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Original Article

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Inflammation and Oxidative Stress Markers and Their Relationship in Kidney Transplant Recipients

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ABSTRACT

Objective: Inflammation and oxidative stress are the 2 well-known physiopathological processes involved in the onset and progression of atherosclerosis and can play role in the poor prognosis of kidney transplantation. However, there is no satisfactory evidence for their markers to be used for the diagnosis and/or follow-up of cardiovascular disease in daily practice. We aimed to investigate inflammation and oxidative stress markers in kidney transplant recipients long after transplantation.
Methods: This study was carried out with 62 kidney transplant recipients (34 females and 28 males) who had received a successful transplant at least before 6 months. A group of 50 healthy individuals (28 females and 22 males) were selected as controls.
Results: Homocysteine, advanced glycation end products, high sensitivity C-reactive protein, insulin-like growth factor-1, protein S-100B, and vitamin A levels were higher; vitamin E levels and paraoxonase and arylesterase activities were significantly lower in kidney transplant recipients.
Conclusion: Kidney transplant recipients are exposed to inflammation and oxidative stress a long time after kidney transplantation. These processes initiated by the body in order to defend itself may damage the tissues after a certain stage, so further studies investigating treatment strategies for reducing inflammation and oxidative stress load and their effects on the prognosis of kidney transplant recipients are needed.
Keywords: Kidney transplantation, oxidative stress, inflammation

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INTRODUCTION

Atherosclerotic cardiovascular disease (CVD) is the most frequent causation of late allograft loss and deaths in kidney transplant recipients (KTRs). Although kidney function is recovered by transplantation, it is still unknown why and how KTRs suffer from atherosclerosis and related disorders. Inflammation and oxidative stress are the 2 well-known physiopathological processes involved in the onset and progression of atherosclerosis and can play role in the poor prognosis of kidney transplantation.[1]

It is well known that atherosclerosis has been associated with chronic inflammation, and high-sensitivity C-reactive protein (hs-CRP) is one of the minor risk factors of CVD; however, its use in daily practice is limited.[2] Advanced glycation end products (AGEs) are among the molecules that were shown to be involved in both of the physiopathologic mechanisms mentioned above. Advanced glycation end products have been accepted as a marker of oxidative stress, and it was shown that these molecules lead to release of inflammatory molecules. Increased AGEs formation had been

reported in many diseases including CVD and chronic kidney failure.[3] Advanced glycation end products act through receptor for AGE (RAGE), and protein S100B is one of the ligands for RAGE. It was reported that protein S100B activates RAGE-related inflammatory mechanisms and stimulates the expression of adhesion molecules and inflammatory cytokines leading to atherosclerosis formation.[4]

Paraoxonase (PON 1) is a high-density lipoprotein (HDL)-bound antioxidant enzyme that protects low-density lipoprotein (LDL) from being oxidized. Inhibition of PON 1 activity plays a role in atherogenesis.[5] Vitamin E is the most abundant antioxidant found in lipoproteins and also the first-step antioxidant defender against LDL oxidation.[6] Paraoxonase exerts various activities toward different substrates; such as paraoxon (PON 1 activity), phenylacetate (arylesterase activity), and homocysteine thiolactone (lactonase activity). It was shown that lactonase activity was reduced in KTRs, which might be one of the contributing factors to the increased homocysteine (Hcy) levels in this group.[7] Hyperhomocysteinemia is another minor risk factor of CVD; however, so as hs-CRP, its use in daily practice is limited.[8]

Insulin-like growth factor-1 (IGF-1) is associated with atherogenesis; however, data about its effects on inflammatory and oxidative–antioxidative mechanisms are confusing. Insulin-like growth factor-1 binds to IGF-binding proteins (IGFBP), and IGFBP-3 is the most abundant one.[9] It was suggested that IGFBP-3 is associated with coronary events and intima–media thickness and exerts anti-inflammatory effects.[10] Both IGF-1 and IGFBP-3 need to be further investigated in atherogenesis and CVD.

Although inflammation and oxidative stress are believed to be fundamental mechanisms of atherogenesis and CVD, there is no satisfactory evidence for their markers to be used for the diagnosis and/or follow-up of CVD in daily practice. However, in the case of kidney transplantation, some authors suggested that the development of coronary events could not solely be explained by traditional risk factors and risk factors other than traditional ones may additionally play important role in the progression of CVD in those patients. We aimed to investigate inflammation and oxidative stress markers in KTRs. Therefore, we measured serum PON 1 and arylesterase activities and serum AGEs, vitamin E, vitamin A, protein S100B, hs-CRP, IGF-1, IGFBP-3, and plasma Hcy levels, which were associated with either inflammatory pathways or oxidative stress or both.

MAIN POINTS

- Serum advanced glycation end products, high sensitivity C-reactive protein, insulin-like growth factor-1, protein S-100B, homocysteine, and vitamin A levels were higher in kidney transplant recipients.
- Reduced levels of vitamin E and paraoxonase and arylesterase activities might be the reflection of oxidative stress in kidney transplant recipients and be one of the contributing factors to the increased risk of cardiovascular disease in these patients.
- Kidney transplant recipients are exposed to inflammation and oxidative stress a long time after kidney transplantation.

METHODS

Subjects

This study was performed on 62 KTRs (age range: 21-59 years, 34 females and 28 males) who had received a successful transplant at least before 6 months. During the study period, the patients were selected consecutively from the outpatient clinic of Nephrology Department who were admitted for routine follow-up control examinations. Five patients that had been previously diagnosed as having CVD were excluded from the study. The time since transplantation ranged from 8 to 155 months, with a mean of 37 months. All patients examined in this study received kidney replacement therapy before kidney transplantation, with a mean of 45 months. Kidney transplant recipients received tacrolimus or cyclosporine, mycophenolate mofetil or azathioprine, and prednisolone. Forty-four patients were taking 1 or more antihypertensive agents: 16 were on angiotensi n-converting enzyme inhibitor or angiotensin receptor blocker, 22 were on beta blocker, 35 were on calcium channel blocker, and 8 were on alpha blocker. Moreover, 10 patients were under statin therapy.

We excluded patients with the history of CVD, acute or chronic liver disorders, and inflammatory diseases. Causes of kidney failure were hypertensive nephrosclerosis (n = 11), reflux nephropathy (n = 6), chronic glomerulonephritis (n = 9), polycystic kidney disease (n = 5), nephrolithiasis (n = 3), diabetic nephropathy (n = 2), lupus nephritis, Wegener granulomatosis, analgesic nephropathy (1 patient each), and uncertain etiology (n = 23).

A group of 50 healthy subjects (28 females and 22 males) was selected as controls based on laboratory values and no history of kidney, liver, endocrinologic, or inflammatory disorders.

The study was approved by the Uludağ University Ethics Committee (Approval Date: June 09, 2009; Approval Number: 11/65). All participants gave their written informed consent to participate.

Blood was obtained after an 8-hour overnight fast. Plasma samples for Hcy and serum aliquots for protein S100B, AGEs, vitamin E, vitamin A, and enzyme activity measurements were kept at −80°C. For the measurement of vitamin E and vitamin A, samples were stored and protected from light exposure. Glucose, urea, creatinine, uric acid, hs-CRP, IGF-1, IGFBP-3, and lipid parameters were determined in fresh sera.

Biochemical Assays

Serum glucose, urea, creatinine, uric acid, triglyceride (TG), total cholesterol (TC), and HDL-C levels were measured with routine laboratory methods. Low-density lipoprotein cholesterol was estimated with the Friedewald's formula. Serum apolipoprotein A1 (Apo A1), apolipoprotein B (Apo B), and lipoprotein (a) [(Lp (a)] concentrations were measured on an Architect c16000 autoanalyzer (Abbott Diagnostics, IL, USA). Creatinine clearance was obtained by the traditional formula (U × V/P). Hcy, hs-CRP, IGF-1, and IGFBP-3 levels were measured with an Immulite 2000 (Diagnostic Products Corporation, LA, USA). Vitamin A and E levels were determined by a high-performance liquid chromatography device (Thermo Finnigan, MA, USA) using ClinRep Complete Kit (Recipe Chemicals Instruments GmbH, Munich, Germany). Protein S100B concentrations were analyzed using a Liaison automated chemiluminescence analyzer (DiaSorin S.p.A., Saluggia, Italy). Serum AGEs were studied with enzyme-linked immunosorbent assay (ELISA) kit, OxiSelect AGE (Cell Biolabs Inc., San Diego, USA). Serum PON 1 and arylesterase activities were determined by using paraoxon and phenylacetate as substrates, respectively.[11,12]

Statistical Analysis

Statistical analyses were carried out with the Statistical Package for the Social Sciences software 20.0 statistical package (IBM Corp., Armonk, NY, USA). Normality of distribution was analyzed with the Kolmogorov–Smirnov test. Results are expressed as mean ± standard deviation or median and interquartile range (25th-75th percentiles), depending on data distribution. Differences between the groups were tested by Student's unpaired *t*-test or Mann–Whitney *U* test. Categorical variables were analyzed with chi-square test. Spearman correlation was used to assess the relationship between variables. Multiple regression analysis, using the stepwise method, was also performed. A *P*-value less than .05 was considered statistically significant.

RESULTS

Control and the patient groups were matched for age, sex, and body mass index (BMI). No significant differences were detected considering serum levels of glucose, TC, LDL-C, HDL-C, apo A1, apo B, and Lp (a). However, serum urea, uric acid, creatinine, and TG levels were significantly high in KTR group (Table 1). Plasma Hcy concentration was significantly high in KTRs. Serum AGEs and hs-CRP levels were approximately 2.5-fold higher in the KTR group compared with the control group. In KTR group, IGF-1, protein S-100B, and vitamin A levels were higher, and vitamin E level and PON 1 and arylesterase activities were lower (Table 2).

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were used in 16 patients. No difference was observed between the patients who used and did not use these agents in terms of the parameters examined. When we analyzed the results against statin treatment, we found that all the above-mentioned values were similar (data not shown).

Table 1. Clinical and Biochemical Variables of the Study Groups

	Controls	KTRs	*P*
Age, years	37 ± 10	38 ± 11	>.05
Gender, male/female	22/28	28/34	>.05
Body mass index, kg/m^2	25.6 ± 3.6	25.8 ± 4.5	>.05
Systolic blood pressure, mm Hg	116 ± 17	135 ± 17	<.001
Diastolic blood pressure, mm Hg	74 ± 10	80 ± 12	<.01
Mean arterial pressure, mm Hg	88 ± 12	98 ± 13	<.001
Urea, mg/dL	25 ± 8	44 ± 18	<0.001
Creatinine clearance, mL/min	-	57 ± 23	
Creatinine, mg/dL	0.80 (0.70-0.90)	1.33 (1.09-1.52)	<.001
Uric acid, mg/dL	4.2 ± 1.4	6.1 ± 1.7	<.001
Glucose, mg/dL	90 (83-97)	90 (80-95)	>.05
Total cholesterol, mg/dL	188 ± 42	201 ± 46	>.05
Triglycerides, mg/dL	102 (75-137)	141 (97-185)	<.01
LDL-cholesterol, mg/dL	112 ± 33	119 ± 35	>.05
HDL-cholesterol, mg/dL	52 ± 13	52 ± 23	>.05
Apolipoprotein A1, mg/dL	197 ± 30	188 ± 30	>.05
Apolipoprotein B, mg/dL	87 ± 23	97 ± 26	>.05
Lipoprotein (a), mg/dL	6.5 (3.8-17.8)	9.8 (4.0-27.3)	>.05

Data are given as mean ± standard deviation or median (interquartile range).
P-value was obtained using the unpaired Student's *t*-test, Mann–Whitney *U* test, or chi-square test.
HDL, high-density lipoprotein; KTRs, kidney transplant recipients; LDL, low-density lipoprotein.

The relationships of the selected parameters performed in the entire study population are given in Table 3. Homocysteine was related inversely to arylesterase activity and positively to hs-CRP, IGF-1, AGEs, and vitamin A. There were significant correlations between IGF-1 levels and vitamin A, arylesterase, age, and BMI. Similar associations with AGEs were present for vitamin A and arylesterase activity. Protein S100B was inversely correlated with arylesterase activity. Both PON 1 and arylesterase were positively correlated with vitamin E. Serum urea, creatinine, and uric acid correlated positively with Hcy, IGF-1, AGEs, protein S100B, and hs-CRP and correlated inversely with arylesterase activity in the whole study population (data not shown).

Table 2. Oxidative Stress and Inflammatory Markers of Control Subjects and Kidney Transplant Recipients

	Controls	KTRs	*P*
Homocysteine, µmol/L	10.0 (8.3-12.5)	18.3 (13.8-22.7)	<.001
hs-CRP, mg/L	0.96 (0.47-1.54)	2.50 (0.70-6.00)	<.001
IGF-1, ng/mL	187 ± 67	254 ± 113	<.001
IGFBP-3, µg/mL	4.44 ± 1.12	4.83 ± 1.01	.053
AGEs, µg/mL	0.56 (0.37-1.12)	1.51 (0.69-1.88)	<.001
Protein S100B, µg/L	0.07 (0.05-0.10)	0.11 (0.08-0.15)	<.001
Paraoxonase, U/L	201 (153-282)	153 (120-249)	<.01
Arylesterase, U/L	127 ± 23	92 ± 21	<.001
Vitamin A, µmol/L	3.15 ± 0.83	3.85 ± 1.17	<.01
Vitamin E, µmol/L	33.0 ± 7.3	29.7 ± 8.5	<.05

Data are given as mean ± standard deviation or median (interquartile range). *P*-value was obtained using the unpaired Student's *t*-test or Mann–Whitney *U* test.
AGEs, advanced glycation end products; hs-CRP, high-sensitivity C-reactive protein; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor-binding protein-3; KTRs, kidney transplant recipients.

In the kidney transplant group, Hcy levels correlated positively and significantly with serum urea (r = 0.304, P = .018), creatinine (r = 0.507, P < .001), and transplant duration (r = 0.312, P = .015) and correlated inversely and significantly with diastolic blood pressure (DBP) (r = −0.258, P = .047). However, after performing multiple regression analysis, only serum creatinine concentration and transplant duration remained statistically associated with Hcy (Table 4). Serum IGF-1 was related positively to urea (r = 0.276, P = .030) and vitamin A levels (r = 0.300, P = .018); and negatively to TC (r = −0.278, P = .029), LDL-C (r = −0.313, P = .013), age (r = −0.439, P < .001), BMI (r = −0.377, P = 0.003), and transplant duration (r = −0.274, P = .031) in the KTR group. After multiple regression analysis, the association of urea, TC, vitamin A, and BMI with IGF-1 level remained statistically significant (Table 4). In the KTR group, PON 1 correlated significantly with TC (r = 0.253, P = .048), TG (r = 0.293, P = .021), Lp (a) (r = 0.380, P = .005), and vitamin E (r = 0.348, P = .006), whereas arylesterase correlated with AGEs (r = −0.256, P = .048), HDL-C (r = 0.275, P = 0.031), apo A1 (r = 0.362, P = .005), and systolic blood pressure (SBP)and DBP (for both, r = 0.314, P = .013). Apolipoprotein A1and DBP were independent predictors of arylesterase activity after adjusting AGEs, HDL-C, and SBP. Multiple regression analysis showed that PON 1 activity was independently related to vitamin E (Table 5). Serum hs-CRP levels correlated positively only with uric acid (r = 0.336, P = .009) and BMI (r = 0.407, P = .002).

Table 4. Determinants of Homocysteine and Insulin-Like Growth Factor-1 Levels by Multiple Regression Analysis

Dependent Variable	Model	B	β	*t*	*P*
Homocysteine	Constant	7.369		2.524	.014
	Creatinine	7.478	0.433	3.832	<.001
	Transplant duration	0.006	0.262	2.317	.024
IGF-1	Constant	447.239		4.883	<.001
	BMI	−8.720	−0.337	−3.095	.003
	Vitamin A	27.908	0.292	2.659	.010
	TC	−0.687	−0.283	−2.549	.014
	Urea	1.416	0.224	2.009	.049

BMI, body mass index; IGF-1, insulin-like growth factor-1; TC, total cholesterol.

DISCUSSION

Our study demonstrated that KTRs were exposed to inflammation and oxidative stress after a minimum of 6 months period

Table 3. Spearman's Correlation Coefficients in the Whole Study Population

	CRP	S100B	IGF-1	Hcy	AGEs	PON	ARE	Vit E	Vit A
Age	0.081	0.022	**−0.423****	−0.008	−0.078	−0.163	−0.061	0.159	0.057
BMI	**0.345****	−0.018	**−0.253****	0.065	0.047	0.037	0.078	0.004	0.031
CRP		0.138	0.158	**0.365****	0.155	0.026	−0.123	0.035	0.186
S100B			0.005	0.188	0.006	−0.029	**−0.255****	−0.168	−0.003
IGF-1				**0.302****	0.091	−0.034	**−0.260****	−0.152	**0.219***
Hcy					**0.219***	−0.119	**−0.363****	−0.004	**0.360****
AGEs						0.002	**−0.297****	−0.015	**0.285****
PON							**0.437****	**0.303****	−0.076
ARE								**0.288****	−0.161

Correlation coefficients (rho) in bold are significant at P < .05*, P < .01**.
AGEs, advanced glycation end products; ARE, arylesterase; BMI, body mass index; CRP, C-reactive protein; Hcy, homocysteine; IGF-1, insulin-like growth factor-1; PON, paraoxonase; S100B, protein S100B; Vit A, vitamin A; Vit E, vitamin E. .

Table 5. Determinants of Paraoxonase and Arylesterase Activities by Multiple Regression Analysis

Dependent Variable	Model	B	β	*t*	*P*
Paraoxonase	(Constant)	81.209		1.895	.064
	Vitamin E	3.744	0.348	2.680	<.010
Arylesterase	(Constant)	6.844		0.282	.779
	Apolipoprotein A1	0.243	0.339	2.754	.008
	DBP	0.508	0.273	2.219	.031

DBP, diastolic blood pressure.

following transplantation. Serum levels of AGEs were higher in the KTRs compared to those of the controls, and this can be accepted as a marker of ongoing oxidative stress and inflammation. Several mechanisms have been proposed for the increased blood levels of AGEs after kidney transplantation. Detoxification of AGEs depends on the degradation of these molecules by macrophages and clearance by the kidneys.[3,13,14] It was reported that KTRs had disproportionally higher levels of blood AGEs when related to renal function which was suggested to be related to several factors, including nutritional status and cyclosporine usage.[14,15]

In the current study, decreased levels of PON 1 and arylesterase activities were other markers of oxidative stress in KTRs. Decreased levels of arylesterase activity, observed in the KTRs, might be the sign of reduced synthesis of the PON 1 which might be one of the results of increased oxidative stress since increased oxidative markers such as AGEs might disturb the synthesis of this enzyme. Reduced serum PON 1 activity might be a result of decreased synthesis and/or the activity of the enzyme since it was shown that PON 1 activity could be inhibited by oxidative stress markers, including AGEs. Bansal et al[16] reported that AGEs negatively correlated with PON 1 activity in diabetic patients; however, we found no association between AGEs and PON 1 activity. In line with our findings, Sztanek et al[7] and Locsey et al[17] reported reduced PON 1 activity in the KTR group. However, Locsey et al[17] found no difference in arylesterase activity. In their studies, Sztanek et al[7] and Locsey et al[17] reported reduced levels of thiolactonase activity. Since thiolactonase activity prevents proteins from homocysteinylation, it had been suggested to be one of the protective effects of PON 1 against CVD. Both Sztanek et al[7] and Locsey et al[17] also found a negative correlation between the PON 1 activity and Hcy levels; however, we did not observe any correlation between those parameters. In line with other studies, we observed increased levels of Hcy in the KTR group.[4,18] Homocysteine level of the KTR group was significantly correlated with serum creatinine levels, which is parallel to other studies in which authors suggested that Hcy levels were associated with kidney functions.[18,19] We also observed that Hcy was influenced by transplant duration in our study group.

We suggest that reduced PON 1 activity might also be associated with decreased levels of vitamin E since results of multivariate analysis yielded that serum vitamin E concentration was the major determinant of PON 1 activity in KTRs. Vitamin E is an important defender of the lipoproteins against free radical attack and it might be depleted when lipoproteins are exposed to increased oxidative stress.[6] As mentioned above, PON 1 activity may be disturbed when lipoproteins are exposed to free radical damage since PON 1 is an HDL-associated enzyme.

Vitamin A has a weak antioxidant capacity, and kidneys play a crucial role in the metabolism of vitamin A.[20,21] In line with other studies, we observed high levels of vitamin A in the KTR group.[21,22] Connoly et al[23] reported a negative correlation between retinol and hs-CRP in KTRs. In this study, vitamin A was found to show a significant positive relationship with IGF-1 level in KTRs.

The poor prognosis and high risk of mortality in KTRs had been partly associated with chronic low-grade inflammation. In the present study, in line with other studies, CRP level was high in the KTR group.[7,17] This finding is one of the evidences of ongoing enhanced inflammatory process in post-transplant patients. Since inflammation had been accepted to play a consequential role in the survival of KTR, we investigated other parameters associated with inflammation and/or oxidative stress. Protein S100B has been reported to be involved in inflammatory signaling through RAGE. We observed that protein S100B level of the KTR group was significantly higher compared with the healthy subjects. Additionally, protein S100B level was correlated with serum creatinine level when all study population was included, which suggested a possible association between kidney function and protein S100B. We also observed significant inverse association of protein S100B with arylesterase activity. To our knowledge, this relationship had not been described before; additional studies are therefore required to confirm this finding. Gross et al[24] investigated the association between inflammation and protein S100B levels in post-transplant patients and those authors did not find any association between hs-CRP and protein S100B levels; however, in parallel to our finding, they observed an inverse association between creatinine clearance and protein S100B levels.

Insulin-like growth factor-1 and IGFBP-3 levels in the KTR group were significantly higher than those of the control group. However, Unal et al[25] did not find any difference in IGF-1 levels between the adult transplant group and the controls. Arbeiter et al[26] investigated both IGF-1 and IGFBP-3 levels in children after renal transplantation and did not find any differences in terms of those parameters.[26] It has been reported in various studies that IGF-1 levels decrease with age.[27,28] In our study, negative correlations were found between age and IGF-1 and IGFBP-3 levels. While some studies have reported a significant negative relationship between IGF-1 and BMI, there are also studies reporting that there is no significant relationship.[29,30] In

this study, BMI was found to show a significant negative relationship with IGF-1 levels in both KTRs and the whole study group.

There are some limitations to our study. The study includes a relatively small number of patients from 1 center. Since this was a cross-sectional study, we could not declare a cause and effect relationship from our findings.

CONCLUSION

Chronic inflammatory processes are common in KTRs, and this might be related to many underlying factors, including kidney function, elevated pro-inflammatory cytokines, oxidative stress, and malnutrition inflammation syndrome. The findings of this study showed that KTRs are exposed to inflammation and oxidative stress a long time after kidney transplantation. These processes initiated by the body in order to defend itself may damage the tissues after a certain stage, so further studies investigating treatment strategies for reducing inflammation and oxidative stress load and their effects on the prognosis of KTRs are needed.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Uludağ University (Approval Date: June 9, 2009; Approval Number:11/65).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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