Adiponectin as a Novel Indicator of Malnutrition and Inflammation in Hemodialysis Patients

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Introduction. Protein-energy malnutrition and inflammation are common and overlapping conditions in hemodialysis patients, which are associated with increased risk of morbidity and mortality. Adiponectin is an adipocytokine exclusively produced by adipose tissue. The aim of this study was to further elucidate the association between serum adiponectin levels and the nutritional status of hemodialysis patients.

Materials and Methods. Seventy-three patients on hemodialysis for at least 3 months, three times weekly, without any acute illness, were divided into 2 groups of well-nourished (n = 25) and malnourished (n = 48) based on their nutritional status, measured by the subjective global assessment. Serum levels of adiponectin, albumin, blood urea nitrogen, and creatinine; body mass index; and the malnutrition-inflammation score were measured in all patients. These values were compared between well-nourished and malnourished patients. The correlations of nutritional variables with serum levels of adiponectin were determined, as well.

Results. Except for the malnutrition-inflammation score, which was significantly higher in the malnourished patients compared to the well-nourished ones (11.1 ± 3.6 versus 4.2 ± 2.0, $P < .001$), no other significant differences were found between the two groups. A weak but significant positive correlation was found between the serum levels of adiponectin and subjective global assessment scores (r = 0.25, $P = .03$).

Conclusions. The results of our study point to potential utility of serum adiponectin level as an indicator of nutritional status in hemodialysis patients. Further studies are needed to clarify the role of adiponectin in the pathogenesis of malnutrition in hemodialysis patients.

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INTRODUCTION

Hemodialysis patients are prone to malnutrition, inflammation, and depression.[1] Malnutrition-inflammation complex syndrome (MICS) is a common finding in hemodialysis patients, which is associated with poor prognosis.[2] Possible causes of MICS include comorbid illnesses, oxidative stress, nutrient loss through dialysis, hyporexia, uremic toxins, decreased clearance of inflammatory cytokines, volume overload, increased blood phosphate, and dialysis-related factors.[2] High oxidative stress is considered as the main

cause of MICS in hemodialysis patients.[3,4] This syndrome is characterized by coexistent protein-energy wasting and inflammation.[5] Low appetite secondary to inflammation is considered to be the main cause of malnutrition in these patients.[5] Malnutrition-inflammation complex syndrome leads to atherosclerotic cardiovascular disease,[5] which is the main cause of morbidity and mortality in maintenance hemodialysis patients.[6] Dyslipidemia, increased serum levels of low-density lipoprotein cholesterol, triglyceride, and lipoprotein(a), and lower serum levels of high-density lipoprotein cholesterol are considered as the main risk factors of cardiovascular disease in hemodialysis patients.[6] Also, it has been suggested that inflammation may have an important role in atherosclerotic disorders.[7]

Adiponectin is a cytokine which is exclusively produced by adipose tissue and has multiple roles in glucose and lipid metabolism, insulin resistance and inflammation.[8] Generally, adiponectin has an inverse relationship with the degree of adiposity.[9] Serum levels of adiponectin were reported to be 2 times higher in hemodialysis patients than general population.[10] Adiponectin is considered as an anti-inflammatory and anti-atherogenic protein which has an inverse association with common cardiovascular risk factors.[11] Unlike the healthy population, in hemodialysis patients, obesity is paradoxically associated with better outcomes, meaning that patients with higher body mass index (BMI) have better nutritional status.[12] Moreover, in 2 recent studies, serum levels of adiponectin in hemodialysis patients were reported to have positive correlations with subjective global assessment (SGA) and malnutrition-inflammation score (MIS) and also negative correlation with BMI[12,13]; in other terms, well-nourished hemodialysis patients with higher BMI were found to have lower serum levels of adiponectin compared to malnourished hemodialysis patients with lower BMI. As there is still no evidence of adiponectin status and its relationship with malnutrition and inflammation biomarkers in Iranian hemodialysis patients, we conducted this study to further clarify the association between serum levels of adiponectin and nutritional status of hemodialysis patients based on SGA and MIS scores and also to see if it is in accordance with the idea of "reverse epidemiology" in this group of patients or not.

MATERIALS AND METHODS

All 130 patients on regular hemodialysis at Namazi Hospital Hemodialysis Center were evaluated for enrollment in this study, and only those stable on hemodialysis for at least 3 months without any acute illness or admission were considered eligible for enrollment. Patients who were on antibiotics or nutritional supplements, including multivitamins except for folic acid, within 3 months prior to this study, were excluded. Eligible patients provided informed consent to participate in this study. This study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Ethics Committee of Shiraz University of Medical Sciences. All enrolled patients were on hemodialysis 3 times a week for 3 hours using low-flux dialysis filters with polysulfone/polyamide membranes and reverse osmosis purified water and bicarbonate-containing dialysis solution.

In all hemodialysis patients, blood samples were taken after a long dialysis-free weekend interval before the next hemodialysis treatment. Serum levels of adiponectin were measured using an enzyme-linked immunosorbent assay kit (DRG ELISA kit, EIA-4177, Germany). Blood urea nitrogen, serum albumin, serum total iron binding capacity, and serum creatinine were measured with standard automated techniques.

The nutritional statuses of all patients were investigated using both the SGA and the MIS. The nutritional status (any changes in weight during the preceding 2 weeks and 6 months, dietary intake, appetite, and gastrointestinal symptoms) and also functional capacity were evaluated through the SGA questionnaire.[14] An experienced dietitian working with hemodialysis patients read all the questions of the SGA questionnaire to each patient, and the physical examination related to SGA (loss of subcutaneous fat, muscle wasting, and the presence of ankle or sacral edema) were also done by the same person. According to the sum of points assigned to each item (from zero to 5 points for each item), the interpretation of the results were as follow: A score of less than 10 points was regarded as well-nourished; 10 to 17 points indicated being at risk for malnutrition or mildly to moderately malnourished; and higher than 17 points was considered as severely malnourished.[14]

The MIS questionnaire that is more quantitative

and complete than SGA has 4 sections (nutritional history, physical examination, BMI, and laboratory values) and 10 components. The first three sections are similar to the original SGA items but the fourth MIS section includes 2 laboratory markers of serum albumin and transferrin. Each component ranges from zero (normal) to 3 (severely abnormal), and a higher score is indicative of a more severe degree of malnutrition and inflammation.[15] The MIS can be a better indicator of MICS because the status of some visceral proteins such as albumin is assessed by this questionnaire.[16,17]

Data were evaluated using the SPSS software (Statistical Package for the Social Sciences, version 11.5, SPSS Inc, Chicago, Ill, USA). All the data were assessed for normality of distribution, using the Kolmogorov-Smirnov test. The results were presented as mean ± standard deviation. Interquartile ranges were also mentioned for nonparametric data. The correlations were calculated by the Spearman correlation test. To compare variables according to the SGA score, independent sample *t* test and Mann-Whitney U test were used for parametric and nonparametric data, respectively. A *P* value of less than .05 was considered significant.

RESULTS

A total of 73 hemodialysis patients were enrolled in this study. As shown in Table 1, the patients were divided into 2 groups of well-nourished (n = 25; SGA score < 10) and malnourished (n = 48; SGA score ≥ 10). There was no difference in serum levels of measured factors between the two groups of well-nourished and malnourished except for MIS scores that was significantly higher and BMI that was significantly lower in the malnourished patients compared to well-nourished ones.

Table 2. Correlations Between Serum Adiponectin Levels and Nutritional Variables in Patients on Hemodialysis

Parameter	Correlation Coefficient	*P*
Subjective Global Assessment	0.25	.03
Malnutrition-Inflammation Score	0.21	.07
Body mass index, kg/m^2	-0.10	.40
Serum albumin, g/dL	-0.04	.70

The correlations between serum adiponectin levels and measured variables are shown in Table 2. No correlation was found between serum adiponectin levels and measured variables except for SGA (r = 0.25, *P* = .03).

DISCUSSION

In our study, a weak but significant positive correlation was found between serum levels of adiponectin and SGA scores. Inflammation and malnutrition are two main components in the context of MICS in hemodialysis patients.[2] The overlap between these two components creates an intricate clinical status on the basis of a vicious cycle in which inflammation and malnutrition could trigger each other in a mutual manner. Malnutrition is a consequence of chronic inflammatory response.[5] Dialysis patients with inflammation are more prone to anorexia, weight loss and negative protein balance.[5] On the other hand malnutrition itself could be one of the possible causes of inflammation in patients with end-stage renal disease.[5] The expression of adiponectin gene is inversely related to adiposity in general population.[18] A reverse

Table 1. Clinical and Nutritional Parameters in Hemodialysis Patients by Nutritional Status Based on Subjective Global Assessment Scores*

Parameter	Well-nourished (n = 25)	Malnourished (n = 48)	*P*
Age, y	53.6 ± 13.2	52.4 ± 14.7	.75
Duration on hemodialysis, mo	22.8 ± 16.7	17.2 ± 11.2	.14
Daily Kt/V	1.36 ± 0.24	1.40 ± 0.23	.42
Serum albumin, g/dL	4.3 (3.9, 4.8)	4.2 (3.7, 4.5)	.48
Total iron binding capacity, µg/dL	300 (199.5, 435.0)	301.5 (164.2, 492.7)	.93
Blood urea nitrogen mg/dL	71 (44, 87)	69 (55, 84)	.85
Serum creatinine, mg/dL	9.20 (5.85, 12.75)	8.40 (6.37, 10.75)	.25
Adiponectin, ng/mL	24.50 (14.25, 37.39)	29.37 (21.64, 49.18)	.06
Body mass index, kg/m^2	24.62 ± 4.46	21.69 ± 2.90	.001
Malnutrition-Inflammation Score	4.28 ± 2.01	11.12 ± 3.60	< .001

*Data with normal distributions are expressed as mean ± standard deviation and those with skewed distributions as median (interquartile range).

epidemiology of cardiovascular risks could be seen in hemodialysis patients because MICS itself results in low body mass index, hypocholesterolemia, hypocreatininemia, and hypohomocysteinemia. Therefore, unlike healthy population, in these patients obesity is paradoxically associated with better survival.[5] According to recent studies in hemodialysis patients, obese subjects with hypoadiponectinemia display lower mortality rates while higher adiponectin concentrations in lean subjects correlate with an elevated cardiovascular risk.[19] Therefore, unlike protective role of higher levels of adiponectin in healthy individuals, high levels of adiponectin have been considered as an important predictor of all-cause mortality in hemodialysis patients, meaning that the role of adiponectin under chronic wasting states may be different from that for the general population.[20]

In our study, the significant positive correlation between the serum levels of adiponectin and SGA indicated that the patients with better nutritional status and lower SGA scores had lower adiponectin levels, and this supports the idea of reverse epidemiology in hemodialysis patients. These findings are in accordance with the results of the study by Lee and coworkers, in which serum adiponectin levels had positive correlations with the SGA and the MIS and negative correlations with BMI and triglyceride levels.[13] Moreover, in another study by Dervisoglue and colleagues, a positive correlation between serum levels of adiponectin and worse nutritional inflammation status was found in peritoneal dialysis patients; however this correlation was not found in hemodialysis patients.[21] Additionally, in the study by Malgorzewics and colleagues, overweight hemodialysis patients were reported to have decreased serum levels of adiponectin.[12]

The quality of our study would be improved if we had a healthy control group with normal kidney function to compare their measured variables with those measured in hemodialysis patients.

CONCLUSIONS

The results of our study point to potential utility of serum adiponectin level as an indicator of nutritional-inflammation status in hemodialysis patients. Further studies are needed to clarify the role of adiponectin in pathogenesis of malnutrition and inflammation in hemodialysis patients and also to investigate its inverse clinical significance compared to the healthy population. More Longitudinal studies are also needed to evaluate the association of serum adiponectin levels with mortality in hemodialysis patients.

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CONFLICT OF INTEREST

None declared.

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