Variations in adiponectin levels in patients with chronic kidney disease: a prospective study of 12 months

Authors
Maria Ayako Kamimura[1]
Maria Eugênia Fernandes Canziani[2]
Fabiana Ribeiro Sanches[3]
Claudia Modesto Velludo[3]
Juan Jesus Carrero[4]
Ana Paula Bazanelli[5]
Sergio Antonio Draibe[6]
Lilian Cuppari[7]

[1] Postdoctoral Fellow (Professor of the Postgraduate Program in Nutrition at the Federal University of São Paulo (Unifesp/EPM) Associate Visiting Professor of Nephrology at Unifesp/EPM).
[2] PhD (Affiliate Professor of Nephrology at the Federal University of São Paulo [Unifesp/EPM]).
[3] MSc (Postgraduate Student at the Federal University of São Paulo [Unifesp/EPM]).
[4] PhD (Division of Renal Medicine and Baxter Novum, Centre for Molecular Medicine and Centre for Gender Medicine, Karolinska Institute, Stockholm, Sweden).
[5] PhD (Postgraduate Student at the Federal University of São Paulo [Unifesp/EPM]).
[6] Postdoctoral Fellow (Associate Professor of Nephrology at the Federal University of São Paulo [Unifesp/EPM]).
[7] PhD (Affiliate Professor of Nephrology at the Federal University of São Paulo [Unifesp/EPM]).

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Correspondence to:
Maria Ayako Kamimura.
Universidade Federal de São Paulo, SP, Brazil. Karolinska Institutet, Estocolmo, Suécia.
Rua Pedro de Toledo, nº 282, São Paulo, SP, Brazil. CEP: 04039-000
E-mail: m.kamimura@uol.com.br
Tel: (11) 5904-8499. Fax: (11) 5572-1862.

ABSTRACT

Background: Cardiovascular complications remain the main cause of mortality in patients with chronic kidney disease (CKD). Adiponectin is an adipose tissue-derived protein that carries important cardioprotective properties. We aimed at investigating the determinants of adiponectin levels in CKD patients. **Methods:** This prospective observational study included 98 CKD patients [glomerular filtration rate (GFR) 36.1+-14.4 ml/min, 56.5+-10.4 y, 63% male, 31% diabetics, and body mass index (BMI) 27.1+-5.2 kg/m^2]. Evaluation of adiponectin (imunoenzimatic assay), laboratory parameters, nutritional status (subjective global assessment), total body fat (dual x-ray energy absorptiometry), and visceral and subcutaneous abdominal fat (computed tomography) was performed at baseline and after 12 months. **Results:** Adiponectin correlated with GFR (r = -0.45; $p < 0.001$), proteinuria (r = 0.21; $p = 0.04$), BMI (r = -0.33; $p < 0.01$), and visceral fat (r = -0.49; $p < 0.001$). In the linear regression analysis, the determinants of adiponectin levels were sex (female $\beta = 3.8$; $p < 0.01$), age ($\beta = 0.14$; $p = 0.03$), GFR ($\beta = -0.15$; $p < 0.01$) and visceral fat ($\beta = -0.04$; $p < 0.001$) ($R^2 = 0.41$). After 12 months, a progression of the disease was evidenced by the reduction of GFR (-1.6+-6.3 ml/min; $p = 0.01$) and increase of proteinuria (0.3+-0.8 g/d; $p < 0.01$). An accumulation of visceral fat was observed, from 97+-73 cm^2 to 111+-82 cm^2 ($p < 0.001$), with a concomitant reduction of adiponectin concentration, from 27.6+-7.5 mg/l to 22.2+-11.6 mg/l ($p < 0.001$). Body weight, BMI, total body fat, and subcutaneous abdominal fat remained unchanged. After adjustments for the baseline determinants of adiponectin, the increase in visceral fat was independently associated with overtime decrease in adiponectin levels ($\beta = -0.04$; $p = 0.025$; $R^2 = 0.21$). **Conclusion:** Age, sex, renal function and visceral fat were independently associated with adiponectin levels in nondialyzed CKD patients. However, variation in visceral fat was the only predictor of variation in adiponectin levels over 12 months.

Keywords: adipokines, adiponectin, obesity, obesity, abdominal, renal insufficiency, chronic.

INTRODUCTION

Adiponectin is the most abundant peptide produced by adipose tissue. This adipokine plays a regulatory role in insulin sensitivity in addition to its important anti-atherogenic and anti-inflammatory properties.[1] In contrast to other adipokines, the expression and secretion of adiponectin in adipose tissue are inversely proportional to the amount of body fat.[2]

In patients with chronic kidney disease (CKD), the loss of renal function results in an increase of adiponectin concentrations. Yilmaz *et al.*[3] showed that adiponectin accumulates gradually as the glomerular filtration rate decreases. In fact, several studies have consistently shown that the serum concentration of adiponectin significantly increases in CKD patients.[4,5] However, in spite of the cardioprotective properties attributed to adiponectin, cardiovascular complications remain the main cause of

mortality in this population, which are responsible for more than 50% of deaths.[6] Therefore, investigating the determinants of adiponectin levels in CKD patients is important to understand the controversial relationship between this adipokine and mortality, which is extremely high from the very early stages of CKD.

The present study assessed the determinants of adiponectin levels and their changes over a period of 12 months in patients in the non-dialysis phase of CKD.

Methods

Patients

This 12-month observational prospective study included 98 CKD patients in the non-dialysis phase monitored at a conservative treatment outpatient clinic. The exclusion criteria for the study were as follows: age < 18 years, amputation of limbs, ascites, hepatitis, presence of malignant diseases, and use of immunosuppressants and/or glucocorticoids. All patients were instructed to routinely consume a diet including 0.6-0.8 g/kg/day of proteins and 30-35 kcal/kg/day, according to the recommendations of the Kidney Disease Outcomes Initiative (K-DOQI) practice guidelines.[7]

The study was approved by the Research Ethics Committee of the University, and informed consent was obtained from all the study participants.

Laboratory tests

The following laboratory parameters were analyzed from serum samples taken after 12 hours of fasting: creatinine, urea, glucose, albumin (bromocresol green), and high sensitivity C-reactive protein (immunochemiluminescence) levels. Adiponectin concentrations were determined by the enzyme-linked immunosorbent assay (ELISA) method (Linco® Research, St. Charles, MO, USA) from serum samples stored at -70°C. Proteinuria was measured from 24-hour urine samples and the glomerular filtration rate was estimated by the simplified Modification of Diet in Renal Disease (MDRD) equation.[8]

Nutritional status and body composition

The patients were weighed while wearing light clothes and no shoes, by using an electronic scale (Filizola, SP, Brazil). The body mass index (BMI) was calculated as weight divided by the square of the height (kg/m^2). A 7-point subjective global assessment (SGA) was used to assess the nutritional status.[9] Total body fat was assessed using dual-energy X-ray absorptiometry (Lunar Radiation Corporation, Madison, WI, USA), and abdominal fat (visceral and subcutaneous) was measured using computed tomography at vertebrae L4-L5 (Helical Picker PQ 5000, Cleveland, OH, USA).

Statistical analysis

The results have been expressed as mean and standard deviation, median and interquartile range, or ratios. For the comparative analyses, the paired or independent Student's *t* tests were applied for normally distributed variables, and the Mann-Whitney or Wilcoxon tests were used for non-normally distributed variables. The chi-squared test was used for the comparison of categorical variables. Pearson's correlation coefficient was used to assess the associations between the variables, given that the non-normally distributed variables were log transformed. Multiple linear regression analyses were conducted to verify the determinants of adiponectin concentrations and the factors independently associated with variations in their levels over a period of 12 months.

The variables with significant results in the simple correlation test or those that might influence adiponectin levels were included in the regression models. Values of $p < 0.05$ were considered statistically significant. The analyses were conducted using the Statistical Package for the Social Sciences (SPSS) program for Windows, version 16 (SPSS Inc., Chicago, IL, USA).

Results

Cross-sectional analysis

The patient age varied from 28-79 years (56.5 ± 10.4 years), the majority of the cohort were men (63%), and 31% of the patients had diabetes. The causes of CKD were hypertensive nephrosclerosis (27%), diabetic nephropathy (23%), tubulointerstitial nephropathy (12%), glomerulonephritis (8%), unspecified (7%), and others (22%). C-reactive protein levels indicative of inflammatory status (> 0.50 mg/dL) were present in 35% of the patients, and levels indicative of cardiovascular risk (> 0.11

mg/dL) were noted in 78% of the patients. Most patients (79%) were eutrophic according to the subjective global assessment. BMI values of ≥ 25 kg/m^2 were observed in 60% of the patients, of whom 46% presented values that were ≥ 30 kg/m^2. Only 3 patients had a BMI < 18.5 kg/m^2. The main nutritional and laboratory characteristics are listed in Table 1.

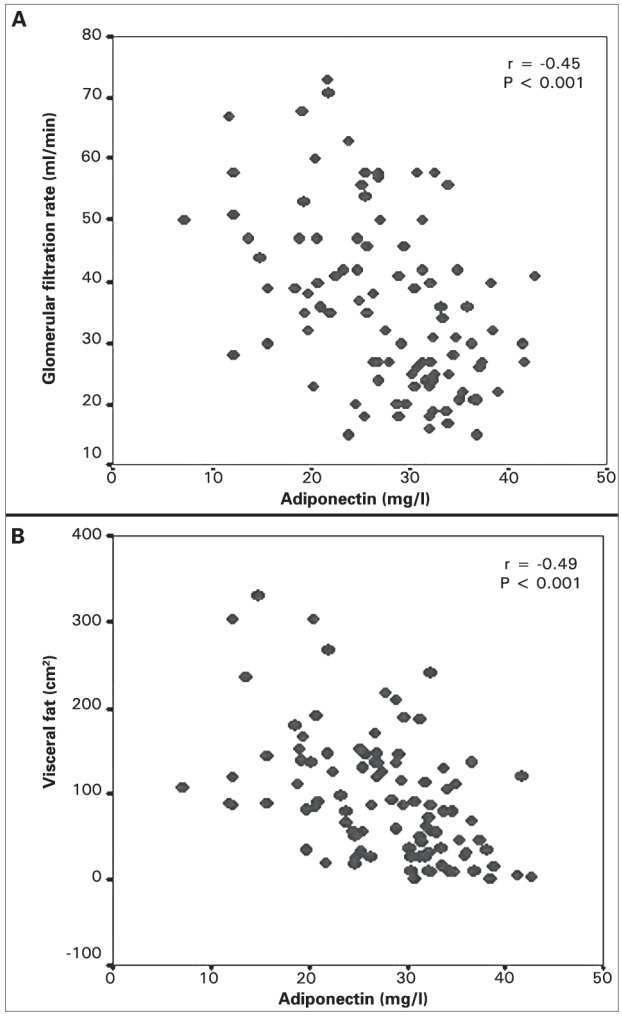
Table 1 Characteristics of the patients in the beginning of the study period and after 12 months (n = 98)

	Beginning	12 months	*p*
Glomerular filtration rate (mL/min)	36.1 ± 14.4	34.5 ± 16.6	0.01
Serum creatinine (mg/dL)	2.1 ± 0.7	2.3 ± 1.0	< 0.001
Proteinuria (g/day)	1.1 ± 0.1	1.5 ± 0.2	0.002
C-reactive protein (mg/dL)	0.28 (0.12–0.70)	0.25 (0.08–0.74)	0.02
Adiponectin (mg/L)	27.6 ± 7.5	22.2 ± 11.6	< 0.001
Body mass index (kg/m^2)	27.3 ± 5.1	27.2 ± 5.1	0.55
Total body fat (kg)	20.8 ± 9.2	21.2 ± 9.6	0.20
Total abdominal fat (cm^2)	281 ± 147	288 ± 149	0.20
Visceral abdominal fat (cm^2)	97 ± 73	111 ± 82	< 0.001
Subcutaneous abdominal fat (cm^2)	184 ± 103	178 ± 98	0.15

Mean ± standard deviation or median and interquartile range; paired Student's *t*-test.

Adiponectin levels were higher in women than in men (31 ± 6.6 mg/L *vs.* 25.6 ± 7.2 mg/L, $p < 0.001$). Women showed higher body fat percentages (38.4% ± 9.3% *vs.* 25% ± 6.8%, $p < 0.001$) and had more subcutaneous abdominal fat (234 ± 133 cm^2 *vs.* 155 ± 66 cm^2, $p = 0.002$), while showing less visceral body fat (69 ± 61 cm^2 *vs.* 113 ± 75 cm^2, $p = 0.002$) than men. Adiponectin levels were inversely correlated with BMI (r = -0.33, $p < 0.01$), visceral fat (r = -0.49, $p < 0.001$), and glomerular filtration rate (r = -0.45, $p < 0.001$) and were positively correlated with serum creatinine levels (r = 0.31, $p = 0.002$) and proteinuria (r = 0.21, $p = 0.04$). The correlations between adiponectin levels and the glomerular filtration rate and visceral fat are shown in Figure 1A-B, respectively. The results of the linear regression model that more accurately described the determinants of adiponectin concentrations in the beginning of the study is shown in Table 2. Inflammation, nutritional status, and the presence of diabetes were not associated with adiponectin levels in these patients.

Figure 1. Correlations between adiponectin and the glomerular filtration rate (A) and visceral fat (B).



Prospective analysis

The characteristics of the patients in the beginning of the study and after 12 months are shown in Table 1. During the monitoring period, CKD progression was evidenced by a decrease in the glomerular filtration rate and an increase in serum creatinine level and proteinuria. An accumulation of visceral fat and the concurrent reduction of adiponectin levels were observed in both men and women. Weight,

Table 2 Determinants of adiponectin levels in the beginning of the study (n = 98, R^2 = 0.41)

	Coefficient	*p*	95% confidence interval
Sex (female)	3.8	0.007	1.1 to 6.6
Age (years)	0.14	0.032	0.01 to 0.27
Glomerular filtration rate (mL/min)	-0.15	0.001	-0.24 to -0.06
Visceral fat (cm^2)	-0.04	< 0.001	-0.06 to -0.02
Constant	23.6	< 0.001	13.0 to 34.2

Multiple linear regression analysis.

BMI, total body fat, and subcutaneous abdominal fat were unchanged in this period. The correlation coefficient (r) between the variations of adiponectin and visceral fat was -0.20 (p = 0.05). Changes in adiponectin levels were not correlated with the renal function parameters. With adjustment for the adiponectin determinants, only the changes in visceral fat were independently associated with the changes in adiponectin levels (Table 3).

Table 3 Determinants of adiponectin level variation over 12 months (n = 98, R^2 = 0.21)

	Coefficient	*p*	95% confidence interval
Sex (female)	2.2	0.14	-0.7 to 5.2
Age (years)	0.01	0.92	-0.13 to 0.15
Glomerular filtration rate (mL/min)	-0.10	0.046	-0.19 to -0.002
Visceral fat (cm^2)	-0.02	0.039	-0.04 to -0.001
Δ Glomerular filtration rate (mL/min)	-0.01	0.89	-0.22 to 0.19
Δ Visceral fat (cm^2)	-0.04	0.025	-0.07 to -0.01
Constant	-2.91	0.61	-14.2 to 8.4

Multiple linear regression analysis.

Discussion

The present study demonstrated that sex, age, renal function, and visceral fat were the determinants of adiponectin levels in CKD patients in the non-dialysis phase, and the variation in visceral fat was a predictor of variation in adiponectin levels over a period of 12 months.

For several years, it was believed that adipose tissue played a passive role in body energy homeostasis, being responsible for storing excess energy as triglycerides and releasing fatty acids for use as needed. The discovery of adipose tissue as a source of leptin hormone in 1994 initiated a new era of research, focusing on the endocrine role of adipose cells.[10] Currently, adipose tissue is known to communicate with other tissues, organs, and systems through the synthesis and secretion of a collection of molecules referred to as adipokines, which have important biological activities.[11] Among the adipokines, adiponectin has increasingly attracted attention in studies of CKD patients, as this protein plays a protective role in atherosclerotic processes by inhibiting the adhesion of monocytes to the vascular endothelium.[12]

However, in the presence of renal failure, which results in adiponectin accumulation, its role becomes even more complex, which translates into controversial findings in the literature regarding the true effects of adiponectin in CKD patients.[13-15] While some researchers support the protective role of adiponectin,[16,17] others do not corroborate such a concept.[18,19] Furthermore, the literature suggests that, among low, medium-, and high-molecular-weight adiponectin, the protective effect of this adipokine appears to be linked to its higher molecular weight fraction.[20,21] This finding indicates the need for future investigations regarding the different molecular weights of adiponectin in the CKD population.

Although adiponectin synthesis occurs exclusively in adipose tissue, it is inversely related to total body fat.[2] In the present study, an inverse correlation was observed between adiponectin level and BMI and visceral fat. It is believed that the cytokine tumor necrosis factor-alpha (TNF-α), which is upregulated if there is excess fat, inhibits the production of adiponectin by adipose tissue.[1] However, in spite of the recent understanding of some of the physiological aspects of adipokines, the exact mechanisms involved in the production of adiponectin by adipocytes remain under investigation to date.

As a secretory organ, adipose tissue shows distinct peculiarities, beginning with its structural constitution. Adipose tissue comprises different cells, including mature adipocytes, preadipocytes, fibroblasts, and macrophages, which may participate

differently in the secretory function. Additionally, adipose tissue exhibits a wide and varied organic distribution, which does not always seem to be linked.[22]

Finally, the metabolic capacity of the adipose tissue may vary due to its location, either visceral or subcutaneous, which may contribute more or less intensely to the secretion of adipokines.[23] It is postulated that visceral fat secretes between 2-3 times more pro-inflammatory cytokines than subcutaneous fat.[24] Recent studies have shown that the expression of pro-inflammatory cytokines[25,26] and the infiltration of immunocompetent cells[26] are accentuated more in the subcutaneous and visceral adipose tissue of CKD patients than in healthy individuals. Teplan *et al*.[27] showed that the expression levels of TNF-α mRNA, CD68 antigen, monocyte chemotactic protein-1, and adiponectin receptor-1 increase in the visceral fat of CKD patients, particularly in those who are obese. Furthermore, the authors showed that the expression of cytokines was significantly higher in the visceral fat compared to the subcutaneous fat.

Therefore, although the contribution of adipose tissue to systemic inflammation has yet to be fully elucidated,[28] it is possible to assume that a mechanism involving inflammation is the most plausible explanation for the increase in visceral fat as the main determinant of the circulating levels of adiponectin observed in the present study.

The findings regarding visceral fat in the population with CKD using gold standard methods such as computed tomography or magnetic resonance imaging are based on association studies.[29-34] Odamaki *et al*.[31] showed that patients undergoing hemodialysis showed a larger area of visceral fat, as measured by computed tomography, than healthy individuals. Furthermore, researchers found that excess visceral fat is linked to changes in lipid profile. These associations were confirmed by other researchers who have also shown a direct link between visceral fat and the prevalence of carotid atherosclerosis in hemodialysis patients.[32,33] Gohda *et al*.[34] showed that, in addition to being directly linked to insulin resistance, visceral fat was closely related to the presence of inflammation in hemodialysis patients, as visceral fat was an independent determinant of C-reactive protein levels in these patients. A recent study with hemodialysis patients showed that visceral fat is the most important determinant of high-molecular-weight adiponectin concentrations.[35]

A spontaneous accumulation of visceral fat has been shown in the few prospective studies involving non-dialysis phase patients[36] and patients undergoing peritoneal dialysis.[37,38] However, the association between visceral fat changes and cardiometabolic marker changes was not assessed in these studies. To our knowledge, the present study is the first to demonstrate the association between visceral fat changes and variations in adiponectin levels in the CKD population. The results of this work can contribute to a better understanding of the missing link between abdominal obesity and cardiovascular complications in patients with CKD.

This study has a limitation with regard to sample size, which was relatively small. However, this is a representative sample of the CKD population in the non-dialysis phase in terms of age, sex distribution, proportion of diabetic patients, and nutritional status. The advantage of the current study is the prospective design and the use of adequate methodologies considered as reference standards.

In the present study, we concluded that age, sex, renal function, and visceral fat are important determinants of adiponectin levels in CKD patients in the non-dialysis phase. However, the accumulation of visceral fat over time is the predictor of adiponectin level reduction in these patients. The implications of this finding in terms of clinical outcomes, including cardiovascular events and mortality, need to be investigated further. Nevertheless, the results of this study emphasize the need for preventive and therapeutic measures regarding visceral obesity present in the initial stages of CKD.

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