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Original Article

Soluble Adiponectin is a New Predictor for Cardiovascular Complications in Patients with End Stage Renal Disease

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Mortality due to cardiovascular complications (CVC) in patients with end stage renal disease (ESRD) is 20 fold higher than in general population. Adiponectin (ADPN) hormone from adipose tissues accumulation in serum is attributed to reduced renal clearance. The aim of this study was to investigate the possible role of ADPN as a predictor of CVC in adult patients with ESRD on hemodialysis (HD), and to evaluate the relationship between its levels and other CVC risk factors. 30 ESRD patients on regular HD with evidence of CVC (group 1), 30 ESRD patients on regular HD without evidence of CVC (group 2) and 20 age and sex matched healthy subjects (group 3) were enrolled into the study. All participants were subjected to clinical examination and laboratory investigations. Serum C-reactive protein (CRP) and ADPN concentrations were measured by ELISA. Echocardiography was performed for cardiac abnormalities estimation. The most common CVC in patients with ESRD was angina (53.33%) followed by myocardial infarction (33.33%). Patients with CVC had significant increased frequencies of risk factors (body mass index, total cholesterol, triglyceride and low density lipoprotein, and CRP in comparison with patients without CVC ($P< 0.05$). Additionally, both patient groups had a significant higher serum ADP levels in comparison with controls ($P<0.001$), with ADPN concentrations being higher in patients with CVC than those without CVC ($P<0.001$). Echocardiography showed significant differences between group 1 and group 2 regarding ejection fraction (EF %) and wall motion ($P <0.002$ and <0.001 respectively). Correlation studies in patients with CVC revealed that there were significant negative correlations between ADPN levels and duration of dialysis ($r= - 0.346$, $P = 0.049$), low density lipoprotein ($r= - 0.542$, $P= 0.002$), CRP ($r= - 0.605$, $P< 0.001$) and EF% ($r= - 0.337$, $P= 0.049$). ADPN sensitivity and specificity were 93.3%, and 83.3%, respectively, with 84.8% positive predictive value and 92.6% negative predictive value compared to 56.7% sensitivity, 90% specificity, 82.4% positive predictive value and 62.8% negative predictive value for EF%. Low serum ADPN level could be used as a predictive marker of CVC in ESRD and progression of CKD and may help in planning preventive strategies for ischemic heart disease.

Keywords: Adiponectin, chronic kidney disease, adipokines

Chronic kidney disease (CKD) is a worldwide public health problem that progresses gradually over a period of months or years and is associated with a variety of complications (1).

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Patients with CKD have an increased risk of end-stage renal disease (ESRD) and cardiovascular complications (CVC). Cardiovascular mortality is the main cause of death in patients with ESRD on hemodialysis (HD) and can be 20-fold higher than in general population (2).

Many classical risk factors such as age, gender, smoking, hypertension, dyslipidemia, diabetes and obesity are observed. Metabolic alterations in the uremic milieu such as inflammation hyperphosphatemia, hyperhomocysteinemia and anemia may also contribute to the excessive risk of cardiovascular disease (CVD) in those patients. Uremia and renal replacement therapies result in markedly enhanced oxidative stress, the production of complement fragments and cytokines, increased adhesion molecules in endothelial cells, and other proinflammatory factors. These factors may provide the proper media for the development of accelerated atherosclerosis (3).

Adiponectin (ADPN) is one of the most abundant adipocytokines produced by adipocytes (4). It plays an important role in the regulation of body weight, lipid metabolism and insulin sensitivity. Adiponectin was also demonstrated to have anti-inflammatory and anti-atherogenic properties (5). Reduction in ADPN level is associated with endothelial dysfunction; which in turn plays an important causal role in the development of insulin resistance, type-2 diabetes and metabolic disease, thereby indirectly causing atherosclerosis. Recent findings have shown a protective function of ADPN for the cardiovascular system, suggesting an inverse association with cardiovascular disease risks (6). In healthy population, low circulating level of ADPN seems to be a predictive factor for the development of atherosclerosis and CVC (7).

Adiponectin circulates in blood and is excreted by the kidneys. It is expected that it accumulates in serum due to reduced renal clearance. Its clinical significance as a CVD risk factor in patients with CKD is obscure and its association with the outcome of chronic kidney failure patients are scares especially in advanced disease stages on HD (8).

The aim of this study was to find out the possible role of ADPN as a predictor of CVC in adult patients with ESRD on HD, and to evaluate the relationship between ADPN levels and other risk factors of CVC, in a trial to avoid the development of these complications and/or find out therapeutic strategies targeting ADPN's bioavailability.

Materials and methods

Subjects

This study was conducted on 60 adult patients with ESRD on regular HD (GFR<15 ml/min/1.73m²). Patients were collected from HD unit at Helwan General Hospital, from January 2015 till October 2015. Patients were classified into 2 groups: group 1 included 30 ESRD patients on regular HD with evidence of CVC (angina episodes, myocardial infarctions, heart failure, arrhythmia, transient ischemic attacks, strokes, peripheral vascular diseases, arterial or venous thrombotic episodes). They were under antihypertensive, anti-ischemic and lipid lowering drugs. Group 2 included 30 ESRD patients on regular HD without evidence of CVC.

Adult patients with CKD, age ranges from 20-60 years, under regular HD (stage V: ESRD, 3-4 h dialysis using polysulfone membrane three times a week, for at least six months) were enrolled into the study. Patients with recent infections, autoimmune diseases, diabetes mellitus, obesity, malignancy, hepatitis C, hepatitis B, age > 60 years, and patients who received blood transfusion during the last 6 months were excluded from the study. The study also included 20 age and sex matched apparently healthy subjects, not hypertensive, with normal kidney function tests and glucose levels (group 3). They were colleagues from Helwan General Hospital. An informed written consent was obtained from all patients and controls before getting them involved in the study.

Clinical and bichemical evaluations

All patients and healthy controls were subjected to full medical history for cardiovascular risk factors (diabetes mellitus, hypertension, smoking, duration of CKD, duration of HD, the membrane used in HD and the underlying disease for CKD). Past history of previous cardiovascular events (anginal episodes, myocardial infarction, arrhythmia, transient ischemic attacks, cerebrovascular stroke and other thrombotic events) were recorded. Full clinical examination, anthropometric measurements and routine investigations (kidney function tests, blood urea nitrogen (BUN), serum creatinine levels, serum calcium and phosphorous levels, serum total cholesterol (TC) and triglycerides (TG) levels, high density lipoprotein (HDL) and low density lipoprotein (LDL) levels, complete blood count (CBC) and C-reactive protein (CRP) level) were also done at Helwan General Hospital. Echocardiography using standard transthoracic M. mode, two dimensional and pulsed wave doppler echocardiograms were carried out soon after a session of routine HD, using 2.5 MHz transducer to detect evidence of left ventricular hypertrophy and evidence of ischemic heart disease.

Serum adiponectin evaluation

Five milliliters of venous blood were obtained from each patient and control subjects with a sterile syringe. Three milliliters were drawn without anticoagulant, sera were collected and divided into two aliquots: one aliquot was stored at -20 ˚C till the time of use, the other aliquot was used for biochemical laboratory investigations. Two milliliters of blood were drawn on EDTA solution for complete blood count (CBC). Measurement of serum ADPN concentrations was carried out by a standard sandwich enzyme-linked immuno-sorbent assay (ELISA) using a commercial kit (Boster Biological, Pleasanton, CA, USA) and mouse monoclonal antibody specific for ADPN that has been precoated on ELISA plates. The ELISA assay was carried out at the Microbiology Department Al-Azhar University according to the manufacturer's instructions. The optical density (OD) of the color is proportional to the human ADPN concentrations in samples after subtraction of the OD at 450 of zero well of sample diluent. The standard curve was plotted as the relative OD at 450 of each standard solution (Y) vs. the respective concentration of the standard solutions (X). The human ADPN concentrations of the samples were interpolated from the standard curve.

Statistical analyzes

Data were analyzed using statistical program for social science (SPSS) version 20.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Chi-square test was used to compare proportions between two qualitative parameters. Pearson's correlation coefficient (r) test was used for correlating data. Receiver operating characteristic (ROC curve) analysis was used to find out the best cut-off values, overall predictive values, and calculation of sensitivity and specificity of parameters.

Results

Demographic data

Group 1 included 30 ESRD patients on regular HD with evidence of CVC; angina episodes (53.33%), myocardial infarctions (33.33), peripheral vascular diseases (10%) and cerebrovascular stroke (3.33 %). Males accounted for 66.7% of the cases. The mean± SD of age was 50.57± 9.64 years and the BMI was 28.63± 5.05 Kg/m². Group 2 included 30 ESRD patients on regular HD without evidence of CVC. Among them 66.7% were males. The mean± SD of age was 48.90± 12.48 years and the BMI was 25.7±3.73 Kg/m². A significant difference was found between group 1 and group 2 only in BMI (P= 0.005). The most common causes of CKD in both groups were hypertension (43.3%) and obstructive uropathy (20% and 23.3%, respectively).

Risk factors for CVC

Several risk factors may contribute to CVC

such as age, sex, duration of CKD, duration of HD, BMI, smoking, blood pressure, TC, TG, LDL, and HDL. However, the only risk factors that were detected in this study were BMI, TC, TG and LDL P (= 0.005, = 0.004, = 0.016, and = 0.004, respectively) since significant differences in the mean values between group 1 and group 2 were found (Figure 1).

Biochemical and hematological parameters

Laboratory analyzes revealed highly significant decreases (P<0.001) in Hb (10.37± 1.12) g/dL and platelet counts (189.73± 57.52x10^9/L) in group 1, and in group 2 (10.14 ±1.21) g/dL and (183.50± 50.2x10^9/L), respectively as compared to controls (12.48± 0.87) g/dL and (299.40±78.05 x10^9/L), respectively, while no significant differences were detected between group 1 and group 2 for Hb levels and platelet counts. However, a significant increase (P<0.001) in the mean values of CRP was detected in group 1 (7.51± 1.52 mg/L) and group 2 (6.63± 1.86 mg/L) compared to controls (2.15± 0.77 mg/L) and also between groups 1 and 2 (P= 0.049).

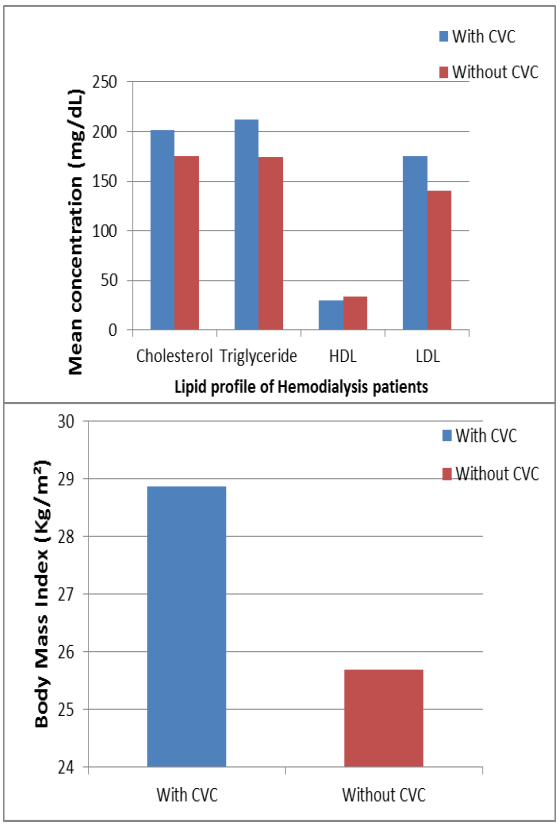

Figure 1. Lipid profile and body mass index as risk factors for cardiovascular complications.

Echocardiographic data

Although, there were significant increases in the values of end diastolic dimensions (EDD; mm), end systolic dimensions (ESD; mm), diastolic dysfunction (DD%) and wall motion (WM%) and significant decrease in ejection fraction (EF%) in group 1as compared to controls (P= 0.030, 0.022, 0.023, 0.001, and 0.001, respectively) yet there were no significant differences in all the cardiac parameters between group 1 and group 2 except in EF% and WM% P (< 0.002 and < 0.001, respectively), (Table 1).

Serum adiponectin concentrations

A highly significant increase in the mean values of ADPN concentrations in all ESRD patients (185.99± 44.63 ng/ml) was observed in comparison with controls (87.99± 17.72 ng/ml), (P< 0.001). In addition, both groups of CVC and non CVC patients had significant increases (P< 0.001) in ADPN concentrations; (152.47± 23.3 ng/ml) and (219.25± 34.96 ng/ml), respectively, compared with controls. However, patients with CVC had a significant decrease (P< 0.001) in ADPN concentrations compared to patients without CVC. Among patients with CVC and without CVC, 93.33% and 16.67%, respectively showed lower ADPN serum concentrations than the cut off of the normal controls. A highly significant difference was found between both groups of patients (P< 0.001) (Figure 2).

Diagnostic performance of adiponectin and ejection fraction in discrimination of the patients

Receiver operating characteristics (ROC) curve was used to define the best cut off values of ADPN and EF percentage which were <190.51 ng/ml and <57%, respectively, with sensitivity of 93.3% and 56.7%, respectively, specificity of 83.3% and 90%, respectively, positive predictive value of 84.8% and 82.4%, respectively, negative predictive value of 92.6% and 62.8, respectively, area under curve (AUC) of 94 .8% and 71.6% of the patients with

Table 1. Echocardiographic data of the studied population

Parameter	ESRD patients (N= 60)		Controls (N= 20)	P value
	With CVC	Without CVC		
EDD (mm) mean±SD Range	54.32±8.02 40-72	52.67±8.94 35-75	49.80±5.11 39-57	P1=0.030 P2=0.200 P3=0.456
ESD (mm) mean±SD Range	37.51±7.49 24-51	33.75±8.03 20-52	33.10±4.3825-40	P1=0.022 P2=0.744 P3=0.066
FS% mean±SD Range	34.60±9.64 21-57	36.21±5.62 18-46.5	33.60±3.86 27-40	P1=0.662 P2=0.077 P3=0.434
EF% mean±SD Range	57.13±10.48 30-71	64.97±6.5 50-76	63.20±5.78 54-76	P1=0.023 P2=0.331 P3= 0.002
Diast.Dys. % No Yes	13 (43.3%) 17 (56.7%)	13 (43.3%) 17 (56.7%)	20 (100%) 0 (0%)	P1<0.001 P2<0.001 P3=1.000
WM% No Yes	12 (40%) 18 (60%)	30 (100%) 0 (0%)	20 (100%) 0 (0%)	P1<0.001 P2=1.000 P3<0.001

EDD: end diastolic dimension; ESD: end systolic dimension; FS: fraction shortening; EF: ejection fraction; Diast. Dys: diastolic dysfunction; WM: wall motion.P1: significance between group 1 and group 3; P2: significance between group 2 and group 3; P3: significance between group 1 and group 2.

CVC and without CVC (Figure 3).

Correlation Coefficient between serum Adiponectin concentrations and risk factors

In CVC patients there were negative correlations between ADPN concentrations (ng/ml) and duration of dialysis (years) (r= -0.346, P = 0.049), EF (%) (r= -0.337, P= 0.049), LDL values (mg/dl) (r= -0.542, P= 0.002) and CRP values (mg/L) (r= -0.605, P< 0.001). In patients without CVC there were negative correlations between ADPN concentrations (ng/ml) and BMI (Kg/m²) (r= -0.811, P<0.001), CRP (mg/L) (r= -0.648, P< 0.001), LDL (mg/dl) (r= -0.785, P< 0.001) and TG (mg/dl) (r= -0.804, P< 0.001) (Figures 4-7).

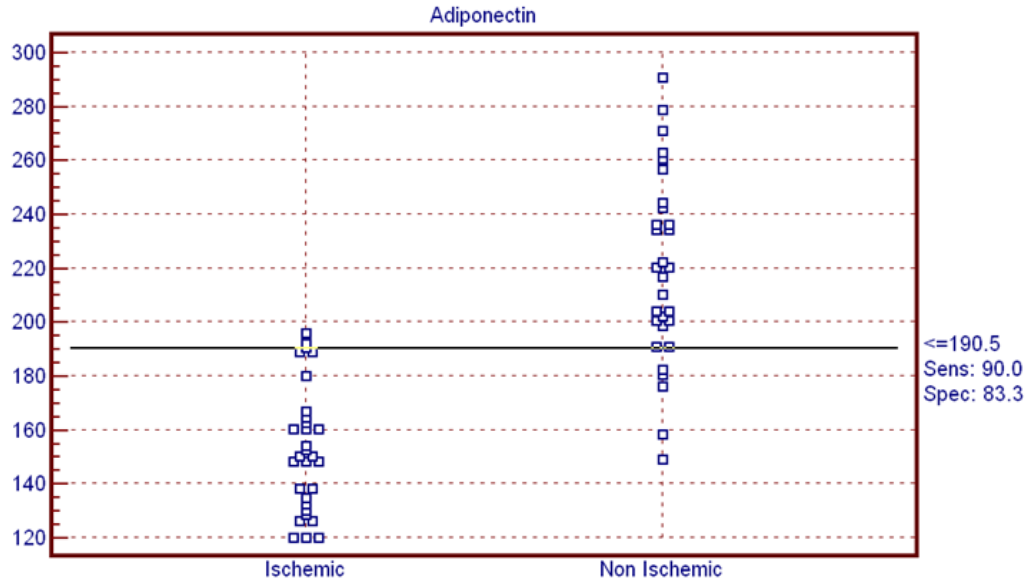

Figure 2. Adiponectin concentrations in patients with CVC and without CVC.

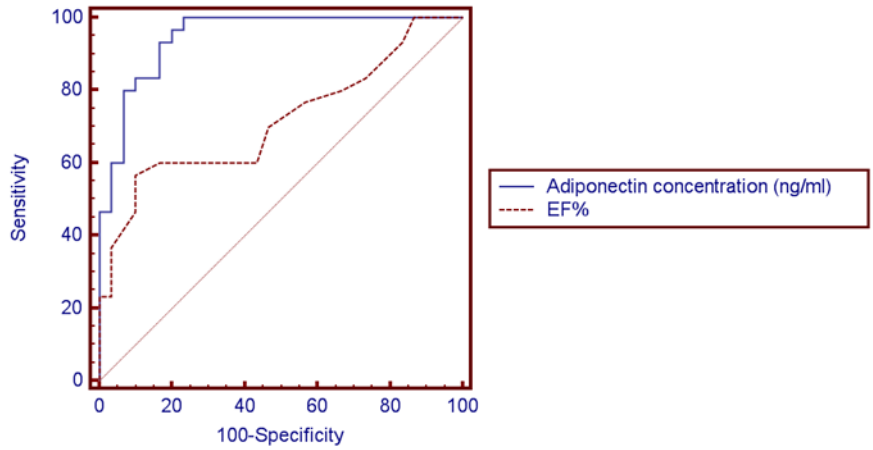

Figure 3. Receiver operating characteristics (ROC) curve to define the best cut off values of adiponectin concentrations and EF%.

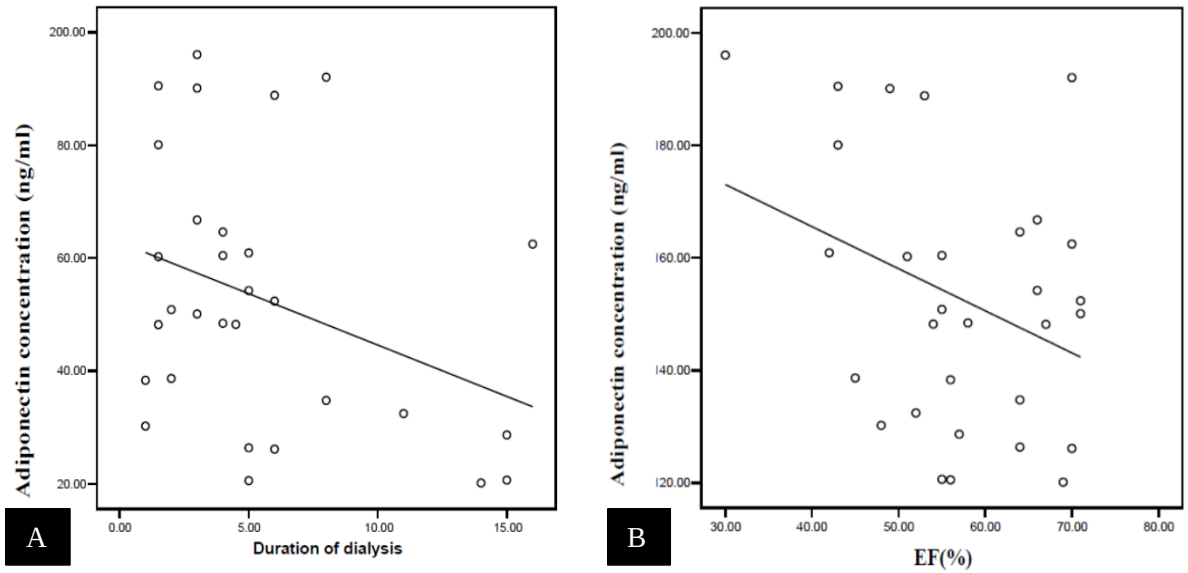

Figure 4. Correlation coefficient in CVC patients. A: between ADPN concentrations (ng/ml) and duration of dialysis (years) (r= -0.346, P= 0.049) B: between ADPN concentrations and EF (%) (r= -0.337, P= 0.049).

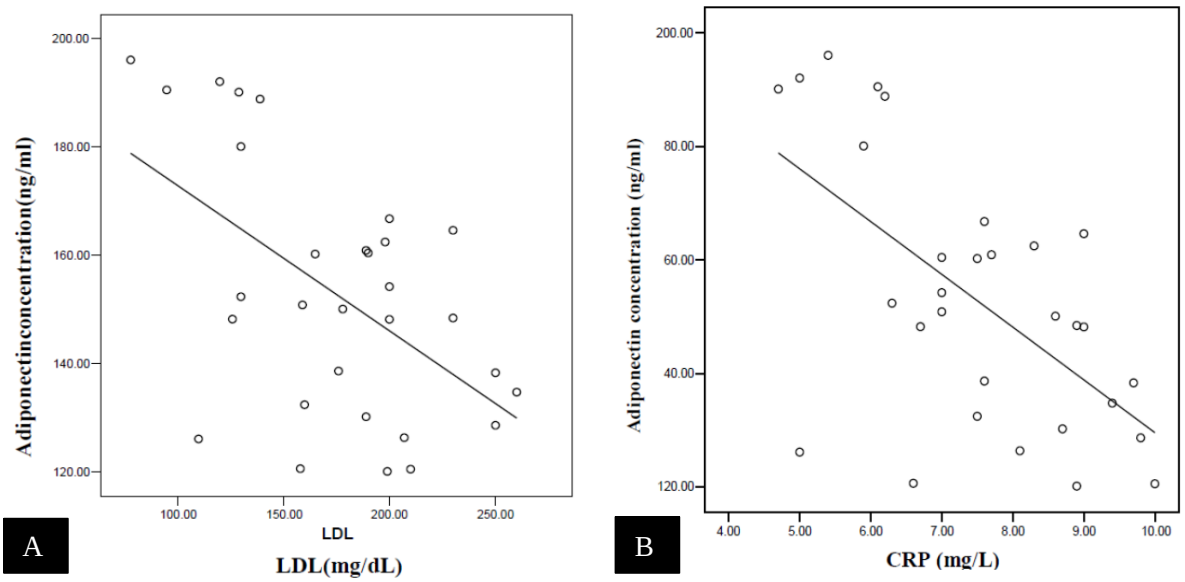

Figure 5. Correlation coefficient in CVC patients. A: between ADPN concentrations (ng/ml) and LDL values (mg/dl) (r= -0.542, P= 0.002); B: between ADPN concentrations (ng/ml) and CRP values (mg/L) (r= -0.605, P< 0.001).

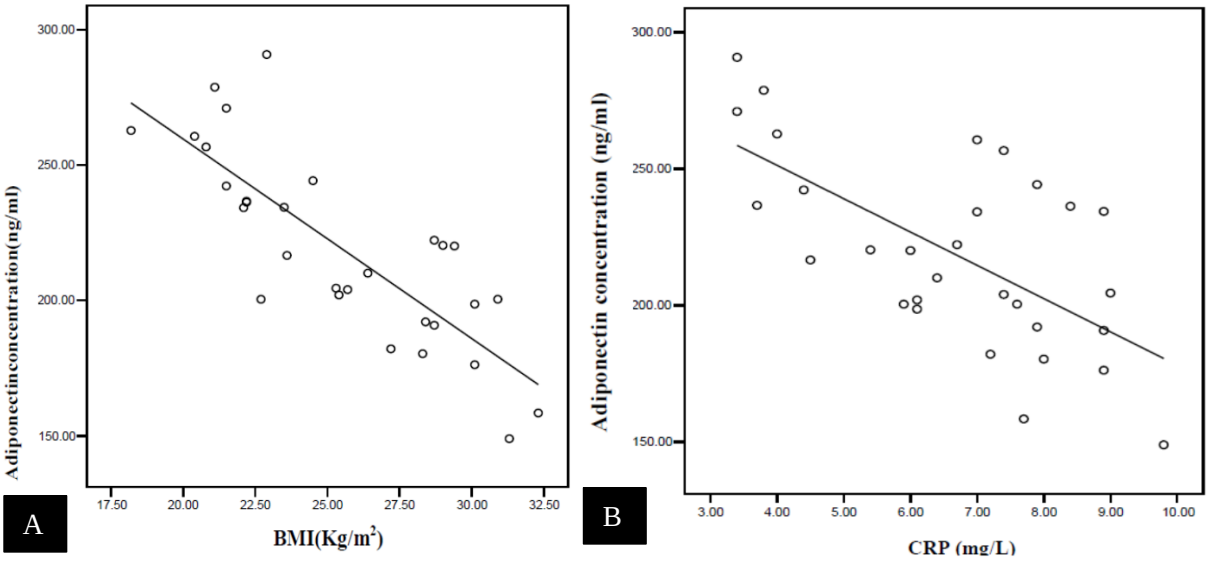

Figure 6. Correlation coefficient in patients without CVC. A: between ADPN concentrations (ng/ml) and BMI (Kg/m²) (r= -0.811, P< 0.001); B: between ADPN concentrations (ng/ml) and CRP (mg/L) (r= -0.648, P< 0.001).

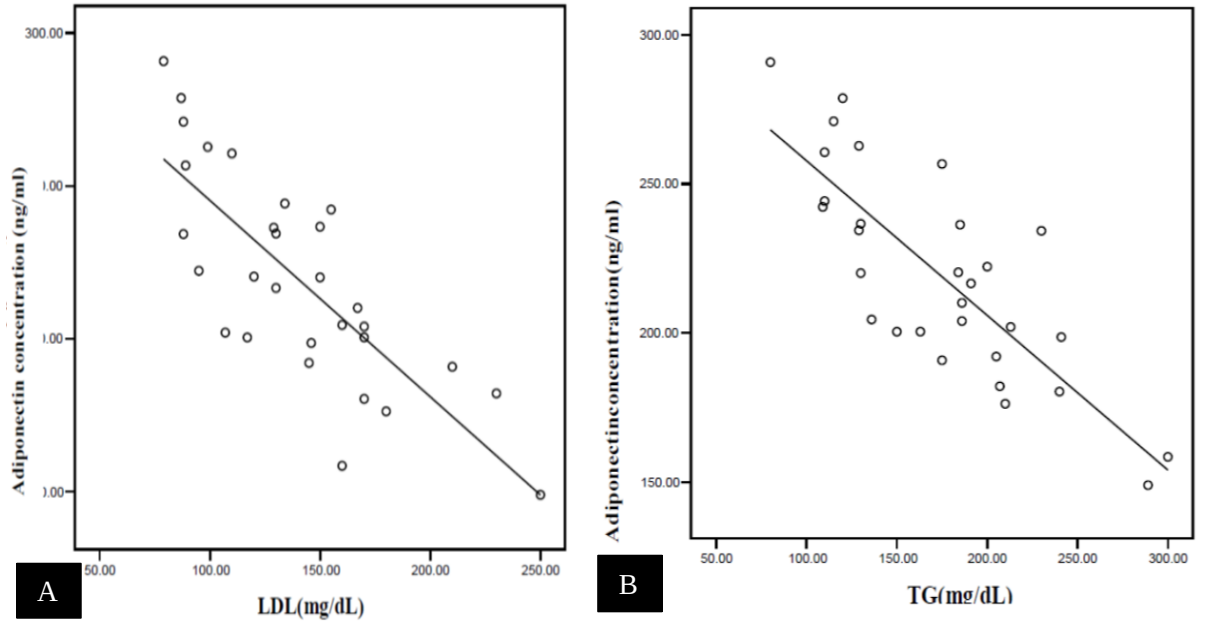

Figure 7. Correlation coefficient patients without CVC. A: between ADPN concentrations (ng/mland LDL (mg/dl) (r= -0.785, P< 0.001); B: between ADPN concentrations (ng/ml) and TG (mg/dl) (r= -0.804, P< 0.001).

Discussion

Cardiovascular disease is the most common complication and the chief cause of death in patients with ESRD. The mortality rate is 10 fold higher than in the general population. 80 percent of patients on maintenance HD developed CVC in China (9). The risk of developing CVC is associated with changes in the structure and function of the arterial system since atherosclerosis is the major cause of CVD and mortality globally (10). Several traditional and uremia-related risk factors are known to participate in the development of CVC and vascular calcification (1).

It has been suggested that ADPN has anti-inflammatory antiatherogenic effects and its levels may be influenced by the kidney diseases since it is excreted by the kidneys (11). Accordingly, the present study was designed to examine the possible role of ADPN as a predictor of CVC in adult patients with ESRD under HD and to evaluate the

relationship between ADPN levels and other risk factors of CVC in patients with CVC and without CVC compared to normal controls.

The mean BMI in patients without CVC was lower than patients with CVC and controls (P= 0.005, P=0.004) while in patients with CVC it was comparable with that of controls. This result may be due to exclusion of patients with diabetes and obesity from the study since the gene for ADPN is localized on chromosome 3q27; a region highlighted in affecting genetic susceptibility to type-2 diabetes and obesity (12). This result is consistent with that of- Elokely et al. (13) who reported that there was a significant differences in BMI between ESRD and controls, but disagreed with Abdallah et al. (11) who reported a significant higher BMI in ESRD without CVC than patients with CVC which is attributed to the metabolic alterations observed in the uremic milieu leading to malnutrition complication which is common in ESRD.

The finding that the most common cause of ESRD after exclusion of diabetes in both groups of patients was hypertension (43.3%) followed by obstructive uropathy (20%) is consistent with that of Adel et al. (14) in Egypt who reported that the first cause of ESRD is hypertension followed by diabetic nephropathy, and then chronic glomerulonephritis. Hypertension has long been considered as one of the most important traditional risk factors for CVC since it leads to the development of hypertensive nephrosclerosis with intimal thickening of the large and small vasculature (15). However, in the current study, patients with CVC had a significant lower blood pressure than patients without CVC which could be explained by the proper control of blood pressure in CVC group using nitrates that causes reduced blood pressure and lower EF. Previously, Larivière et al. reported that improved cardiovascular outcomes have been associated with blood pressure control (16). This result is in disagreement with the report of Moezzi et al. (11) who showed higher systolic pressure in ESRD patients with CVC compared to patients without CVC.

The present study showed that the most common cardiovascular manifestations in ESRD patients were angina 53% followed by myocardial infarction (MI) 33.33%. This result was in agreement with the findings of Abdallah et al. (11). In addition, Buraczynska et al. reported that CVC in ESRD patients may include coronary artery disease, congestive heart failure, ischemic stroke and left ventricular hypertrophy (17). Frequent episodes of hypotension during dialysis sessions are the leading cause of angina, arrhythmias and sudden cardiac arrest (18).

Dyslipidemia is a well-established risk factor for CVD morbidity and mortality (19). Although, our patients with CVC were receiving lipid lowering drugs yet, their TC, TG and LDL levels were higher than patients without CVC and controls (P= 0.004, P= 0.016, P< 0.001, respectively). These results were in agreement with the findings of other researches (3, 11, 20) who reported that the presence of lipids in the vascular wall has been regarded as one of the most important triggering factors for atherosclerosis. High levels of plasma lipids, particularly LDL are among the pathophysiologic stimuli that induce endothelial dysfunction. LDL particles but not HDL become glycated which lengthens their half-life and therefore increases their ability to promote atherogenesis (21).

Other risk factors such as duration of CKD, duration of HD, age and smoking were not recorded in patients with CVC. Although 50% of patients with CVC were smokers compared to 30% of patients without CVC, yet the difference was not significant. In contrast, other researches have reported that smoking is a risk factor for CVC since it causes oxidative stress that may cause DNA mutation and promote atherosclerosis (3, 22). Additionally in patients older than 60 years, it was reported that every additional year increases the mortality risk by about 3% (19).

In the current work, ADPN levels were found to be markedly elevated in all patients with ESRD compared with controls (P< 0.001). This study confirms earlier reports in which ADPN levels were 3 times higher among HD patients compared with controls (11). These results are also in concordance with other findings reporting consistent elevated ADPN levels among patients with advanced chronic kidney disease and differential ADPN retention after glomerular filtration rate declination (3, 23). The findings that both patient groups have significant ADPN concentrations increase compared with controls (P<0.001), and significant decrease in patients with CVC compared with patients without CVC (P<0.001) are in agreement with the report of Abdallah et al. (11) who found lower levels of ADPN among CVC patients compared to CVC-free patients. Moreover, they reported lower ADPN levels in males, as well as in patients with obesity, insulin resistance, type-2 diabetes mellitus, coronary artery disease, and essential hypertension. Kaysen et al. showed that each 1 µg/ml increase in ADPN was associated with a 3% risk reduction in new cardiovascular events in hemodialysis patients (24).

Interestingly, the present study confirms the association of serum ADPN with several risk factors, in a way consistent with the hypothesis that ADPN has a protective effect in patients at high risk of CVC among HD patients. In ESRD patients with CVC, correlation studies revealed that ADNP levels were negatively correlated with duration of dialysis (r= -0.346, P= 0.049), serum LDL levels (r= -0.542, P= 0.002), CRP levels (P< 0.001) and EF% (r= -0.337, P= 0.049). However, in ESRD patients without CVC it is negatively correlated with BMI (r= -0.811, P< 0.001), TC (r= -0.475, P= 0.008), TG (r= -0.804, P< 0.001), LDL (r= -0.785, P< 0.001) and CRP (r= -0.648, P< 0.001) and positively correlated with HDL level (r= 0.411, P= 0.024). These results suggest that ADPN has a potential protective role against the development of cardiovascular events in patients with kidney disease. ADPN regulates the metabolism of lipids and glucose, influences the body's response to insulin (antidiabetic), and has anti-inflammatory effects on the cells lining the walls of blood vessels (25, 26). Evidence suggests also that ADPN has anti-atherogenic properties by improving endothelial function by suppressing TNF-α induced expression of adhesion molecules, prevents macrophage's transformation into foam cells, suppresses human aortic smooth muscle cells proliferation, and exerts indirect antioxidant effects on human myocardium. Low levels of adiponectin are found in people who are at increased risk of a heart attack and contribute to atherogenesis (27).

The current results are in concordance with previous results reporting that ADPN levels were inversely correlated with BMI, insulin levels, TG, LDL, CRP and left ventricular index, and directly related to HDL (11, 13, 28). The link between BMI and ADPN seems to be a causal one because weight loss induces a marked increase in plasma ADPN levels among both normal people and HD patients (3). In addition, it was demonstrated that ADPN affects the regulation of lipid metabolism in peripheral tissues decreasing tissue fatty acids content and serum levels by activation of the cAMP dependent kinase pathway and subsequent fatty acid oxidation increase which seems to be the main mechanism of action of the hormone in the regulation of lipid metabolism (13, 29). The present study failed to show a significant correlations in CVC patients between ADPN and total cholesterol, TG, and HDL. These findings were in agreement with the report of Amani et al, (30), but in disagreement with the findings of Elokely et al. (13). This can be explained by the use of lipid lowering drugs in CVC group of patients.

The finding that ADPN levels varied inversely with CRP (P= 0.001) is in agreement with multiple studies, that proved ADPN to be inversely associated with inflammation markers including CRP (3). In HD patients, CRP is a strong predictor of death in CVC. ADPN seems to play an important

role in vascular homeostasis by affecting important inflammatory mechanisms involved in CVD and atherogenesis. It interferes with NF-kB suppressing adhesion molecules and TNF-α, induces the production of anti-inflammatory mediators IL-10 and IL-1RA in human inflammatory cells, and impairs IFN-γ. Lower ADPN levels were reported to be independent predictor for the composite outcome of fatal and non-fatal CVD but not for all-cause mortality among ESRD patients (31).

In the present study, there was a significant negative correlation between serum ADPN concentrations and echocardiographic parameters of systolic function such as EF and fractional shortening. This suggests a strong relationship between ADPN levels and systolic dysfunction in HD patients. Other studies demonstrated that ADPN accumulates in myocardial tissue that has been damaged by ischemia and protects it by inhibiting inducible NOS and NADPH-oxidase, and the oxidative stress. The same finding was reported previously (32, 33) by others who claimed that ADPN regulates energy homeostasis in cardiac muscle, increases cardiac fatty acids oxidation and exerts therefore a direct cardio-protective action if not alters its course and outcome (32).

The sensitivity of ADPN detection was found to be higher (93.3%) than that of EF% (56.7%) while their specificity was comparable with each other (83.3% vs. 90%). The positive predictive value and negative predictive value for ADPN were found to be higher than EF% (84.8% vs. 82.4% and 92.6% vs. 62.8%, respectively).

The results of the current study point out to the possibility to use serum ADPN level as a predictive marker of CVC in ESRD and progression of CKD, and may help in planning preventive strategies for ischemic heart disease.

Conflict of interest

The authors declared no conflict of interest.

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