

Comparison of Intima-media Thickness of the Common Carotid Artery in Dialysis and Kidney Transplant Recipient Patients

Daryoush Saedi,¹ Minoo Narooinejad,¹ Samira Saffari,¹ Mohammad Khak²

Abstract

Objectives: Cardiovascular events are a major cause of mortality and morbidity of chronic renal failure causing 40% to 50% of all deaths in these patients. The intima-media thickness of the common carotid artery is used to predict atherosclerosis. To assess the effect of early renal transplant on the vascular atherosclerosis, we compared the common carotid intima-media thickness between dialysis and transplant patients.

Materials and Methods: In a cross-sectional study, 75 kidney transplant recipients and 75 dialysis patients were assessed in a subspecialized renal and urethral diseases center from April 2008 to March 2010. Demographic characteristics, smoking history, and information on comorbid and kidney diseases were recorded through a checklist. The common carotid intima-media thickness was measured using ultrasonography. Spearman's rank correlation coefficient was used to find any correlation between duration of dialysis and intima-media thickness.

Results: In all, 79 patients (53%) were male. The mean age (SD) of dialysis and transplant patients was 55 ± 11 and 51 ± 15 years. The 2 groups had no statistically significant sex or age differences ($P > .05$). Considering all patients, 54 (36%) had a history of hypertension, 30 (20%) had a history of diabetes mellitus, 15 (10%) had a history of hyperlipidemia, and 41 (27.3%) had a history of smoking. There were no significant differences

between the 2 groups when these variables were considered ($P > .05$). The mean thickness of the common carotid intima-media was 1.2 mm (0.35 mm) in the dialysis patients, which was higher compared with 0.73 mm (0.18 mm) in the transplanted group ($P < .001$). There was a significant correlation between duration of dialysis and intima-media thickness ($P < .001$, $r=0.882$) in the dialysis group.

Conclusions: Common carotid intima-media thickness in dialysis patients is significantly higher compared with kidney transplant recipients. Carotid intima-media thickness increases by prolongation of dialysis duration.

Key words: Ultrasonic imaging, Artery narrowing, Hemodialysis, Kidney grafting

Introduction

Cardiovascular events are the major causes of mortality and morbidity in patients with advanced renal failure causing more than 40% to 50% of mortalities in these patients.¹ As a result, predicting the incidence of cardiovascular events in these patients is of great importance. Currently, the intima-media thickness of common carotid artery is quite a well-known index of atherosclerosis. Compared with coronary angiography (the criterion standard in evaluating coronary artery atherosclerosis), intima-media thickness is a noninvasive, easy to tolerate for the patient, and repeatable method. However, there is a direct association between the risk of cardiovascular or cerebrovascular events and intima-media thickness; its dynamic changes (according to the patient metabolic status) make it as a good tool for evaluating the efficacy of therapeutic interventions in subsequent follow-ups.^{1,2} According to the results of many studies, intima-media thickness

From the ¹Department of Radiology, Hasheminejad Kidney Center, School of Medicine, Iran University of Medical Sciences, and the ²Department of Internal Medicine, Tehran University of Medical Sciences, Tehran, Iran

Acknowledgements: The author would like to thank Farzan Institute for Research and Technology for technical assistance.

Address reprint requests to: Daryoush Saedi, MD, PO Box: 13185-1678, Tehran, Iran
Phone: +9821 66439463 Fax: +9821 66423304 E-mail: svet_f@yahoo.com

Experimental and Clinical Transplantation (2011) 1: 26-31

is accepted (like the normal population) as an independent predicting factor for mortality due to cardiovascular events in dialysis patients.³⁻⁵ Renal failure, using different mechanisms (including hypertension, calcium and phosphorus metabolism disorders, hyperlipidemia) leads to intensified and accelerated atherosclerotic process in the body, and, as a result, increased risk of cardiac and cerebral vascular accidents that increase intima-media thickness of the carotid artery as a reliable sign.⁶

On the other hand, in patients with renal failure of various causes, transplant is better done as soon as possible, because it has been proven that cardiovascular morbidity in patients with renal failure is 20 times that of the normal population.^{7, 8} Besides, correcting the metabolic status of the body by applying effective treatments such as kidney transplant can at least modify the cardiovascular damage process. Lima and associates showed a significant decrease in carotid intima-media thickness in a 3-year follow-up of 22 adult transplant patients.⁹ Other studies have shown that kidney transplant could reduce patient intima-media thickness by modifying blood pressure and glucose.¹⁰ Considering the previously mentioned facts, and to evaluate the effect of kidney transplant on vascular atherosclerosis and the accompanying mortality, this study sought to compare common carotid artery intima-media thickness (as an index of vascular atherosclerosis and a risk indicator for cardiovascular disease) in 2 groups of patients; a group of patients under dialysis for a certain duration, and a group of kidney transplant recipients.

Materials and Methods

The study protocol was approved by the Institutional Ethics Committee of the Iran University of Medical Sciences and follows the ethical guidelines of the 1975 Helsinki Declaration. After written, informed consent was obtained, a cross-sectional study was performed on dialysis patients and kidney transplant recipients referred to Shahid Hasheminejad Sub-specialized Renal and Urethral Diseases Center, Tehran, Iran, for dialysis or postoperative follow-up during 2008-2010. The center is a referral one, accepting patients with renal failure for dialysis or kidney transplant. The majority of the transplant patients refer to the nephrology clinic at regular intervals (varying from 6 to 12 months) for follow-up.

Among patients receiving kidney transplant before this time, we studied patients referred to us for follow-up during April 2008 to March 2010; 75 patients were included. For the control group, we studied 75 dialysis patients by randomly choosing from the available patients' data in the Hasheminejad center data set.

A check list was completed to evaluate the demographic characteristics (age and sex), history of smoking, comorbidities (hypertension, hyperlipidemia, diabetes mellitus), and renal disease including cause of renal failure, dialysis duration, and duration after transplant. Intima-media thickness of the common carotid artery was measured in all patients.

Determination of the common carotid intima-media thickness

Using a high-resolution ultrasonography machine (Technus MP; Esaote, Genoa, Italy) provided us with a variable band 4- to 13-MHz linear array transducer (model LA 523), the common carotid artery was scanned for each subject in the supine position with the neck semiextended. All measurements were done blindly by the same operator. The distance from the leading edge of the first echogenic line, to the leading edge of the second echogenic line, at the level of the lower segment of the common carotid artery, 0.5, 1, and 2 cm distant from where the diastolic phase bifurcates was measured bilaterally. Intima-media thickness was considered as the mean of 6 measurements (3 on each side). No measurements were made on the sites where a plaque existed.

Statistical Analyses

Statistical analyses were performed with SPSS software for Windows (Statistical Product and Service Solutions, version 16.0, SSPS Inc, Chicago, IL, USA). Qualitative variables were expressed as frequency and relative frequency (expressed in percentages). To test distribution normality, a Kolmogorov-Smirnov 1-sample test was used; quantitative variables with normal distribution range included age and intima-media thickness, while dialysis and transplant duration were nonnormal distributed quantitative variables. To compare the 2 groups for comorbidities (history of hypertension, hyperlipidemia, and diabetes mellitus), history of smoking, and increased risk of stroke and cardiovascular disease, the chi-square test was used.

As duration of dialysis and intima-media thickness were not distributed normally, Spearman's rank correlation coefficient was used for any correlation between these 2 variables.

Results

A total of 150 patients (75 dialysis and 75 transplant patients) were included in the study. There was no statistically significant difference in age, sex, hypertension, diabetes mellitus, and smoking between the 2 groups ($P > .05$), but there was a significant difference in serum calcium, phosphate, and systolic blood pressure between the 2 groups (Table 1).

Table 1. Basic clinical characteristic of the 2 groups.

Group	Dialysis	Transplant	P value
No. of patients	75	75	—
Male/female	37/38	42/33	.5
Age (y)	55 ± 11	51 ± 15	.06
Smoker (n)	17	24	.28
Hypertension	26	28	.78
Systolic BP (mm Hg)	128 ± 13	123 ± 15	.030*
Diastolic BP (mm Hg)	75 ± 16	73 ± 11	.373
Diabetes mellitus (n)	13	17	.49
Hyperlipidemia (n)	9	6	.48
Total cholesterol (mmol/L)	4.13 ± 0.96	3.95 ± 0.98	.258
HDL (mmol/L)	0.91 ± 0.90	0.67 ± 0.96	.116
LDL (mmol/L)	2.45 ± 0.69	2.58 ± 0.61	.224
Triglyceride (mmol/L)	1.59 ± 0.83	1.49 ± 0.77	.446
Serum calcium (mmol/L)	2.26 ± 0.15	2.21 ± 0.125	.028*
Serum phosphate (mmol/L)	1.58 ± 0.38	1.20 ± 0.48	< .001*

* $P < .05$ significant

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein

The most-common causes of chronic renal failure in all patients were hypertension (34, 24.2%) and diabetes mellitus (24, 17.1%). For 17 dialysis patients (22.6%) and 12 transplant patients (18.4%), the cause of chronic renal failure was unknown (Table 2).

Mean duration of dialysis for dialysis patients and transplant patients before transplant was 66 ± 14 months and 11 ± 6.5 months, which was significantly more in the dialysis group compared with the transplant group ($P < .001$). The mean duration of renal transplant was 60 ± 17 months. Mean duration of renal replacement therapy in the 2 groups was not significantly different ($P > .05$). Serum analysis before measuring intima-media thickness showed a serum creatinine of 123.6 ± 70.72 $\mu\text{mol/L}$ in the transplant group and 689.52 ± 194.48 $\mu\text{mol/L}$ in the dialysis group ($P < .001$).

The mean common carotid intima-media thickness was 0.8 ± 0.26 mm in all patients, which

Table 2. Causes of chronic renal failure in dialysis and transplant recipients.

Cause of CRF	Dialysis patients n (%)	Transplant patients n (%)	Total n (%)
HTN	20 (26.6)	16 (21.5)	36 (24)
Diabetes mellitus	14 (18.6)	11 (15.3)	25 (16.6)
Infection	4 (5.3)	3 (4.6)	7 (5)
Glomerulonephritis	2 (2.6)	7 (10.7)	9 (6.4)
Kidney stones	5 (6.6)	2 (3)	7 (5)
Reflux nephropathy	2 (2.6)	5 (7.6)	7 (5)
Congenital disease	1 (1.3)	2 (3)	3 (2.1)
Hereditary diseases	-	2 (3)	2 (1.4)
Alport syndrome	-	2 (3)	2 (1.4)
Preeclampsia	1 (1.3)	1 (1.5)	2 (1.4)
Surgery	2 (2.6)	-	2 (1.4)
PKD	4 (5.2)	2 (3)	4 (2.8)
Lupus	2 (2.6)	1 (1.5)	3 (2.1)
Ureteral stricture	1 (1.3)	-	1 (0.7)
Renal artery stenosis	-	1 (1.5)	1 (0.7)
Body building drugs	-	1 (1.5)	1 (0.7)
Unknown	17 (26.6)	19 (25.3)	36 (24)

Abbreviations: CRF, Chronic renal failure; HTN, hypertension; PKD, polycystic kidney disease

was significantly higher in dialysis patients (1.2 ± 0.35 mm) than in transplanted patients (0.73 ± 0.18) ($P < .001$). Also, in data analysis, there was a significantly high correlation between duration of dialysis and intima-media thickness in the dialysis group ($P < .001$, $r=0.882$).

Discussion

Sonographic intima-media thickness measurement in carotid arteries is considered a tool in evaluating silent atherosclerosis in chronic, renal-failure patients.¹²⁻¹⁴ Because some studies considered carotid artery intima-media thickness of more than 0.8 mm abnormal,¹⁵ most dialysis patients in this study had an abnormal carotid artery intima-media thickness, and thus, a higher risk of cardiovascular disease. Besides, we demonstrated that increased dialysis duration is associated with higher intima-media thickness. Studies on carotid artery intima-media thickness in hemodialysis patients, when compared with healthy individuals, show that level of this index was higher in dialysis patients.¹⁶ In children with chronic kidney disease, increased carotid artery intima-media thickness occurred early in the course of the disease.⁸ However, the type of dialysis did not influence carotid artery intima-media thickness, resulting in an increased intima-media thickness in both types (hemodialysis and stable peritoneal dialysis).¹⁷ As expected, serum creatinine level was higher in dialysis patients compared with transplant ones. On the other hand, a larger carotid artery

intima-media thickness is predicted with a lower creatinine clearance; hence, a creatinine clearance level less than 75 mL per minute at 1.73 m² of the body surface, and a change in carotid artery intima-media thickness more than 0.008 mm per year, is associated with a worse prognosis. In other words, reduced kidney function is strongly associated with a faster change in carotid artery intima-media thickness; while both of these factors are associated with future cardiovascular events.⁴

Cardiovascular diseases are the most-important causes of mortality and morbidity in patients with chronic kidney disease. High prevalence of cardiovascular disorders in these patients at the beginning of kidney replacement therapies showed the presence of cardiovascular disease risk factors in early stages of chronic kidney disease; therefore, professionals must consider early diagnosis and treatment of amendable risk factors during the first patient visit.¹⁸

Subclinical atherosclerosis occurs in early stages of renal function reduction. Disease progression occurs as a result of several cardiovascular conditions, including increased volume (secondary to sodium retention), high blood pressure, insulin resistance, and glucose intolerance. Also, patients with decreased renal function have abnormal vascular biological characteristics. As a result, progress in renal disease results in a series of disruptions including oxidative stress, exacerbated inflammation (increased C-reactive protein), and increased serum levels of homocysteine; microalbuminuria and proteinuria are also predictive for cardiovascular disease in end-stage renal disease patients. In a study on elderly patients, impaired renal function also was accompanied by harmful changes in the arterial structure⁴; the changes occurred early in the course of worsening of renal disease and were prognostic of cardiovascular consequences.

Cardiovascular disorders in dialysis patients are multifactorial including uremia, increased volume, arteriovenous fistula (resulting in increased preload) and high blood pressure (resulting in increased afterload). Uremic toxins including increased amounts of parathyroid hormone and hemodialysis also can cause myocardial dysfunction.^{19, 20} Hemodialysis or peritoneal dialysis are unable to fully remove uremic toxins and reduce cardiovascular risk factors. Uremic cardiomyopathy characterized with impaired systolic function, and left ventricular hypertrophy or dilatation, is a strong predictor of heart failure,^{21, 22} and

many researchers have reported that many dialysis patients may have electrocardiographic evidence of congestive cardiomyopathy and left ventricular hypertrophy.^{23, 24} Accelerated atherosclerosis and vascular calcification increased mortality and morbidity in dialysis patients.¹⁷ By starting dialysis, uremic status and dialysis-related risk factors intensify cardiovascular disorders (as a result of superimposed stress of increased intravascular volume on the myocardial muscle). Left ventricle constructional and functional abnormalities commonly occur in patients with chronic renal failure; high blood pressure is the main factor in left ventricular hypertrophy, while other factors (eg, anemia, increased volume, poor nutrition, secondary hyperparathyroidism, ischemic heart disease, arteriovenous fistula, and myocardial calcification) also are important.²⁵

In this study, the carotid artery intima-media thickness in transplant patients was significantly less than in dialysis patients, and this was associated with low risk of stroke and cardiovascular disease in the future. Various studies conducted in this area proved a reduction in the carotid artery intima-media thickness accompanying kidney transplant, and in children with chronic kidney disease, increased carotid artery intima-media thickness may be, to some extent, reversible after transplant.¹⁷

Cardiovascular mortality after kidney transplant long after surgery (in patients with a good performance) was low (in the absence of risk factors for cardiovascular disease such as diabetes and hypertension).²⁶ These findings indicate that cardiovascular mortality risk after kidney transplant gradually decreases, unlike the highly increased mortality in dialysis patients. Therefore, the function of transplanted kidney is discussed as a major risk factor for cardiovascular disease and resultant mortality,²⁷ and decreased kidney function and gradual loss are expected to increase the risk of cardiovascular disease over the time.²⁸ Regarding progressive arteriopathy associated with inflammation²⁹ and calcification³⁰ in dialysis patients and underlying vasculopathy mechanisms, due to reduced or lack of kidney function, it is not surprising that the risk of cardiovascular disease and the resultant death is extremely less in dialysis patients in the transplant patients who partially recovered their renal function.

As recently indicated, mild decrease in renal function is associated with increased risk of

cardiovascular mortality,³¹ and increased serum creatinine level is one of the strongest predictors of mortality.³² As a result, kidney transplant has important advantages compared with long-term dialysis, especially in patient survival.³³ Although postoperative drugs are also added to previous cardiovascular risk factors, increased patient survival indicates the effective role of kidney transplant in control of cardiovascular disease.

High blood pressure, diastolic interventricular septum, posterior left ventricular wall thickness, and low ejection fraction existing before kidney transplant, regress with a successful transplant. Also, significant improvement in cardiovascular function occurred owing to increased ejection fraction and improved fractional shortening.³⁴ This might be a result of improved cardiac metabolism owing to elimination of uremic toxins in the circulation. Autopsy showed a less intermyocardiocytic fibrosis in transplant patients compared with advanced dialysis patients, suggesting an improved cardiac condition after correction of a uremic state.³⁵ Hyperparathyroidism and hypocalcemia are of the main risk factors of uremic cardiomyopathy.^{36, 37} After successful kidney transplant, hyperparathyroidism is significantly reduced. Improved anemia after kidney transplant can improve cardiac function as the treatment of anemia in dialysis patients with erythropoietin may reduce the cardiovascular disease.³⁷

Although a reduction in cardiovascular events after transplant as a result of improved uremic state, decreased platelet activity and improved endothelial and microfilament function is expected,³⁸⁻⁴⁰ however, a combination of other factors (eg, smoking, hypertension, diabetes mellitus, anemia, and physical inactivity) accompanied by transplant-specific risk factors (including immunosuppressive drugs [cyclosporine]), tends to overcome new-onset, posttransplant diabetes.^{41, 42} As a result, atherosclerosis remains one of the early posttransplant events in asymptomatic patients and those with major risk factors (including cardiovascular disease, diabetes, and smoking) which makes early diagnosis and treatment in these patients of great importance.¹¹

Conclusions

Common carotid intima-media thickness is higher in dialysis patients than it is in transplant patients, which was independent of age, sex, or other effects.

Prolonged dialysis duration is associated with increased carotid intima-media thickness. Because higher common carotid intima-media thickness is predictive of atherosclerosis and is associated with higher risk of stroke and cardiovascular disease, special attention should be paid to the metabolic status of dialysis patients and transplant must be considered as soon as possible.

References

1. United States Renal Data System. VI. Causes of death in ESRD. *Am J Kidney Dis.* 1999;34(2 Suppl 1):S87-S94.
2. Bennett WM, Kloster F, Rosch J, Barry J, Porter GA. Natural history of asymptomatic coronary arteriographic lesions in diabetic patients with end-stage renal disease. *Am J Med.* 1978;65(5):779-784.
3. Benedetto FA, Mallamaci F, Tripepi G, Zoccali C. Prognostic value of ultrasonographic measurement of carotid intima media thickness in dialysis patients. *J Am Soc Nephrol.* 2001;12(11):2458-2464.
4. Desbien AM, Chonchol M, Gnahn H, Sander D. Kidney function and progression of carotid intima-media thickness in a community study. *Am J Kidney Dis.* 2008;51(4):584-593.
5. Braun WE, Phillips DF, Vidt DG, et al. Coronary artery disease in 100 diabetics with end-stage renal failure. *Transplant Proc.* 1984;16(3):603-607.
6. Schmidt A, Stefanelli T, Schuster E, Mayer G. Informational contribution of noninvasive screening tests for coronary artery disease in patients on chronic renal replacement therapy. *Am J Kidney Dis.* 2001;37(1):56-63.
7. Modi N, Kapoor A, Kumar S, Tewari S, Garg N, Sinha N. Utility of carotid intimal medial thickness as a screening tool for evaluation of coronary artery disease in pre-transplant end stage renal disease. *J Postgrad Med.* 2006;52(4):266-270.
8. Litwin M, Wühl E, Jourdan C, et al. Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. *J Am Soc Nephrol.* 2005;16(5):1494-1500.
9. De Lima JJ, Vieira ML, Viviani LF, et al. Long-term impact of renal transplantation on carotid artery properties and on ventricular hypertrophy in end-stage renal failure patients. *Nephrol Dial Transplant.* 2002;17(4):645-651.
10. Van Bortel LM. What does intima-media thickness tell us? *J Hypertens.* 2005;23(1):37-39.
11. Nafar M, Khatami F, Kardavani B, Farjad R, Pour-Reza-Gholi F, Firoozan A. Atherosclerosis after kidney transplantation: changes of intima-media thickness of carotids during early posttransplant period. *Urol J.* 2007 Spring;4(2):105-110. Erratum in: *Urol J.* 2007;4(4):254.
12. Craven TE, Ryu JE, Espeland MA, et al. Evaluation of the associations between carotid artery atherosclerosis and coronary artery stenosis. A case-control study. *Circulation.* 1990;82(4):1230-1242.
13. Ekart R, Hojs R, Hojs-Fabjan T. Balon blood pressure. Predictive value of carotid intima media thickness in hemodialysis patients. *Artif Organs.* 2005;29(8):615-619.
14. Salonen R, Seppänen K, Rauramaa R, Salonen JT. Prevalence of carotid atherosclerosis and serum cholesterol levels in eastern Finland. *Arteriosclerosis.* 1988;8(6):788-792.
15. Jadhav UM, Kadam NN. Carotid intima-media thickness as an independent predictor of coronary artery disease. *Indian Heart J.* 2001;53(4):458-462.
16. Brzosko S, Lebkowska U, Malyszko J, Hryszko T, Krauze-Brzosko K, Mysliwiec M. Intima media thickness of common carotid arteries is associated with traditional risk factors and presence of ischaemic heart disease in hemodialysis patients. *Physiol Res.* 2005;54(5):497-504.
17. Stompór T, Kraśniak A, Sułowicz W, et al. Changes in common carotid artery intima-media thickness over 1 year in patients on peritoneal dialysis. *Nephrol Dial Transplant.* 2005;20(2):404-412.

18. Locatelli F, Pozzoni P, Tentori F, del Vecchio L. Epidemiology of cardiovascular risk in patients with chronic kidney disease. *Nephrol Dial Transplant*. 2003;(suppl 7):vii2-9.
19. Lai KN, Ng J, Whitford J, Buttfield I, Fassett RG, Mathew TH. Left ventricular function in uremia: echocardiographic and radionuclide assessment in patients on maintenance hemodialysis. *Clin Nephrol*. 1985;23(3):125-133.
20. Capelli JP, Kasparian H. Cardiac work demands and left ventricular function in end-stage renal disease. *Ann Intern Med*. 1977;86(3):261-267.
21. London GM, Fabiani F, Marchais SJ, et al. Uremic cardiomyopathy: an inadequate left ventricular hypertrophy. *Kidney Int*. 1987;31(4):973-980.
22. Ibanez LE, Lowen J, Sarbaga E. Uremic myocardiopathy. *Nephron*. 1975;15(1):17-28.
23. Miach PJ, Dawborn JK, Louis WJ, McDonald IG. Left ventricular function in uremia: echocardiographic assessment in patients on maintenance dialysis. *Clin Nephrol*. 1981;15(5):259-263.
24. Drüeke T, Le Pailleur C, Sigal-Saglier M, Zingraff J, Crosnier J, Di Mattéo J. Left ventricular function in hemodialyzed patients with cardiomegaly. *Nephron*. 1981;28(2):80-87.
25. Lopez-Gomez JM, Verde E, Perez-Garcia R. Blood pressure, left ventricular hypertrophy and long-term prognosis in hemodialysis patients. *Kidney Int Suppl*. 1998;68:S92-S98.
26. Meier-Kriesche HU, Schold JD, Srinivas TR, Reed A, Kaplan B. Kidney transplantation halts cardiovascular disease progression in patients with end-stage renal disease. *Am J Transplant*. 2004;4(10):1662-1668.
27. Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation*. 2003;75(8):1291-1295.
28. Kaplan B, Meier-Kriesche HU. Death after graft loss: an important late study endpoint in kidney transplantation. *Am J Transplant*. 2002;2(10):970-974.
29. Suliman ME, Heimbürger O, Bárány P, et al. Plasma pentosidine is associated with inflammation and malnutrition in end-stage renal disease patients starting on dialysis therapy. *J Am Soc Nephrol*. 2003;14(6):1614-1622.
30. Chertow GM, Raggi P, McCarthy JT, et al. The effects of sevelamer and calcium acetate on proxies of atherosclerotic and arteriosclerotic vascular disease in hemodialysis patients. *Am J Nephrol*. 2003;23(5):307-314.
31. Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int*. 1999;56(6):2214-2219.
32. Shulman NB, Ford CE, Hall WD, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension*. 1989;13(suppl 5):I80-I93.
33. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*. 1999;341(23):1725-1730.
34. Nakajima K, Ochiai T, Suzuki T, et al. Beneficial effects of renal transplantation on cardiovascular disorders in dialysis patients. *Surg Today*. 1998;28(8):811-815.
35. Levin A, Foley RN. Cardiovascular disease in chronic renal insufficiency. *Am J Kidney Dis*. 2000;36(suppl 3):S24-S30.
36. Drüeke T, Fauchet M, Fleury J, et al. Effect of parathyroidectomy on left-ventricular function in haemodialysis patients. *Lancet*. 1980;1(8160):112-114.
37. Silberberg J, Racine N, Barre P, Sniderman AD. Regression of left ventricular hypertrophy in dialysis patients following correction of anemia with recombinant human erythropoietin. *Can J Cardiol*. 1990;6(1):1-4.
38. da Silva CD, Brunini TM, Reis PF, et al. Effects of nutritional status on the L-arginine-nitric oxide pathway in platelets from hemodialysis patients. *Kidney Int*. 2005;68(5):2173-2179.
39. Diaz-Buxo JA, Woods HF. Protecting the endothelium: a new focus for management of chronic kidney disease. *Hemodial Int*. 2006;10(1):42-48.
40. Brunini TM, da Silva CD, Siqueira MA, Moss MB, Santos SF, Mendes-Ribeiro AC. Uremia, atherothrombosis and malnutrition: the role of L-arginine-nitric oxide pathway. *Cardiovasc Hematol Disord Drug Targets*. 2006;6(2):133-140.
41. Małyszko J, Małyszko JS, Takada A, Myśliwiec M. Effects of immunosuppressive drugs on platelet aggregation in vitro. *Ann Transplant*. 2002;7(1):55-68.
42. Morris ST, McMurray JJ, Rodger RS, Farmer R, Jardine AG. Endothelial dysfunction in renal transplant recipients maintained on cyclosporine. *Kidney Int*. 2000;57(3):1100-1106.