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CLINICAL STUDY

Adiponectin, leptin, nitric oxide, and C-reactive protein levels in kidney transplant recipients: comparison with the hemodialysis and chronic renal failure

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ABSTRACT

Background: Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in patients with chronic kidney disease (CKD) including kidney transplant recipients (KTR). Secondary lipid metabolism disorders, endothelial dysfunction, and inflammation enhance the risk of CVD development in these patients. The aim of the present study was to investigate the lipid profile, adiponectin, leptin, nitric oxide (NO), and high sensitivity C-reactive protein (hs-CRP) levels in KTR and to compare these parameters with those of the patients with chronic renal failure (CRF), hemodialysis (HD) patients, and healthy controls.

Methods: Serum adiponectin and leptin levels were measured by radioimmunoassay; hs-CRP was determined immunoturbidimetrically. Determination of NO was based on the Griess reaction.

Results: Compared with the control group, serum NO and adiponectin levels were significantly higher in the KTR, CRF, and HD groups; hs-CRP levels were significantly higher in the KTR and HD groups; leptin levels were significantly higher in the KTR. In addition, serum NO level was significantly higher in the KTR compared to CRF cases. Adiponectin correlated positively with high density lipoprotein-cholesterol in the control and patient groups. A positive correlation was observed between hs-CRP and NO in the KTR and the patients with CRF. Serum adiponectin levels were inversely correlated with hs-CRP and leptin in the HD group.

Conclusion: KTR suffer from inflammation and accompanying changes in levels of adipocytokines and NO which contribute to the increased risk of CVD in these patients.

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Kidney transplantation; nitric oxide; C-reactive protein; adiponectin; leptin

Introduction

Cardiovascular disease (CVD) is the major cause of mortality in patients with chronic kidney disease (CKD).[1] Kidney transplantation, that offers a significant improvement in renal function as well as in metabolic disorders associated with uremia, is considered as the best treatment option for patients with end-stage renal disease (ESRD). However, when compared to the general population, kidney transplant recipients (KTR) have a fourfold higher risk of CVD, and a twofold higher risk of cardiovascular death.[2] The increased risk of CVD in patients with CKD, including KTR, is not fully explained by classical risk factors such as dyslipidemia, hypertension, etc. and several authors suggest that CVD in KTR is partially attributed to non-classical cardiovascular risk factors, including nitric oxide (NO) and adipocytokines.[3,4]

Endothelial dysfunction, which is related to inflammation, is characterized by diminished endothelial NO production and is associated with the development and progression of atherosclerosis.[5] NO maintains proper vascular function by enhancing vasodilation and inhibiting platelet aggregation, monocyte adhesion, smooth muscle cell proliferation, and by its anti-inflammatory effects.[6,7] Adipocytokines, particularly adiponectin and leptin, have been implicated in the pathogenesis of CVD through a crosstalk between adipose tissue and blood vessels and they are suggested to be associated with inflammation and NO production.[8] Leptin and adiponectin generally elicit opposing pro-inflammatory and anti-inflammatory effects.[9] It has been reported that adiponectin exerts vascular-protective effects by improving endothelial function and having anti-inflammatory potency in the vascular wall. It was shown that adiponectin stimulates the production of NO in endothelial cells and improves NO bioavailability and endothelial dysfunction.[10]

Leptin may participate in the development and progression of the atherogenesis through activation of

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inflammatory processes, endothelial cell dysfunction, platelet aggregation, and oxidative stress.[11,12] Most clinical studies alluded that leptin augments the risk of cardiovascular events.[13,14] However, some clinical studies failed to find a significant association between leptin and the incidence of CVD.[15,16] The interaction between leptin and NO production is also controversial. In an animal model study, leptin injection induced systemic oxidative stress and reduced the bioavailability of NO in male Wistar rats.[12] At the molecular level, the effect of leptin on endothelial function is unclear as leptin both stimulates the activity of endothelial nitric oxide synthase (eNOS) and reduces the bioavailability of L-arginine required for NO synthesis.[17,18] However, in another study, leptin promoted NO production, thereby generating antiatherogenic effects.[19] Ku et al.[20] and Basati et al.[21] reported that low leptin levels are correlated with higher cardiovascular events and mortality in patients with stable coronary artery disease. Furthermore, some cardio protective effects of leptin have been reported in experimental settings.[22,23]

In CKD, the clinical significance and prognostic implications of leptin and adiponectin are not well understood. Patients with CKD have increased circulating levels of both adipokines that may result from an increase in their systemic production and/or decrease in their renal clearance.[24–27]

In KTR, the most common cause of late allograft loss and leading cause of KTR deaths is CVD.[28] There are still unanswered points about how and why KTR keep on suffering from CVD despite the restoration of glomerular dysfunction. The interaction between adiponectin, leptin, and NO seems to affect inflammation and endothelial dysfunction which play important role in the pathophysiology of atherosclerosis and need to be well understood since they can predict CVD or may help to develop new treatment strategies. In the present study, our aim was to compare the levels of these parameters in KTR, patients with chronic renal failure (CRF), patients under hemodialysis (HD) treatment, and healthy controls.

Materials and methods

Study population and design

The study was approved by the Ethics Committee of Uludag University Medical Faculty. All participants gave their written informed consent.

The study was performed on 18 non-diabetic patients with CRF (Stages 3 and 4) on conservative treatment (mean age 42 ± 13 years, eight female, 10 male), 18 non-diabetic HD patients (mean age 31 ± 8 years, nine female, nine male), and 18 non-diabetic KTR (mean age 36 ± 10 years, nine female, nine male). Exclusion criteria were having overt atherosclerotic disease, congestive heart failure, and <6 month post transplantation. Recipients were receiving tacrolimus ($n=9$) or cyclosporine ($n=9$), mycophenolate mofetil, or azathioprine and corticosteroids. All HD patients were on dialysis three times weekly. The control group consisted of 18 healthy subjects (10 males, eight females, mean age 34 ± 7 years) without clinical or laboratory evidence of renal disease or diabetes.

Blood specimens were collected after an 8-h overnight fast. Samples were immediately centrifuged and serum stored at −80 °C until assayed.

Laboratory assays

Serum glucose, urea, creatinine, total cholesterol (TC), triglyceride (TG), and high density lipoprotein-cholesterol (HDL-C) levels were evaluated by routine methods used in our laboratory. Low density lipoprotein-cholesterol (LDL-C) was calculated according to Friedewald's formula. Serum high-sensitivity-C-reactive protein (hs-CRP), apolipoprotein A1 (Apo A1), apolipoprotein B (Apo B), and lipoprotein (a) [(Lp (a)] concentrations were measured by immunoturbidimetric assays (Aeroset, Abbott, IL).

Serum adiponectin and leptin were measured using commercially available radioimmunoassay kits (Human Adiponectin RIA Kit and Human Leptin RIA Kit, Linco Research, Inc., St Louis, MO, respectively). Total serum level of nitrite and nitrate (NO) was measured with enzymatic conversion and followed by Griess reaction (Nitric Oxide Colorimetric Assay Kit, Roche, Mannheim, Germany). The inter- and intra-assay coefficients of variation were $<10\%$.

Statistical analysis

Data were analyzed using the SPSS 13.0 statistical package. Conformity of variables with normal distribution was tested with the Kolmogorov–Smirnov test. Results are expressed as mean ± standard deviation or median (interquartile range), depending on data distribution. Differences between groups were tested by the Wilcoxon or Mann–Whitney *U* test as appropriate. Associations between variables were estimated using Pearson or Spearman correlation coefficients. Values of $p<.05$ were considered statistically significant.

Results

Comparison of demographic data of the patient groups and healthy volunteers are presented in Table 1.

Table 1. Demographic and clinical characteristics of kidney transplant recipients, patients with chronic renal failure, hemodialysis patients, and the control group.

	Control	CRF	HD	KTR
Age (years)	34 ± 7	42 ± 13[a,d]	31 ± 8[b,d]	36 ± 10[b,d,c,d]
Male/female	10/8	10/8	9/9	9/9
BMI (kg/m^2)	24.6 ± 4.4	24.5 ± 5.1	21.7 ± 6.9[a,d,b,d]	26.2 ± 4.5[b,e,c,d]
Hypertension	0 (0%)	12 (66%)[a,e]	3 (17%)[b,e]	11 (61%)[a,e,c,d]
Smokers	7 (38%)	4 (22%)	4 (22%)	4 (22%)
Duration of disease/HD/Post-Tx (months)	–	49 ± 41	85 ± 51	57 ± 50

Data are provided as means ± standard deviations or *n* (%).
KTR: kidney transplant recipients; BMI: body mass index; Post-Tx: post-transplantation.
[a]vs. controls.
[b]vs. chronic renal failure (CRF).
[c]vs. hemodialysis (HD).
[d]$p < .05$.
[e]$p < .01$.

Table 2. Biochemical characteristics (mg/dL) of the groups.

	Control	CRF	HD	KTR
Urea	28 ± 7	98 ± 51[a,e]	124 ± 21[a,e,b,d]	40 ± 16[a,d,c,e]
Creatinine	0.9 ± 0.1	2.4 ± 1.1[a,e]	8.7 ± 1.9[a,e,b,e]	1.3 ± 0.3[a,e,c,e]
TC	185 ± 89	216 ± 55	157 ± 85[a,d,b,e]	206 ± 51[c,d]
TG	122 ± 72	197 ± 92[a,d]	151 ± 81	176 ± 83[a,d]
LDL-C	109 ± 82	128 ± 40	83 ± 22[a,d,b,d]	125 ± 40[c,e]
HDL-C	53 ± 14	57 ± 28	40 ± 9[a,d,b,d]	48 ± 10[c,d]
Apo A1	114 ± 31	126 ± 25	101 ± 24[b,d]	125 ± 19[c,d]
Apo B	77 ± 26	125 ± 43[a,e]	76 ± 22[b,e]	92 ± 25[b,d,c,d]
Lp (a)	12.5 (2–39)	48.0[a,d] (13.3–114.8)	14.0 (8.5–60.5)	4.5[b,d] (1.8–45)

Data are given as means ± standard deviations or as medians (interquartile ranges 25–75%).
KTR: kidney transplant recipients; TC: total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; Apo A1: apolipoprotein A1; Apo B: apolipoprotein B; Lp (a): lipoprotein (a).
[a]vs. controls.
[b]vs. chronic renal failure (CRF).
[c]vs. hemodialysis (HD).
[d]$p < .05$.
[e]$p < .01$.

The CRF group was older than the control, the HD and the KTR groups and KTR group was older than the HD group ($p < .05$ for each group comparison). The CRF and KTR groups had a higher proportion of patients with hypertension than the control and the HD groups ($p < .01$, except the comparison of KTR vs. HD which is $p < .05$). Body mass index (BMI) of the HD group was lower than all the study groups ($p < .05$) and BMI of the CRF group was lower than the KTR group ($p < .01$).

Biochemical data from patients and controls are presented in Table 2. In patients with CRF, HD, and KTR, serum urea ($p < .01$, $p < .01$, and $p < .05$, respectively) and creatinine ($p < .01$ for each comparison) were significantly higher than in those of healthy subjects. TC levels were lower in the HD group compared to those of the CRF ($p < .01$), KTR ($p < .05$), and control ($p < .05$) groups. LDL-C levels were significantly lower in HD patients when compared to CRF ($p < .05$), KTR ($p < .01$), and control subjects ($p < .05$). HDL-C levels of HD patients were statistically lower compared to those of CRF, KTR, and controls ($p < .05$). Apo A1 levels were lower ($p < .05$) in the HD group than those of the CRF and KTR groups and apo B levels were lower in the control ($p < .01$), HD ($p < .01$), and KTR ($p < .05$) groups compared with the CRF group. Apo B levels were lower ($p < .05$) in the HD group compared with the KTR group. Serum TG levels were significantly higher ($p < .05$) in the CRF and KTR patients than those of the healthy volunteers. Lp (a) was significantly higher ($p < .05$) in CRF cases compared to control and KTR groups.

In patients with CRF, HD and KTR, serum NO and adiponectin were significantly higher than in healthy volunteers ($p < .01$ for each comparison, except $p < .05$ for NO between the CRF and the control groups). The KTR cases had the higher levels of NO compared with the CRF group ($p < .05$). The patients were similar in regard to adiponectin levels. Leptin concentrations were also higher in the patient groups compared to the controls; however, statistical significance was observed merely in the KTR group ($p < .01$). HD ($p < .01$) and KTR ($p < .05$) groups exhibited significantly increased hs-CRP levels relative to control subjects and HD patients had higher

Table 3. Serum concentrations of nitric oxide, adiponectin, leptin, and hs-CRP in the control subjects and the patient groups.

	Control	CRF	HD	KTR
Nitric oxide, μmol/L	15.3 ± 18.4	26.9 ± 16.6[a,c]	42.2 ± 26.1[a,d]	43.7 ± 28.9[a,d,b,c]
Adiponectin, μg/mL	6.8 ± 4.9	16.4 ± 10.7[a,d]	14.8 ± 7.1[a,d]	14.4 ± 6.9[a,d]
Leptin, ng/mL	6.9 ± 4.2	24.1 ± 34.1	26.3 ± 35.8	22.9 ± 20.4[a,d]
hs-CRP, mg/dL	0.16 ± 0.17	0.33 ± 0.32	1.09 ± 1.74[a,d,b,c]	0.52 ± 0.81[a,c]

Data are given as means ± standard deviations.
[a]vs. controls.
[b]vs. chronic renal failure (CRF).
[c]$p < .05$.
[d]$p < .01$.

($p < .05$) hs-CRP levels compared with those of the patients with CRF (Table 3).

The KTR, in the present study were divided into subgroups according to immunosuppressive regimen used, to examine the effect of these medications. Nine subjects were treated with cyclosporine and nine with tacrolimus. No significant differences were observed between the two groups of patients with regard to the studied parameters (data not shown).

Correlation analysis: Serum adiponectin levels correlated positively with HDL-C in all four cohorts (Control: $r = .751$; $p < .01$, CRF: $r = .471$; $p < .05$, HD: $r = .499$; $p < .05$, KTR: $r = .624$; $p < .01$). In patients with CRF, leptin was inversely related to LDL-C ($r = -.608$; $p < .05$), whereas in HD patients leptin correlated positively with TG ($r = .627$; $p < .05$). In HD patients, adiponectin correlated negatively with leptin and hs-CRP ($r = -.655$; $p < .05$ and $r = -.390$; $p < .05$, respectively). In KTR group, leptin correlated with Lp (a) and apo B ($r = .568$; $p < .05$ and $r = .656$; $p < .05$, respectively). hs-CRP was positively correlated with NO in the CRF and KTR groups (CRF: $r = .665$; $p < .01$, KTR: $r = .635$; $p < .01$).

Discussion

In the present study, we have demonstrated high levels of hs-CRP in CKD, including KTR which might suggest an ongoing inflammatory process even after transplantation. Our finding is in parallel with several studies.[29–32] The reports of Çankaya et al.[33] and Idorn et al.[34] declaring that there were not any significant differences in CRP levels during a 12-months of follow up after transplantation, support our findings, as well. However Colak et al.[35] and Chitalia et al.[36] reported that CRP levels were not different in KT patients compared to those of the controls. Taking the other patient groups of the present study into consideration, although not statistically significant, hs-CRP level was remarkably higher in the HD group which partly supports the findings of Oflaz et al.[30] and Locsey et al.[31] who reported high levels of CRP in HD patients compared to those of the KT patients. In HD, contamination of dialysate, chlamydial infection and low clearance are kept responsible for elevated CRP levels.[37,38]

In line with Malyszko et al.[39] we found higher levels of adiponectin in KTR patients compared to those of the controls. This finding is in contrast with other studies reporting reduced adiponectin levels after transplantation.[34,40] Chudek et al.[41] found significantly reduced levels in adiponectin (from 20.8 ± 8.3 μg/mL to 15.7 ± 7.0 μg/mL) after (29 ± 14 days) transplantation of patients under HD, however they did not compare their post-transplantation results with those of the healthy control group (8.7 ± 4.8 μg/mL). Several studies have shown that kidney transplantation was followed by a significant reduction of plasma adiponectin level; however, no correlation was found between plasma adiponectin levels and serum creatinine level or glomerular filtration rate in those reports. These findings were interpreted as glucocorticoids and other immunosuppressive drugs affecting the secretion and biodegradation of adiponectin and kidneys having part in elimination of this molecule.[34,41] In the present study, adiponectin levels were significantly higher in all the patient groups than those of the controls and there were not any significant differences among the patient groups. In parallel with our results, Diez et al.[42] and Tentolouris et al.[43] did not find any differences in adiponectin levels between the CRF and HD patient groups. However, Malyszko et al.[39] and Adamczak et al.[44] reported increased levels of adiponectin in HD patients compared with those of the CRF or KT patient groups and KTR or control groups, respectively. In another study, Ambarkar et al.[45] investigated adiponectin levels of CRF patients and reported reduced levels of adiponectin in those patients compared to the healthy subjects; however, those authors found an increment in adiponectin levels as the stage of the CRF advanced and suggested that the increment might be related to the progressed kidney dysfunction.

Several studies reported a negative correlation between adiponectin and CRP levels in patients with

CKD, however in our study there was a significant negative correlation between these two parameters only in the HD group. In another study, Guebre-Egziabher et al.[46] did not find any association between plasma adiponectin levels and CRP in patients with ESRD and this was attributed to these patients' not experiencing any inflammatory event.

In the present study, KT group was the only patient group which had significantly higher levels of leptin than the control group and there were not any significant differences among the patient groups. In line with our findings Tsai et al.[47] reported significantly higher levels of leptin in KT patients compared to the control group. In their study, Malyszko et al.[39] reported increased levels of leptin in CRF, HD and KT groups than the control group and there were not any significant differences among the three patient groups. In contrast with our results, El Haggan et al.[48] reported that increased leptin levels significantly reduced after transplantation and became comparable to those of the control values during six months after transplantation. Nicoletto et al.[49] found decreased leptin levels during one year after transplantation; however those authors observed that after five years leptin levels reached the pre-transplant levels which were significantly higher than those the healthy controls. In the present study, the length of post transplantation period was 57 ± 50 months which might partly explain the discrepancy in leptin levels between the study of El Haggan et al.[48] and ours. We observed significant positive correlations between adiponectin and HDL-C in the control and the patient groups. This finding is consistent with the findings of previous reports.[50,51] On the other hand, it has been reported that adiponectin did not show a relationship with lipids in patients with CRF and KTRs.[36]

Nitric oxide levels were significantly higher in the all of the patient groups than the control group and KT patients had significantly higher NO levels than the CRF group. Increased NO synthesis had been related to an increase in NOS activity in response to uremic toxins and it was suggested that increased NO levels might be a defence mechanism against hypertension of uremia.[52] In addition, in the present study, the significant difference in NO levels between the KT and CRF patients might be related to the immunosuppressive treatment since cyclosporine had been associated with eNOS overexpression.[53] In parallel with our results Calo et al.,[53] Stojanovic et al.,[54] and Minz et al.[55] found increased levels of NO in KT patients compared with those of the control group. In our study, NO levels were significantly positively correlated with hs-CRP levels in the KT and the CRF groups, which might suggest a protective mechanism of endothelium in response to inflammation. However, in the HD group, although both hs-CRP and NO levels were increased, lack of a correlation suggests an inadequate production of NO in response to accelerated inflammation observed in HD patients.

Dyslipidemia has been accepted as a major risk factor for CVD. Castillo et al.[56] concluded that KT was associated with a typical pattern of lipid alterations, characterized by higher levels of TC, LDL-C, HDL-C, and TG. Several clinical studies have shown that immunosuppressants increase serum levels of cholesterol, TG and LDL-C, usually in a dose-dependent manner.[57,58] In the present study, KTR and CRF patients had increased TG levels compared with those of the control group. Lp (a) and apo B were also significantly higher in CRF cases compared to controls. TC, LDL-C, and HDL-C levels of the HD group were significantly lower than those of the all study groups. In line with our finding, Kimak et al.[59] found increased TG levels in KT patients than those of the controls. However, Tsai et al.[47] reported increased TC levels and Çolak et al.[60] did not find any significant differences between the KTR, HD, and the control groups.

There are several limitations of the present study, starting with the limited number of patients in the study groups. The study groups were not homogenous with respect to age and BMI. The KT group consisted of patients under cyclosporine or tacrolimus therapy and also had been using mycophenolate mofetil, or azathioprine and corticosteroids. As we mentioned in the results section there were not any significant differences between KT patients using tacrolimus or cyclosporine with regard to the studied parameters of this study. In line with our results, Stojanovic et al.[54] did not find any difference in NO levels between the tacrolimus and cyclosporine treated KT patients. Hypertension might also be a confusing factor affecting NO levels. In the present study, the distribution of the patients with hypertension were not different between the CRF and the KT groups, however NO levels were significantly higher in the KT group than those of the CRF group. We would like to point out that our aim was to investigate these parameters after KT in daily management and the drugs mentioned above and hypertension are factors that cannot be excluded in daily practice.

Chronic kidney disease is a very heterogeneous condition with several underlying illnesses. The studies investigating CKD are faced with several difficulties, other than the heterogeneity of the underlying disease; the duration of the illness, accompanying diseases, the medication or treatment (such as HD) and their duration. Furthermore, the parameters of the present study, adipokines and NO are affected by age, BMI,

inflammation, medication, etc. Therefore, it is very hard to compare the results of one study with others.

In conclusion, the levels of adiponectin, leptin, NO, and hs-CRP were increased in all patients with CKD. KTR suffer from inflammation and accompany with changes in the levels of adipocytokines and NO, all of which play role in the increased risk of CVD in the post-transplantation period. Higher adiponectin, leptin, and NO levels may represent compensatory response to the inflammatory status. Further studies investigating these parameters in large samples could provide beneficial information for the prediction and treatment strategies for CVD in this population.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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