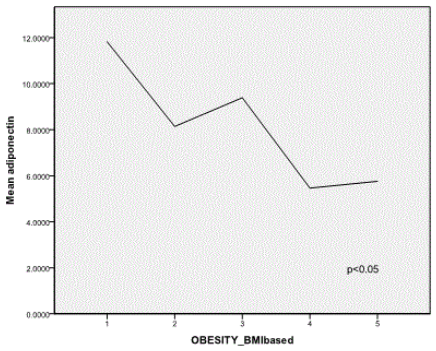

Figure 3: Correlation of serum adiponectin levels and glitazones (where 0=no glitazones, 1=yes glitazones).

Adiponectin				
Glitazones taken	**n**	**Mean**	**Std. Deviation**	**p**
No	100	7.41	6.17	<0.001
Yes	19	13.17	10.57	

Table 6: Correlation of serum adiponectin levels and glitazones ($p<0.001$).

Also, statistically significant higher plasma levels of adiponectin were found in the group of patients in treatment with glitazones in comparison to those without such treatment (Table 6).

Discussion

Adiponectin is a protein of MW 30 kDa that is secreted primarily by fat cells. It has been considered as a prognostic factor for cardiovascular mortality in patients with renal failure [21]. It has been demonstrated that hypoadiponectinemia is associated with endothelial dysfunction. Adiponectin exerts beneficial effects, improving insulin sensitivity and reducing adverse events of inflammation mediators in vascular cells [22]. Moreover, the protective effects of adiponectin are involved in the reduction of oxidative stress, probably by inhibition of NADPH oxidase [23].

In this study, plasma levels of adiponectin in type 2 diabetic patients with CKD and reduced GFR were found to be higher in comparison to those of normal GFR. Elevated levels of adiponectin in patients with end stage kidney failure were also previously reported [24] along with type 2 diabetic patients. This increase might be due to both the decreased elimination as well as the increased production [25]. Additionally, Kim et al. who studied 1442 patients with CKD, found that plasma levels of adiponectin were inversely associated with the stage of renal failure [26], that has been also reported for type 2 diabetics [27]. This study confirms that plasma adiponectin levels are high in diabetic patients with CKD and especially at end-stage renal disease (ESRD).

Furthermore, a positive correlation between plasma adiponectin levels and albuminuria was observed, despite the conflicting results that have been published for the possible relationship between these two parameters. Commonly, albuminuria is expected to be increased in the presence of decreased renal clearance when the plasma adiponectin levels are also increased. This means that people with normoalbuminuria may have slightly increased adiponectin levels, while many investigators reported that plasma adiponectin levels are consistently associated with albuminuria and they appear less stable with low grade proteinuria [28,29].

Given that adiponectin has an important role in the pathophysiology of diabetes and obesity, the non-existence relationship between plasma adiponectin levels and albuminuria may be involved in the onset of proteinuria. The albuminuria is generally considered to have a negative correlation with the levels of plasma adiponectin in obese patients. At the same time, plasma adiponectin levels decrease with increased visceral obesity, and are closely related to insulin resistance and type 2 diabetes mellitus [30]. Similarly, in African-Americans, low adiponectin levels were found in obese people where the appearance of type 2 diabetes was predictable [31,32].

Furthermore, Sharma et al. [29] studied 20 obese African-Americans and found a statistically significant negative correlation between plasma adiponectin levels and albuminuria. The same study also indicated that lack of adiponectin was associated with dysfunction of podocytes (regardless of the systemic and metabolic effects). Adiponectin could be a factor in the activation of protein kinase and oxidative stress [29]. Thus, it is possible to reduce the oxidative stress in a mode through which adiponectin and the activation of protein kinase would protect against proteinuria and increased permeability of podocytes. Consequently, manipulations that may increase levels of adiponectin, such as inhibition of the renin-angiotensin-aldosterone system [33], could have a positive effect on renal and cardiovascular protection of patients at risk. Indeed, adiponectin was found to reduce oxidative stress, inflammation as well as fibrosis in human renal tubular cells caused by angiotensin-II. Accordingly, in podocyte cultures, adiponectin was found to reduce strongly the permeability to albumin [29].

Adiponectin plasma levels are significantly elevated in patients with type 1 diabetes mellitus compared to those with type 2, while they are generally lower in subjects with type 2 diabetes [34]. This may predispose those patients to develop albuminuria probably by losing their nephroprotective effect of adiponectin. It could also explain some increased occurrence of albuminuria in diabetics even from the early stages of the disease. Moreover, lower plasma adiponectin levels indicate more likely worsening of albuminuria in the future, as it has been observed in our study. Obviously, the elevated levels of plasma

adiponectin in type 2 diabetics with advanced albuminuria contradict the existence of insulin resistance in those patients.

In agreement with our findings, Ljubic et al. [27] in a study that included 219 diabetics (87 type 1 and 132 type 2), found that levels of adiponectin in type 2 diabetics were decreased as albuminuria was increasing, a result that has also been described by others [33,35]. In addition, the decreases of adiponectin levels in type 2 diabetic patients were attributed to obesity [36].

However, several investigators found increased levels of plasma adiponectin in patients with macroalbuminuria, compared to those without macroalbuminuria (study with 1442 patients with CKD) (26), results in agreement with our findings. Also Galovicova et al. [37] who studied 120 patients with type 2 diabetics found higher plasma adiponectin levels in those with macroalbuminuria, compared to those who had normoalbuminuria, microalbuminuria, as well as compared to controls (patients with normoalbuminuria had the lower levels of adiponectin). They concluded that diabetic nephropathy potentially plays a very important role in increasing the synthesis and secretion of adiponectin.

In conclusion, in CKD patients with type 2 diabetes, plasma levels of adiponectin are increasing with the progression of renal failure as well as the leveles of albuminuria. Since hypoadiponectinemia is associated with inflammation, atherogenic properties and insulin resistance, adiponectin is secreted more likely so as to alleviate their detrimental effects in diabetic ESRD patients. It may also explain the decreased plasma levels of adiponectin in obese patients, as the degree of the obesity is deteriorating.

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