Arterial Atherosclerosis in Patients With Chronic Kidney Disease and Its Relationship With Serum and Tissue

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Keywords. atherosclerosis, chronic kidney disease, endothelin-1

Instruction. We investigated the correlation between atherosclerosis and tissue and serum levels of endothelin-1 in patients with chronic kidney disease (CKD).

Materials and Methods. Arterial samples were obtained from 35 patients with CKD during arteriovenous fistula placement. Thirty-one patients with cardiovascular disease who underwent coronary artery bypass graft (CABG) were selected as the atherosclerotic group, and a piece of their aorta punched during CABG was obtained. Also, a small piece of the renal artery was dissected during donation in 24 kidney donors (control group). Tissue endothelin-1 level was measured and atherosclerosis grading was determined by pathologic examination. Serum levels of endothelin-1 were also measured in the three groups.

Results. The mean tissue endothelin-1 levels were 10.73±7.57 pg/mL, 12.16 ± 3.95 pg/mL, and 0.93 ± 1.06 pg/mL in the patients with CKD, those with CABG, and donors, respectively ($P < .001$). The mean serum endothelin-1 level was 25.23 ± 15.15 pg/mL in the patients with CKD, 21.13 ± 17.22 pg/mL in the patients with CABG, and 2.66 ± 1.51 pg/mL in the donors ($P < .001$). Atherosclerosis grades correlated with tissue endothelin-1 level ($r = 0.823$, $P < .001$) and serum endothelin-1 level ($r = 0.608$, $P < .001$) in the patients with CKD. Multiple regression analysis showed tissue endothelin-1 level as the main predicting factor of atherosclerosis ($P < .001$).

Conclusions. Tissue endothelin-1 concentration is more important than serum endothelin-1 or lipids levels in prediction of atherosclerosis. Thus, blockade of tissue endothelin-1 receptors with its antagonists may prevent atherosclerosis progression.

IJKD 2009;3:203-9
www.ijkd.org

Original Paper

INTRODUCTION

Generally, atherosclerosis leads to coronary artery disease, stroke, and peripheral vascular problems.[1] In this process, accumulation of cholesterol reduces arterial pliability,[2,3] and fatty streaks, which are the initial phenomena in atherosclerosis, cause local thickening of the intima with smooth muscles and extracellular matrix proliferation due to lipid accommodation.[4] The origin of these smooth muscle cells are the hematogenic processors that migrate into the intima, proliferate, and make fatty streaks. In progressive fibrous plaque formation, connective

tissue expands and the smooth muscles are filled with lipid.[5,6]

Endothelial malfunction, which is due to dyslipidemia, constitutes an essential part of the atherogenesis.[7] Endothelin-1 is an important factor in the pathogenesis of atherosclerosis that has a vasoconstrictive effect and is a mitogenic factor for the smooth muscle cells.[8,9] Endothelin-1 leads to migration and proliferation of these cells. Oxidized low-density lipoprotein cholesterol (LDLC) can promote its production and increase vasoconstrictive effects.[10] Immunoreactivity of endothelin-1 is elevated in the intracellular and extracellular spaces in human atherosclerotic vessels.[11]

Endothelial dysfunction is an important factor in acute and chronic kidney failure. In patients on hemodialysis, vasodilators are impaired in the brachial arteries and vasoconstriction formation is increased.[12] Conversely, endothelial function improvement in chronic kidney disease (CKD) reduces cardiovascular complications by reducing atherosclerosis.[13] In rats with renal mass ablation, elevation of plasma and urine levels of endothelin-1 depends on promoted endothelin-1 production in vascular and glomerular tissues.[14] Endothelin-1 accelerates hypertension, arterial hypertrophy, atherosclerosis, and ultimately, kidney failure.

Endothelium is a cellular monolayer in the lumen of vessels and has many different roles, such as metabolic, regulatory (hemostasis, fibrinolysis and lipid metabolism), vasoconstrictor, and blood pressure alteration effects.[15] Many vasoconstrictor agents such as endothelin-1, thromboxane, angiotensin, prostaglandins, free radicals, and bradykinins are produced in the endothelial cells and regulate vascular smooth muscle cells function.[16] An exact equilibrium is seen between these agents and vascular function, and it is altered with endogenous and exogenous factors, including stresses, psychogenic and physical factors, inflammation, platelet aggregation, thrombosis, atherosclerosis, and hypertension.[16] Endothelial cells are also affected by drugs, toxins, alcohol, and smoking.[17] Endothelial cell dysfunction had been detected in pathogenic conditions like atherosclerosis, congestive heart failure, hyperhomocystinemia, diabetes mellitus, CKD, organ transplantation, and hepatic cirrhosis.[15] Measurement of plasma and tissue endothelin-1 in animals showed elevated level of endothelin-1 in the body as a great risk factor of atherogenesis.[16]

According to previous animal studies and endothelin effects on atherosclerosis progression,[17] we decided to measure endothelin-1 level in the vascular tissue of candidates for arteriovenous fistula placement before staring hemodialysis and studied the correlation between tissue endothelin-1 and atherosclerosis grade.

MATERIALS AND METHODS

Patients and Samples

Approval of the study protocol was obtained from the local ethics committee. Thirty-five patients with CKD but without diabetes mellitus, heart failure, coronary artery disease, or peripheral vascular disease were referred to Sina hospital for arteriovenous fistula placement between June 2006 and June 2008. We enrolled them in the patients group of the study after obtaining informed consent. The patients had an estimated glomerular filtration rate between 15 mL/min and 25 mL/min, and their serum creatinine level was between 4 mg/dL and 8 mg/dL. Receiving dialysis and antilipid therapy during the past 3 months were the exclusion criteria. In this group, we obtained a 0.5-cm piece of the brachial or the radial artery, with no physiologic importance, during arteriovenous fistula placements, in order to examine tissue endothelin-1 level and atherosclerosis grading.

Thirty-five patients with remarkable cardiovascular disease who underwent coronary artery bypass graft (CABG) were selected as the atherosclerotic group. We obtained a piece of their full-thickness aorta which was punched during the operation and insertion of the saphenous vein. Additionally, 35 young kidney donors were selected as the nonatherosclerotic control group, and a 0.5-cm piece of their renal artery was dissected during donation. Characteristics of the participants in the 3 groups of patients with CKD, patients with CABG, and control kidney donors are summarized in Table 1.

Pathology and Laboratory Examinations

Atherosclerosis is a disseminated process and specially affects large- and medium-sized arteries. Therefore, all our samples were from these two groups of arteries and were comparable.[4] The obtained vascular samples were equalized in weight and were sent for measurement of endothelin-1

Table 1. Characteristics of Participants*

Characteristic	Participants Groups			*P*
	CKD	CABG	Donor	
Number of patients	35	31	24	…
Age, y	39.93 ± 10.96	40.58 ± 4.61	36.08 ± 10.40	.02
Sex				
Male	16 (45.7)	16 (51.6)	13 (54.2)	
Female	19 (54.3)	15 (48.4)	11 (45.8)	.79
Smoking	17 (48.6)	20 (64.5)	14 (58.3)	.42
Body mass index, kg/m^2	20.12 ± 1.1	24.15 ± 2.02	24.01 ± 3.01	.12
Body weight, kg	67.20 ± 11.3	68.74 ± 7.04	69.37 ± 7.59	.61

*Values in parentheses are percents. CKD indicates chronic kidney disease and CABG, coronary artery bypass graft.

and assessment of atherosclerosis. The samples were homogenized and the liquid was centrifuged (3000 rpm) for 10 minutes at 4°C. The supernatant was freezed in -80°C, lyophilized for 48 hours, and stored for tissue endothelin-1 level measurement. A piece of the sample was examined by a pathologist for grading of atherosclerosis according to American Heart Association classification.[18] The atherosclerosis grades were as follows: (1) we can see macrophages and foam cells; (2) the lesions are intracellular with lipid accumulation; (3) like grade 2, but with a little extracellular lipid; (4) like grade 3, with great extracellular lipid accumulation (athroma); (5) intracellular lipid accumulation and calcified fibrotic lesions (fibroathroma); and (6) surface of lesion are disrupted with hematoma, hemorrhagic, or thrombotic events.

Blood samples were obtained after an overnight fasting, frozen immediately, and stored at -70°C until analysis. Serum levels of total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDLC) were determined using commercial kits with an automated chemical analyzer (Abbott, Abbott Park, Illinois, USA), and the LDLC was calculated according to the Frieldwald formula.[19] Serum levels of high-sensitivity C-reactive protein (HS-CRP) and endothelin-1 were measured by enzyme-linked immunosorbent assay (Lot: RE-2130, DRG Instrument GmbH, Freudenbergstrasse, Germany) and the human endothelin-1 immunoassay kit (Lot: 29870, R&D systems, Minneapolis, Minnesota, USA), respectively.

Data Analyses

Data on continuous variables were presented as mean ± standard deviation, and their comparisons were done using the *t* test and the 1-way analysis of variance. The relations between dichotomous variables were tested by the chi-square test, and correlations were assessed using the Pearson and Spearman rho correlation coefficients, where appropriate. The multiple regression method was used for analysis of correlations and predicting factors. *P* values less than .05 were considered significant. The analyses were performed by means of the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA).

RESULTS

Thirty-five patients with CKD, 31 in the CABG group, and 24 kidney donors completed the study (Table 1), while others were excluded as they refused to continue the study. Since we required a group without atherosclerosis as controls, we selected kidney donors; consequently they were younger than the patients in the other two groups.

Most of the patients (57.1%) with CKD and those who underwent CABG (58.1%) had an atherosclerosis grade of 3 to 4, while in the donors group, the majority of the participants (95.8%) had a grade between zero and 2 for atherosclerosis ($P < .001$; Table 2).

The mean tissue endothelin-1 level was 10.73±7.57 pg/mL in the patients with CKD, 12.16 ± 3.95 pg/mL in the patients with CABG, and 0.93 ± 1.06 pg/mL in the donors group ($P < .001$). The mean serum endothelin-1 level was 25.23 ± 15.15 pg/mL in the patients with CKD, 21.13 ± 17.22 pg/mL in the patients with CABG, and 2.66 ± 1.51 pg/mL in the donors ($P < .001$). Serum levels of HS-CRP were significantly higher in patients with CKD than the patients with CABG and the donors ($P < .001$). Hyperlipidemia was significant in the two groups of patients, while the donors' lipid profile was unremarkable (Table 2). Comparisons

Table 2. Results of Clinical and Laboratory Studies*

Parameter	Participants Groups			P†
	CKD	CABG	Donor	
Atherosclerosis				
0 to 2	15 (42.9)	0	23 (95.8)	
3 to 4	20 (57.1)	18 (58.1)	1 (4.2)	
5 to 6	0	13 (41.9)	0	< .001
Tissue endothelin-1, pg/mL	10.73 ± 7.57	12.16 ± 3.95	0.93 ± 1.06	< .001
Serum endothelin-1, pg/mL	25.23 ± 15.15	21.13 ± 17.22	2.66 ± 1.51	< .001
HS-CRP, mg/dL	48.24 ± 7.87	26.48 ± 11.02	14.69 ± 5.74	< .001
Systolic blood pressure, mm Hg	159.42 ± 24.60	158.70 ± 26.17	112.08 ± 8.83	< .001
Diastolic blood pressure, mm Hg	92.00 ± 9.33	96.77 ± 8.70	78.33 ± 7.01	< .001
Hypertension	26 (74.3)	15 (48.4)	0	< .001
Serum creatinine, mg/dL	7.56 ± 1.50	1.02 ± 0.14	0.99 ± 0.09	< .001
Blood urea nitrogen, mg/dL	112.42 ± 40.99	15.48 ± 3.77	14.45 ± 4.32	< .001
Serum triglyceride, mg/dL	317.37 ± 222.67	214.67 ± 138.59	145.33 ± 21.82	< .001
Serum cholesterol, mg/dL	276.02 ± 78.60	333.61 ± 84.74	143.37 ± 34.12	< .001
Serum HDLC, mg/dL	38.82 ± 18.34	43.00 ± 14.02	53.12 ± 9.12	< .001
Serum LDLC, mg/dL	182.11 ± 81.03	152.64 ± 49.52	100.45 ± 9.80	< .001
Fasting blood glucose, mg/dL	96.14 ± 11.63	94.49 ± 5.68	92.91 ± 8.73	.41

*Values in parentheses are percents. CKD indicates chronic kidney disease; CABG, coronary artery bypass graft; HS-CRP indicates high-sensitivity C-reactive protein; HDLC, high-density lipoprotein cholesterol; and LDLC, low-density lipoprotein cholesterol.
†Comparisons were done by 1-way analysis of variance.

between the CKD and CABG groups are summarized in Table 3.

The correlation between atherosclerosis grade and tissue endothelin-1 level was significant in the CKD group (r = 0.823, $P < .001$). The same association was seen between the serum endothelin-1 levels and atherosclerosis grade in this group (r = 0.608, $P < .001$; Table 4). Atherosclerosis grade was also associated with serum triglyceride, HDLC, and LDLC levels (Table 4). In the CABG group,

Table 3. Comparison of Patients in Chronic Kidney Disease (CKD) and Coronary Artery Bypass Graft (CABG) Groups

Parameter	Patients Groups		P*
	CKD	CABG	
Tissue endothelin-1, pg/mL	10.73 ± 7.57	12.16 ± 3.95	.11
Serum endothelin-1, pg/mL	25.23 ± 15.15	21.13 ± 17.22	< .001
HS-CRP, mg/dL	48.24 ± 7.87	26.48 ± 11.02	< .001
Serum triglyceride, mg/dL	317.37 ± 222.67	214.67 ± 138.59	.03
Serum cholesterol, mg/dL	276.02 ± 78.60	333.61 ± 84.74	.70
Serum HDLC, mg/dL	38.82 ± 18.34	43.00 ± 14.02	.31
Serum LDLC, mg/dL	182.11 ± 81.03	152.64 ± 49.52	.08

*Comparisons were done using the *t* test.

Table 4. Correlations of Different Factors With Atherosclerosis*

Correlates	Participants Groups					
	CKD		CABG		Donor	
	r	P	r	P	r	P
Tissue endothelin-1	0.823	< .001	…	.12	0.755	< .001
Serum endothelin-1	0.608	< .001	0.412	.045	…	.59
Serum triglyceride	0.729	< .001	…	.34	…	.97
Serum cholesterol	…	.29	0.504	.01	0.780	< .001
Serum HDLC	-0.628	< .001	…	.09	-0.745	< .001
Serum LDLC	0.661	< .001	…	.10	0.655	< .001
HS-CRP	…	.95	…	.15	…	.89

* CKD indicates chronic kidney disease; CABG, coronary artery bypass graft; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; and HS-CRP indicates high-sensitivity C-reactive protein.

Table 5. Regression Model for Predicting Atherosclerosis in Patients With Chronic Kidney Disease

Parameter	B coefficient	*P*
Tissue endothelin-1	1.085	< .001
HS-CRP	0.018	.88
Serum endothelin-1	0.047	.77
Triglyceride	0.406	.04
Cholesterol	0.094	.37
HDLC	-0.185	.17
LDLC	0.832	< .001

*HS-CRP indicates high-sensitivity C-reactive protein; HDLC, high-density lipoprotein cholesterol; and LDLC, low-density lipoprotein cholesterol.

atherosclerosis grade correlated significantly with tissue endothelin-1 level (r = 0.755, $P < .001$). However, the relationship between atherosclerosis grade and tissue endothelin-1 level was not significant in the donors group. In this group, serum endothelin-1 correlated marginally with atherosclerosis grade (r = 0.412, $P = .045$). Multiple regression analysis in the CKD group showed that the most important predicting factor for atherosclerosis was tissue endothelin-1 level (Table 5).

DISCUSSION

Endothelial cell injury is accelerated in patients with chronic kidney injury and leads to atherosclerosis generation. Serum endothelin-1 level is elevated during this process.[20] Tissue levels of endothelin-1 have been measured in animal models, but similar studies are not available in human.[21] To our knowledge, our study is the first detecting tissue endothelin-1 in living human models. Endothelin-1 inhibition effects in CKD and hypertension were studied in uremic rats.[22,23] It was shown that endothelin-1 plasma and urine levels elevated in kidney failure.[23] In another study, the effect of vascular endothelin-1 on establishing of CKD was seen in animal models.[24] The investigators removed five-sixth of the kidneys in rats, to induce kidney failure, and administered an endothelin-1 antagonist (LU135252) in the case group. Increase in blood pressure, serum creatinine, urine volume, and urinary protein excretion were less in the case group. The extracted endothelin-1 from glomerular and arterial tissue was higher in the control group; therefore, effects of endothelin-1 in hypertension, vascular hypertrophy, and progression of kidney failure were distinguished in rats.

Endothelial dysfunction reduces vasodilatation. Hence, it accelerates progression of cardiovascular disease, hypertension, CKD, peripheral vascular disease, and congestive heart failure.[25] Endothelial dysfunction is an early and important event in the pathogenesis of atherosclerosis. Consequently, its correction may reduce the speed of pathologic processes.[19] Major effects of endothelin-1 are pressure control and hemodynamic, glomerular filtration, and sodium regulation.[26] In rats with CKD, endothelin-1 concentration increases in blood vessels of the remnant kidney. These processes depend on preproendothelin-1 concentration and blood pressure elevation that increase cardiovascular mortality and progression to CKD.[27] In patients with elevated blood pressure, atherosclerosis and nephrosclerosis, plasma endothelin-1 level is more elevated than healthy persons. On the other hand, plasma level of endothelin-1 in patients with end-stage renal disease who undergo dialysis is elevated and it is related to their hypertension.[28] Evidence of endothelial dysfunction is shown in hypertension of CKD.[29] Endothelin-1 overproduction leads to accelerated atherosclerosis in kidney failure.[30] In one study, the correlation between endothelial and cardiovascular disease of patients with ESRD was investigated.[31] In comparison with the control group, patients with ESRD had higher serum endothelin-1 levels and correlation of endothelin-1 with cardiovascular disease and atherosclerosis was remarkable ($P < .001$). Serum endothelin-1 level is elevated in different disorders such as pulmonary hypertension, atherosclerosis, kidney failure, coronary artery disease, heart failure, migraine, and vascular disease. According to the abovementioned studies and others, serum level of endothelin-1 is elevated in patients with ESRD, but to date, little data were available about tissue endothelin-1 except for animal models.[32]

More recently, antagonists of endothelin-1 are synthesized and utilized for reducing of endothelin-1 effects.[33] Endothelins are potent vasoactive agents with different effects. They promote an inflammatory response in blood vessels by increasing oxidative stress.[34] We found that tissue endothelin-1 level was elevated in CKD and it was closely related to the grade of atherosclerosis. In these patients, tissue endothelin-1 was the most important predicting factor of atherosclerosis formation than serum endothelin-1, cholesterol,

triglyceride, and LDLC, which were studied previously. Thus, endothelin-1 receptor antagonists may reduce blood pressure in hypertensive patients and can be used in CKD treatment, theoretically. These antagonists were utilized empirically in patients with atherosclerosis, but they had many side effects which limited their administration. We emphasize that endothelin-1 receptor blockers may reduce the effects of endothelin-1 on blood vessels and kidney function, as tissue endothelin-1 is excessive in patients with CKD.

The role of the different endothelins that make up this family of peptides in elevated blood pressure is currently unclear. It is likely that endothelin-1 plays an important vasoconstrictor and growth-promoting role in peripheral resistance vessels and may contribute to blood pressure elevation in some animal models of hypertension, such as deoxycorticosterone acetate-salt-induced hypertensive rats, and in malignant hypertension in spontaneously hypertensive rats, such as in deoxycorticosterone acetate-salt-induced hypertensive rats and possibly stroke-prone spontaneously hypertensive rats.[35] Local injection of an endothelin-1 antagonist (PD147953) has been shown to completely prevent vasoconstriction of human skin vessels caused by intradermal injection of endothelin-1, suggesting that vasoconstriction is mediated mainly by endothelin-1 receptors in this microvascular bed.[36] These findings have implications for the future development of anti-endothelin therapies, because they suggest that full inhibition of vasoconstriction to endogenously generated endothelin-1 may be obtained only by the use of endothelin-1 receptor antagonists or inhibitors of endothelin generation.[37]

CONCLUSIONS

Our study showed that tissue endothelin-1 concentration is more important than serum endothelin-1, cholesterol, triglyceride, and LDLC in prediction of atherosclerosis in humans. According to our results, blockade of tissue endothelin-1 with its antagonists theoretically prevents or reduces the speed of atherosclerosis process. Nonetheless, further studies are warranted to be designed for examination of this possibility.

ACKNOWLEDGEMENTS

We thank Dr H Babaii, Ramona Moludi, and Ehsan Noshad for their valuable contributions and patience.

FINANCIAL SUPPORT

The Drugs Applied Research Center of Tabriz University of Medical Sciences supported us closely for this work.

CONFLICT OF INTEREST

None declared.

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Received April 2009
Revised June 2009
Accepted July 2009