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Original Article

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Relationship between Serum Adipocyte Fatty Acid-Binding Protein Levels and Systemic Inflammation in Hemodialysis Patients

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Abstract

Objective: Adipocyte fatty acid-binding protein (A-FABP) is expressed in adipose tissue and macrophages. It regulates cholesterol trafficking and is involved in atherosclerosis formation. A-FABP levels are associated with cardiovascular diseases (CVDs) in patients with or without chronic kidney disease. In this study, we evaluated A-FABP levels in healthy controls and hemodialysis (HD) patients and compared the results with C-reactive protein (CRP) and interleukin-6 (IL-6) levels to determine their relationship with systemic inflammation.

Materials and Methods: The study comprised 23 healthy controls and 70 HD patients, excluding individuals with an active infection, malignancy, anorexia, obesity, and hypo- or hyperthyroidism. Demographic features, laboratory findings, A-FABP levels, and levels of inflammatory markers were evaluated between and within the groups.

Results: Levels of A-FABP and inflammatory markers were significantly higher in HD patients. In the HD group, 20% of the patients had documented CVD. Levels of A-FABP and inflammatory markers were similar in nondiabetic and diabetic HD patients. Age was negatively correlated with A-FABP levels. Presence of diabetes was not correlated with A-FABP. Serum CRP and IL-6 levels were significantly correlated with A-FABP levels (r=0.354, p=0.003 and r=0.393, p=0.001, respectively).

Conclusion: A-FABP levels are elevated in HD patients. Systemic inflammation is significantly related to A-FABP levels in both nondiabetic and diabetic HD patients and decreases with age. Findings of this study support the adverse cardiovascular effects of systemic inflammation in HD patients.

Keywords: Adipocyte fatty acid-binding protein, cardiovascular diseases, hemodialysis, systemic inflammation

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INTRODUCTION

Adipocyte fatty acid-binding proteins (A-FABPs) are molecules that regulate cell lipid metabolism. FABPs are expressed as 14-15-kDa proteins that reversibly bind to hydrophobic ligands, such as saturated and unsaturated long chain fatty acids, eicosanoids, and other lipids, with high affinity (1). FABPs facilitate the transport of lipids into the cell for various purposes. Lipids are stored for energy and processed in the endoplasmic reticulum for signaling, trafficking, and membrane synthesis. Lipids are also transported to the mitochondria or peroxisome for oxidation. Lipids regulate several intracellular enzyme activities and transcription in the nucleus. A-FABP, also known as fatty acid–binding protein 4 (FABP4), is a member of FABPs that is expressed in both adipocytes and macrophages and has been introduced as a novel adipocyte-expressed factor, which is found in the human bloodstream (2-8).

Studies have shown that the elevation of serum A-FABP is associated with obesity and insulin resistance -risk factors of atherosclerosis- and also associated with carotid atherosclerosis (9-12). A-FABP serum levels were significantly increased in overweight and obese patients as compared with those in lean controls and correlated positively with waist circumference, blood pressure, insulin resistance, and systemic inflammation (9, 13). High serum A-FABP is a very potent risk factor in the develop-

ment of cardiovascular events. Also, higher levels of A-FABP predict worse outcomes in patients with documented coronary artery disease (CAD) (14). It is also demonstrated that the A-FABP level is significantly higher in hemodialysis (HD) patients than in healthy individuals (15) and is a predictor of cardiovascular diseases (CVDs) in this population (16).

CVDs are the most important cause of mortality in patients undergoing renal replacement therapy (17). Both uremia and the dialysis procedure itself trigger systemic inflammation. The relationship between systemic inflammation and atherosclerosis in HD patients was documented in a previous study (18). In the results of studies investigating the relationship between atherosclerosis and obesity, there is evidence that A-FABP is associated with systemic inflammation and is secreted and acts as a proinflammatory cytokine (19). In this study, we evaluated A-FABP levels in HD patients and compared the results with levels of inflammatory markers, C-reactive protein (CRP), and interleukin-6 (IL-6) to demonstrate its relationship with systemic inflammation and determine new insights and goals to improve cardiovascular survival. Also, the results were compared with those in healthy subjects to support presumed higher levels of A-FABP in HD patients.

MATERIALS AND METHODS

Statements of Ethics

The study protocol was approved by the Ethics Committee of the Gazi University School of Medicine (Approval Date: January 2014; Approval No: 15).

Study Design, Participants, and Definitions

This cross-sectional study comprised 23 healthy controls and 70 HD patients, excluding patients with acute cardiovascular events, active infection, active or recent history of malignancy, anorexia, obesity, and hypo- or hyperthyroidism.

All the patients were treated with a standard HD procedure via arteriovenous fistulae; each session lasted for 4 hours, three times a week, using bicarbonate-containing dialysate and polysulfone membrane. The blood flow rate ranged from 300 to 350 mL/min, and the dialysate flow rate was 500 mL/min.

K_t/V was calculated using the second-generation Daugirdas equation, and urea reduction ratio (URR) was calculated by taking the difference between pre- and post-dialysis urea levels and divided by pre-dialysis urea levels.

Blood Specimen Collection

Eight-hour fasting blood samples were collected in the morning shift (8 a.m.-9 a.m.) to prevent prandial and diurnal variations. Serum specimens were allowed to clot by leaving undisturbed at room temperature for 30 min. The clot was removed by centrifuging samples at 3500 rpm for 10 min. Serum was immediately transferred into a polypropylene tube using a Pasteur pipette and stored at -80°C.

Materials and Measurements

Free fatty acids (FFAs), A-FABP, CRP, IL-6, blood urea nitrogen, creatinine, albumin, total protein, hemogram, lipid profile, intact parathormone, insulin, and glucose levels were measured from freshly collected serum and plasma. Patients' demographic features such as age, sex, and body mass index (BMI) were noted. All values were compared between and within the groups.

Biochemical Study

Serum parameters were determined using enzyme-linked immunosorbent assay kits according to the manufacturers' protocol. FFA and A-FABP kits were purchased from Shanghai Sunred Biological Technology, (Shangai, China) and IL-6 and CRP kits from DIASource ImmunoAssays (Louvain-la-Neuve, Belgium). The interassay coefficients of variation were <10% across the range of measured results for A-FABP, FFAs, CRP, and IL-6.

Statistical Analysis

Data were presented as mean and standard deviation for numerical variables and frequency and percentage for categorical variables. Comparisons of numerical data between independent groups were performed with the Mann-Whitney U test for two groups and Kruskal-Wallis test for more than two groups. Comparisons between dependent groups were performed with the Friedman test and Wilcoxon signed-rank test for two and more than two groups, respectively. A Spearman correlation test was used to find the correlation between nonparametric variables. A p-value less than 0.05 was considered a statistically significant result in all comparisons. IBM Statistical Package for the Social Sciences software for Windows version 21.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for the analyses of the study.

RESULTS

Baseline Characteristics and Health Parameters

In this study, 23 healthy controls and 70 HD patients were included. In the HD group, 17 patients (24.2%) had diabetes mellitus, 22 patients (31.5%) had glomerulonephritis, and 13

Main Points

- Adipocyte fatty acid-binding protein is a novel diagnostic marker for acute cardiovascular events and a well-studied predictor of cardiovascular disease risk and outcomes in the healthy population and hemodialysis patients.
- Adipocyte fatty acid-binding protein levels are elevated in hemodialysis patients compared to healthy individuals.
- CRP and IL-6 levels were significantly correlated with adipocyte fatty acid-binding protein levels in both non-diabetic and diabetic hemodialysis patients.
- The findings of this study support the adverse cardiovascular effects of systemic inflammation in hemodialysis patients.

Table 1. Baseline characteristics and health parameters of hemodialysis patients

Age, years	47.6 (18-66)
Sex (F/M), n	19/51
BMI, kg/m^2 (median, min-max)	25.6 (18.7-42.5)
Hb, g/dL (mean±SD)	11±1.6
FPG, mg/dL (median, min-max)	90 (55-455)
Cre, mg/dL (mean±SD)	8.09±2.8
Alb, g/dL (mean±SD)	3.6±0.4
LDL, mg/dL (mean±SD)	114±13.2
Triglyceride, mg/dL (mean±SD)	156±34
HCO_3, mmol/l (mean±SD)	20.1±2.9
Ca, mg/dL (mean±SD)	8.7±0.6
Ph, mg/dL (mean±SD)	5.08±1.4
iPTH, pg/mL (median, min–max)	340 (4.5-2400)
HD vintage, months (mean±SD)	74.2 (±42)
Kt/V, n (SD)	1.8 (±0.5)
URR, % (SD)	74.2 (±8.4)
CVD characteristic	
No CVD, n (%)	56 (80%)
Documented CVD, n (%)	14 (20%)
Medical therapy, n (%)	4 (5.7%)
Coronary stent, n (%)	4 (5.7%)
CABG, n (%)	6 (8.6%)

Alb: albumin; BMI: body mass index; Ca: calcium; CABG: coronary artery bypass graft; Cre: creatinine; CVD: cardiovascular disease; FPG: fasting plasma glucose; Hb: hemoglobin; HD: hemodialysis; iPTH: intact parathormone; LDL: low-density lipoprotein; Ph: phosphate; URR: urea reduction ratio

patients (18.6%) had other diseases such as polycystic kidney disease and vesicoureteral reflux. Eighteen patients (25.7%) had CKD of unknown origin. All patients had targeted levels of K_t/V and URR, according to the 2012 KDIGO guidelines. Fifty-six patients (80%) had no history of CVD. Fourteen patients (20%) had documented CVD. Patient characteristics, laboratory data, and health parameters of HD group are summarized in Table 1.

Comparison of Healthy Subjects and HD Patients

Healthy subjects and HD patients had similar age and sex distribution. A-FABP, IL-6, and CRP levels were significantly higher in the HD group. FFA levels were similar between groups (Table 2).

Comparison of Nondiabetic and Diabetic HD Patients

Nondiabetic patients were significantly younger (p=0.001). Sex distribution, BMI, K_t/V, URR, and HD vintage were similar between nondiabetic and diabetic patients. Levels of A-FABP, FFA, and inflammatory markers were similar in both groups (Table 3).

Table 2. Comparison of demographic features and levels of metabolic and inflammatory markers between hemodialysis patients and healthy subjects

	HD patients (n=70)	Healthy controls (n=23)	p*
Age, years	47.6 (18-66)	45 (18-54)	0.066
Sex (F/M), n	19/51	7/16	0.074
A-FABP, ng/mL (median, min-max)	9.0 (6.9-16)	7.9 (6.4-12.5)	**0.001**
FFA, µmol/L (median, min-max)	136.2 (71.7-317.9)	156 (73.4-261.4)	0.106
IL-6, pg/mL (median, min-max)	39.9 (12.9-199.3)	25.3 (10.1-98.3)	**0.004**
CRP, mg/L (median, min-max)	10.2 (1.1-28.6)	3.8 (1.4-14)	**<0.001**

A-FABP: adipocyte fatty acid–binding protein; CRP: C-reactive protein; FFA: free fatty acid; IL-6: interleukin-6
*Bold text indicates a statistically significant difference with a p-value less than 0.05.

Table 3. Demographic features and levels of metabolic and inflammatory markers in nondiabetic and diabetic HD patients

	Nondiabetic (n=53)	Diabetic (n=17)	p*
Age, years	46 (18-66)	58 (37-66)	**0.001**
Sex (F/M), n	15/38	4/13	0.702
BMI, kg/m^2	25.9 (17.2-46.6)	27.6 (17.1-44.4)	0.507
Kt/V (mean, SD)	1.7 (±0.5)	1.8 (±0.4)	0.801
URR, % (mean, SD)	74.2 (±8.4)	75.4 (±5.9)	0.221
Dialysis vintage	75.9 (±66)	72.0 (±48)	0.745
A-FABP, ng/mL (median, min-max)	9.1 (6.9-16.0)	8.7 (7.2-12.1)	0.431
FFA, µmol/L (median, min-max)	134.8 (71.7-317.9)	140.5 (93.1-250.9)	0.741
IL-6, pg/mL (median, min-max)	43.1 (14.7-199.3)	35 (12.9-144.7)	0.061
CRP, mg/L (median, min-max)	10.6 (1.1-28.6)	8.9 (1.8-23.4)	0.431

A-FABP: adipocyte fatty acid-binding protein; BMI: body mass index; CRP: C-reactive protein; FFA: free fatty acid; IL-6: interleukin-6; URR: urea reduction ratio
*Bold text indicates a statistically significant difference with a p-value less than 0.05.

Comparison of HD Patients with or without CVD

HD patients with CVD were significantly older than HD patients without CVD. Both groups had similar BMI, K_t/V, URR, and HD

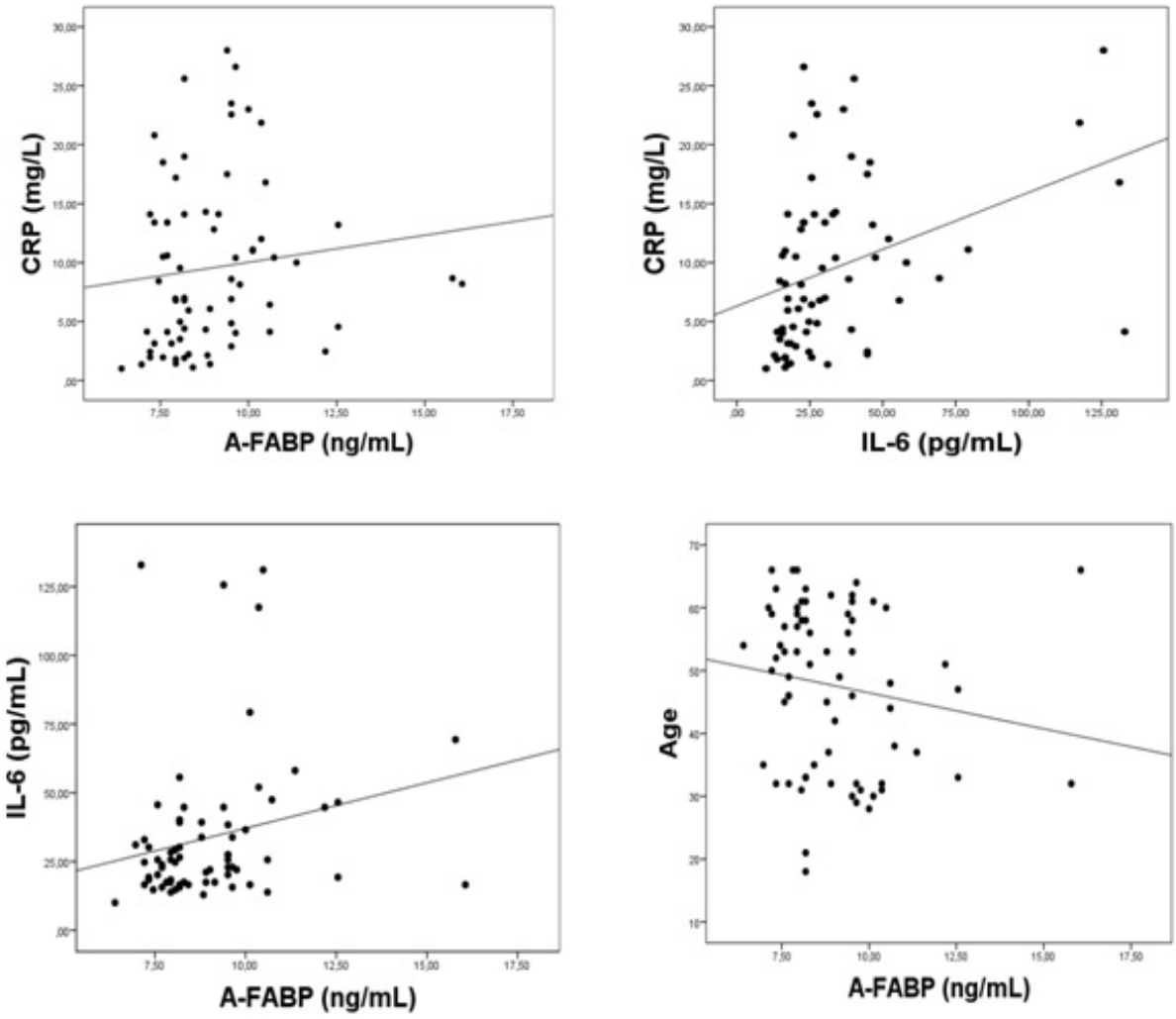

Figure 1. Associations between levels of inflammatory markers, A-FABP levels, and age. (CRP and A-FABP: r^2=0.013, p=0.003; IL-6 and A-FABP: r^2=0.049, p=0.001; CRP and IL-6 r^2=0.132, p<0.001; Age and A-FABP, r^2=0.025, p=0.048).
A-FABP: adipocyte fatty acid-binding protein; CRP: C-reactive protein; IL-6: interleukin-6

vintage. Significantly more patients had diabetes in the CVD group. Levels of metabolic and inflammatory markers were similar between groups (Table 4).

Associations between A-FABP, Patient Characteristics, Inflammatory Status, and CAD

Sex, presence of diabetes mellitus, and FFA levels were not correlated with A-FABP. Serum CRP and IL-6 levels were significantly and positively correlated with A-FABP levels (r=0.354, p=0.003 and r=0.393, p=0.001, respectively). Age was significantly and negatively correlated with A-FABP levels (r=-0.238, p=0.048). No correlation was found between A-FABP levels and CVD (Table 4 and Figure 1).

DISCUSSION

A-FABP is a novel diagnostic marker for acute cardiovascular events and a well-studied predictor of CVD risk and outcomes in healthy population and HD patients (16, 20). In this study, we observed a positive correlation between A-FABP level and systemic inflammatory indices in HD patients. While diabetes did not affect A-FABP levels in HD patients, it is observed that A-FABP levels tend to decrease with age. However, we did not detect an increase in A-FABP levels in HD patients previously diagnosed with CAD.

A-FABP is expressed predominantly in adipose tissue and macrophages (21). In macrophages, A-FABP regulates cholesterol trafficking and inflammatory activities, which are two important functions involved in atherosclerosis formation (22). Systemic inflammation predisposes atherosclerosis not only by directly affecting the endothelium but also by interfering with lipid metabolism, which is one of the best known risk factors for CVDs (23, 24). Also, there is evidence that high lipid intake and modified lipoproteins, such as chylomicrons,

Table 4. Associations between A-FABP level, patient characteristics, inflammatory status, and coronary artery disease

	A-FABP	
	r*	p*
Age	**-0.238**	**0.048**
Sex	-0.029	0.811
BMI	-0.092	0.457
DM	0.096	0.435
Hb	-0.121	0.324
Alb	-0.059	0.630
Insulin	-0.001	0.996
HOMA-IR	-0.001	0.998
iPTH	0.057	0.639
CRP	**0.354**	**0.003**
IL-6	**0.393**	**0.001**
FFA	-0.186	0.183
CVD	0.083	0.076

A-FABP: adipocyte fatty acid–binding protein; Alb: albumin; BMI: body mass index; CRP: C-reactive protein; CVD: cardiovascular disease; DM: diabetes mellitus; FFA: free fatty acid; Hb: hemoglobin; HOMA-IR: homeostatic model assessment of insulin resistance; IL-6: interleukin-6; iPTH: intact parathormone
*Bold text indicates a statistically significant difference with a p-value less than 0.05.

very-low-density lipoproteins, and oxidized low-density lipoproteins, can elevate circulating markers of inflammation, such as CRP and serum amyloid A (25). This phenomenon is presumably one of the essential mechanisms of lipid-lowering drugs' anti-inflammatory effects. In this aspect, A-FABP, a lipid chaperone, is entirely prone to be affected by systemic inflammation. Indeed, A-FABP has recently been classified as a proinflammatory cytokine (26).

The most potent source of A-FABP is fat tissue. A-FABP has been associated with excess fat tissue, especially in obese patients (9). However, most of the HD patients have a chronic catabolic process at a clinical or subclinical level. Body fat was not found to be associated with inflammation and oxidative stress in HD patients (27). On the other hand, although classical body fat volume is not a useful marker, an increase in the visceral adipose tissue, especially the increase in epicardial adipose tissue, was demonstrated to be related to atherosclerosis, malnutrition, and inflammation in HD patients (28-30). Although the increase in body fat tissue does not seem to adversely affect the health in dialysis patients as that in individuals with normal renal function, abnormal visceral adipose tissue seems to trigger inflammation and atherosclerosis in dialysis population. The critical point in this relationship can be A-FABP itself and the inflammatory cytokines increased by this molecule.

The correlation between high A-FABP levels and previous cardiovascular events was not significant in this study. Indeed, A-FABP is known to have prognostic importance, not diagnostic, in patients with previous CVD. In patients with a history of CAD, high levels are accepted as a marker of ongoing clinical and subclinical ischemia or uncompensated heart failure (16, 31). The exclusion of acute cases in this study may have led to A-FABP levels in the CVD group being similar to those in other HD patients.

This study demonstrates the effect of systemic inflammation on A-FABP levels. When results were evaluated separately in nondiabetic and diabetic patients, the levels of inflammatory markers, FFAs, and A-FABP were found to be similar between these groups. Systemic inflammatory status increased A-FABP levels in both nondiabetic and diabetic HD patients and presumably exaggerated atherosclerotic formation in this population. Another finding was that A-FABP levels tend to decrease with age. This may be due to the loss of adipose tissue in older people. Therefore, A-FABP serum levels should probably be adjusted for age and possibly for sex to be used as a quantitative biomarker in the future. However, although significant in this study, the correlation was weak, and there were no patients older than 66 years. In order to evaluate this finding, more extensive studies with a broader age range are required.

The serum FFAs that are strictly related to A-FABPs and believed to be a predictor of cardiovascular events were also measured in this study. It was found that serum FFA levels in HD patients were similar to those in healthy controls and were not related to cardiovascular events. This finding again attracts attention to binding proteins instead of FFA levels.

To our knowledge, this study is the first to demonstrate the relationship between A-FABP levels and systemic inflammation in HD patients. Furthermore, our study suggests that efforts for ameliorating systemic inflammation in HD patients may improve cardiovascular outcomes in this population. However, whether this process is similar in other diseases with high systemic inflammatory responses requires further study.

The main limitations of our study were the low number of patients due to the large exclusion criteria. Therefore, the correlations were statistically significant but relatively weak.

CONCLUSION

A-FABP is known to predict CVDs in patients with or without renal replacement therapies. Systemic inflammation is significantly related to A-FABP levels in both nondiabetic and diabetic HD patients. The present study findings support the adverse cardiovascular effects of systemic inflammation on HD patients.

Ethics Committee Approval: The ethics committee approval was received for this study from the Ethics Committee of the Gazi University School of Medicine (Approval Date: January 2014, Approval No: 15).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - U.D., A.C., M.K.D.; Design - S.M.D.; Supervision - U.D.; Resources - U.D., S.M.D.; Materials - A.C., S.M.D.; Data Collection and/or Processing - A.C., B.K.; Analysis and/or Interpretation - B.K., U.D., S.E., M.K.D.; Literature Search - B.K., O.H., U.D.; Writing - B.K., O.H., S.E., U.D.; Critical Reviews - B.K., O.H., M.K.D., S.E., U.D.

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