

Evaluation of Arterial Stiffness and Pulse Wave Reflection for Cardiovascular Risk Assessment in Diabetic and Nondiabetic Kidney Transplant Recipients

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Introduction. Evidence demonstrates that cardiovascular risk reduces after kidney transplantation, but is still a major cause of death. With increasing inclusion of diabetic patients for kidney transplantation, the evaluation of cardiovascular disease in this population becomes more important. We compared arterial stiffness and pulse wave reflection as well as other cardiovascular risk factors in kidney transplant patients with and without diabetes mellitus.

Materials and Methods. One hundred kidney transplant recipients, including 33 diabetic patients, were evaluated for their renal-cardiovascular risk factors, including blood pressure, lipids, glucose control, homocysteine, and arterial stiffness indexes. The tests were repeated after 1 year in 47 individuals.

Results. There was no significant difference in pulse wave velocity (PWV) between the diabetic and nondiabetic groups, despite a greater augmentation index (AI) in the diabetic group (20.5 ± 2.3 versus 13.1 ± 2.2). Multivariable analysis revealed that diabetes mellitus was a significant determinant for AI independently of age, blood pressure, posttransplant time, gender, and glomerular filtration rate ($R^2 = 39\%$). Repeated test after 1 year demonstrated a significant reduction in the carotid-femoral PWV ($P = .03$) and systolic blood pressure ($P = .007$).

Conclusions. In contrast to nontransplant groups, AI was significantly greater in diabetic kidney transplant patients compared to their nondiabetic counterparts, despite a comparable PWV. However, carotid-femoral PWV improved after 1 year. These may reflect progressive ventricular and large arterial function improvement despite remained small arterial defects after transplantation. It also suggests potential role of arterial evaluation in risk assessment among kidney transplant patients.

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INTRODUCTION

Many national registries, including the Australian and New Zealand Dialysis and Transplant Registry, reported a substantially lower death rate in kidney transplant recipients compared to patients on dialysis. Accordingly, the mortality rate of kidney

transplant recipients is 6 and 8 times less than those of patients on dialysis with and without diabetes mellitus (DM), respectively.¹ Although this observation can be attributed to a younger age and a lower cardiovascular (CV) risk in patients who have been selected for transplantation, it may

also indicate a reduction in CV risk following transplantation.²⁻⁵ Nevertheless, CV disease is still a common cause of posttransplant death,¹ and classic risk factors cannot fully explain the CV risk in this population. It is reported that the Framingham CV risk score significantly underestimates the risk of ischemic heart disease in transplant patients,⁶ and therefore, nonclassic risk factors, including C-reactive protein, homocysteine, and kidney function as well as arterial stiffness, may contribute to CV risk in this population.^{2,7}

While patients with DM were not traditionally preferred candidates for kidney transplant due to a higher probability of posttransplant complications, rejection episodes and mortality, they are now frequently accepted with a 2-fold increase in the number and proportion in Australia over a decade.¹ The evidence regarding the CV prognosis in transplant patients with DM is conflicting, with some studies reporting higher CV events, rejection, and mortality,⁸ whereas a more recent report did not demonstrate a considerable difference between diabetic and nondiabetic patients.⁹ Therefore, the source of this heterogeneity may be the magnitude of vascular remodeling during the pretransplant period.

Since arterial stiffness is an established CV risk marker and an independent predictor of CV events and mortality in various groups of patients, including kidney transplant patients,^{7,10-14} this study compared arterial stiffness and pulse wave reflection as well as other CV risk factors in kidney transplant patients with and without DM.

MATERIALS AND METHODS

Study Subjects

Stable kidney transplant recipients were evaluated during a standard multicenter annual evaluation protocol. In order to evaluate the chronic effects of DM, patients with posttransplant DM (9 individuals) were excluded based on their most recent metabolic screening, to restrict potential biases. Consequently, the remaining 100 patients included 33 diabetic individuals (based on the pretransplant records) who had a good glycaemia control. The patients were routinely referred to their local medical centers, and therefore, only 47 of these patients were available after a year. However, no systematic difference was postulated between this subgroup and the general group.

They underwent repeated same tests for the next year while the observer was blind to the first measurement. The study was approved by the regional health authority ethics committee.

Measurements

Diagnosis of DM was based on the pretransplant assessment and blood samples according to the World Health Organization's criteria. Blood pressure was measured by a validated automatic oscillometric arm-cuff device (Omron HEM-703, Kyoto, Japan).

Pulse wave velocity (PWV) was performed using an automated device (Complior, Colson, France) after placing 3 mechanosensors on the skin overlying the carotid, radial, and femoral arteries. Pulse transit time was determined as the average of 10 consecutive beats. The distance travelled by the pulse wave was measured over the body surface as the distance between 2 sites (without adjustment for the sternal jugular length). Pulse wave velocity was calculated by dividing the distance between the sensors (mm) by the time corresponding to the period between rising phases of the waveform in the sites (foot-to-foot method). Carotid-femoral PWV (CFPWV) was considered as central (large arteries) and carotid-radial PWV as peripheral arterial stiffness indexes. An intra-observer coefficient of variation of 5.5% has been established with this method in our laboratory.

Pulse wave analysis was evaluated using the radial artery pressure waveform recorded over 10 seconds using a validated tonometer (Millar SPC-301B, Huston, USA), and then processed with dedicated software (SphygmoCor, version 7.1, AtCor Medical, Sydney, Australia). Time to peak of the first, second, and reflected wave, augmentation index (AI) and pulse reflection time, as well as ejection duration and coronary artery viability index were calculated, and central arterial pressure was estimated based on a transfer function. Adjusted AI for a heart rate equal to 75 beats per minute was estimated based on an internal normogram in the software.

Glomerular filtration rate (GFR) was measured by the ethylenediamine tetra-acetic acid method and all biochemical tests were performed in a central referral laboratory. All CV events and rejection episodes were recorded on an updated regional transplant registry.

Statistical Analyses

The *t* test for was applied for comparison of normally distributed variables and the Mann-Whitney U test, for variables not normally distributed. Multivariate analyses were performed by linear regression and paired comparison, by the Wilcoxon signed rank test.

RESULTS

Patients' Characteristics

Participants were 100 patients, including 33 diabetic individuals (based on the pretransplant records) who had a good glycemia control. Their mean age was 51 ± 14 years, and 64% were men. The posttransplant time ranged from 11 to 275 months. Sixty percent of the patients used mycophenolate mofetil, 40% were on cyclosporine, and 21% were taking other immunosuppressive medications.

Forty-eight percent of the kidney transplant recipients had at least one rejection episode, and 7% experienced a posttransplant CV event (5 myocardial infarctions and 2 cerebrovascular events). The CV events, rejection episodes, and the proportion of live donors were comparable between the DM and non-DM groups. The frequency distributions of the immunosuppressive and calcium channel blocker medication types were also comparable between the two groups.

Among the measured risk factors, CFPWV and homocysteine were skewed to the right. Therefore, their log transformed forms were used or nonparametric methods were applied for analysis.

Comparison of Diabetic and Nondiabetic Groups

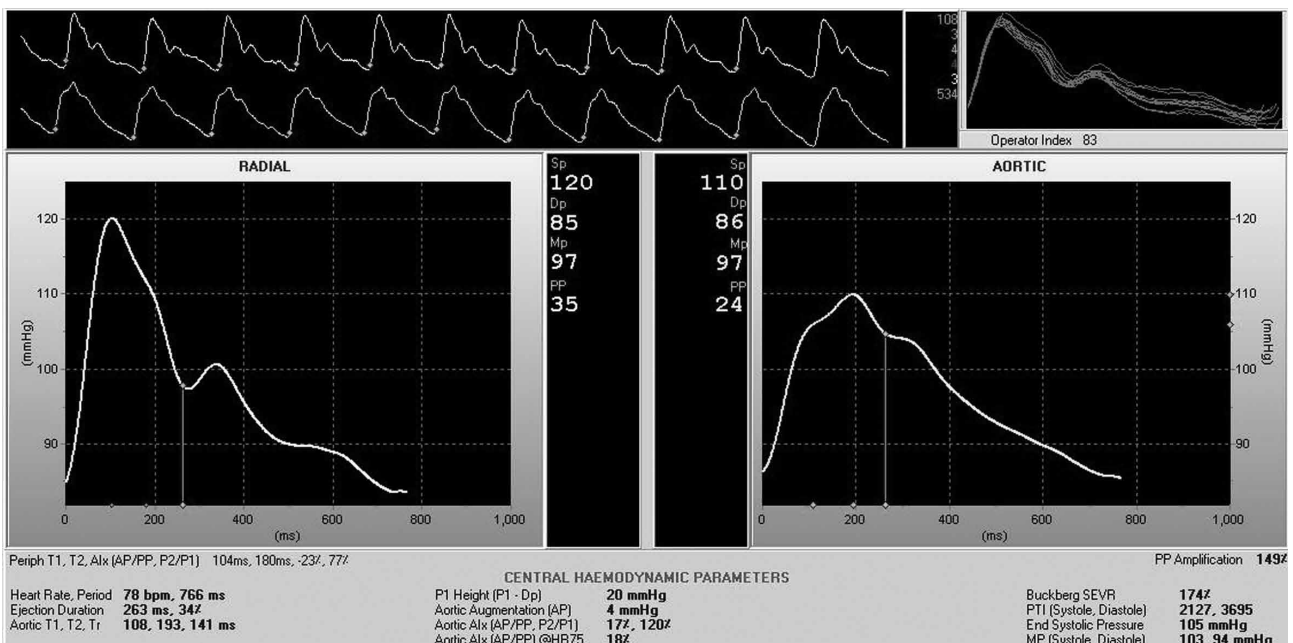
Diabetic patients had comparable blood pressure and heart rate, and serum cholesterol, plasma homocysteine, and GFR levels with nondiabetics. There was no significant difference in central and peripheral PWV between the two groups either, but adjusted AI was significantly greater in diabetic patients (Table 1 and Figure).

Regression Analysis

In multivariate analysis, a model including age, systolic blood pressure, DM, posttransplant time, gender, and GFR, DM was independently correlated with the adjusted AI (Table 2) and this model contributed towards 39% of dependent variable variance. Among all variables, only posttransplant time and homocysteine were independently and significantly associated with GFR ($\beta = -0.35$ and $\beta = -0.29$, $P = .008$ and $P = .02$; respectively).

Cardiovascular Risk Factor Changes Over 1-year Follow-up

A significant reduction in systolic blood pressure and CFPWV was observed over a 12-month follow-



An example of pulse wave analysis output demonstrating pulse wave reflection analysis and related outputs.

Table 1. Comparison Between Diabetic and Nondiabetic Kidney Transplant Recipients*

Parameter	DM (n = 33)	Non-DM (n = 67)	P
Age, y	55.1 ± 2.2	48.8 ± 1.8	.03
Posttransplant time, mo	56.7 ± 12.6	79.9 ± 9.0	.13
SBP, mm Hg	137.0 ± 3.0	134.4 ± 2.4	.51
DBP, mm Hg	75.6 ± 1.9	80.6 ± 1.8	.08
Heart Rate, beats/min	70.9 ± 2.8	68.6 ± 1.7	.47
Cholesterol, mmol/L	4.6 ± 0.2	4.9 ± 0.2	.18
Homocysteine, μmol/L	14.9 ± 1.0	16.6 ± 0.8	.20
HbA1c, %	6.2 ± 0.1	5.5 ± 0.3	< .001
GFR, mL/min	59.2 ± 3.6	54.6 ± 2.5	.29
CFPWV, m/sec	10.8 ± 0.6	10.0 ± 0.3	.19†
CRPWV, m/sec	9.6 ± 0.4	9.6 ± 0.2	.89†
Adjusted AI	20.5 ± 2.3	13.1 ± 2.2	.03

*DM indicates diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; GFR, glomerular filtration rate; CFPWV, carotid-femoral pulse wave velocity; CRPWV, carotid-radial pulse wave velocity; and AI, augmentation index. †P values of nonparametric tests for CFPWV and homocysteine were .33 and .19, respectively

Table 2. Regression Analysis for Determinants of Adjusted Augmentation Index*

Parameter	Standard Error	Beta	t	P
Age	0.114	.398	3.571	.001
Gender	2.964	.249	2.562	.01
DM	3.070	.207	2.032	.046
Posttransplant time	0.022	.195	1.900	.06
SBP	0.081	.161	1.528	.13
GFR	0.073	.024	0.235	.82
Constant	13.524	...	-2.785	.007

*DM indicates diabetes mellitus; SBP, systolic blood pressure; and GFR, glomerular filtration rate.

Table 3. Nonparametric Paired Comparison of Cardiovascular Risk Factors Over 1-year Period of Follow-up in 47 Kidney Transplant Patients*

Parameter	Baseline		Year 1		P
	Mean	Median	Mean	Median	
SBP, mm Hg	134.1 ± 2.4	135.0	129.2 ± 2.4	127.0	.007
DBP, mm Hg	79.4 ± 1.8	80.0	75.7 ± 1.9	76.0	.11
Heart Rate, beats/min	70.6 ± 2.1	68.0	70.1 ± 2.3	68.0	.65
Cholesterol, mmol/L	4.9 ± 0.2	4.7	4.8 ± 0.1	4.8	.90
Homocysteine, μmol/L	16.2 ± 0.9	14.6	16.6 ± 0.8	16.4	.61
GFR, mL/min	57.6 ± 3.4	57.5	61.7 ± 5.7	54.0	.62
CFPWV, m/sec	10.8 ± 0.5	9.85	10.2 ± 0.4	9.76	.03
CRPWV, m/sec	9.8 ± 0.4	9.62	10.0 ± 0.3	9.99	.22
Adjusted AI	14.1 ± 2.5	14.5	11.1 ± 2.6	10.0	.20

*SBP indicates systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; CFPWV, carotid-femoral pulse wave velocity; CRPWV, carotid-radial pulse wave velocity; and AI, augmentation index.

up period. All other changes were statistically nonsignificant (Table 3).

DISCUSSION

The novel finding of this study was the higher adjusted augmentation index in diabetic compared to nondiabetic kidney transplant patients despite comparable hemodynamic and biochemical CV risk markers. It also demonstrated a significant reduction

in central arterial stiffness over a 12-month period in the DM and non-DM population without any change in any other risk markers except systolic blood pressure.

With an increasing number of diabetic patients as kidney transplant candidates, understanding posttransplant CV risk and complications in an already high-risk group is important, particularly since current evidence regarding posttransplant

prognosis in DM is conflicting. While some studies reported a worse outcome,⁸ others showed no difference,^{9,15} or even claimed an improved survival in diabetic patients who undergo kidney transplantation,^{16,17} when compared to nondiabetic individuals. Nevertheless, the risk must be individually identified, particularly since classic CV risk factors that are incorporated into the Framingham risk score underestimate the risk in transplant patients.⁶ Consequently, nonclassic risk markers including arterial stiffness should facilitate the risk stratification in this population.

Several studies, including ours, have demonstrated a greater central arterial stiffness in diabetic than nondiabetic patients in those with normal kidney function, chronic kidney disease, and end-stage renal disease, as represented by central PWV—despite a comparable amount of AI between the DM and non-DM groups^{10,18-23}—and suggested that AI cannot be a surrogate of arterial stiffness in DM in contrast to the non-DM population. This has been partially attributed to ventricular dysfunction with subsequent reduced pulse wave amplitude in DM. In contrast, the present report in kidney transplant patients revealed that the CFPWV was not significantly greater in DM, whereas AI was significantly higher in DM than non-DM groups and independently associated with DM in a multivariate analysis. Since cardiac function in diabetic transplant candidates is carefully evaluated prior to transplantation and left ventricular systolic and diastolic function improves shortly after a successful kidney transplant,^{5,24,25} we speculate that the hidden effect of DM on the arterial pulse waveform appears in this group and a revalidation of the AI as a surrogate of arterial stiffness should occur. The lack of a significant difference in CFPWV, despite a trend, may reflect the low power of the test with this sample size; however, patients' compliance to antihypertensive medications, including calcium channel blockers may have influenced PWV. More importantly, it may indicate a comparable improvement of large arterial compliance in both DM and non-DM groups (due to elimination of uremic toxins and volume control), despite remaining anomalies which can increase the AI, such as small artery abnormalities. This is supported by the finding of an improvement of PWV a year after the baseline measurement despite an unchanged AI. The

amount of the reduction, although looks minimal, can be considered clinically significant, since several studies have shown evidence that every unit reduction in PWV of the central arteries is equivalent to 10 years saving of life.²⁶

Our results contradict those of Ferro and colleagues²⁷ who reviewed 250 transplant patients to identify the main determinants of the AI as a CV risk marker and reported that arteriovenous fistula and cyclosporine treatment, as well as age, systolic blood pressure, heart rate, and gender are independent associates, but not DM. However, only 25 diabetic patients were included in their study.

While the recently available Australia and New Zealand Dialysis and Transplant Registry report indicated that both graft survival and patient survival have gradually improved over the past decade, CV diseases still account for a mortality of 22% among kidney transplant patients.¹ Several studies have also demonstrated a substantial CV risk reduction after kidney transplant when compared to hemodialysis patients.^{2,3} While this observed difference could be due to selection bias (younger age in transplant compared to hemodialysis patients), a large study including 46 164 patients who were placed on a waiting list for kidney transplant (virtually a homogenous population) revealed a long-term mortality reduction of 48% to 82% among patients who underwent transplant surgery.⁴ This is in parallel to the research reporting improved arterial function posttransplant. For instance, Kocak and colleagues reviewed 30 patients during hemodialysis and after transplant and demonstrated an improvement in endothelial function after transplant.²⁸ In addition Zoungas and coworkers evaluated systemic arterial compliance and AI in 36 patients before and after transplant and found a significant decrease in lipids, homocysteine, systolic and diastolic blood pressure, and heart rate as well as the AI and peripheral and central PWV following transplantation.²⁹ However our findings regarding a reduction in CFPWV after 1-year follow-up is the first report which shows continuous improvement in arterial compliance during posttransplant period. However, research is required to see if this benefit continues to occur over the life of the transplant recipient, as well as its cause.

Finally, this study demonstrated that the posttransplant time and plasma homocysteine

are independent determinants for GFR in kidney transplant patients. Previous studies reported a reduction in homocysteine after transplantation.²⁹ Although we did not observe any difference between the first and the second tests, the plasma homocysteine level was comparable to the posttransplant levels in the previous study.²⁹

Our data did not include information about arteriovenous fistula, pretransplant dialysis period, and primary diagnosis for kidney failure. Also we could not compare our patients' test with their pretransplant condition.

CONCLUSIONS

Arterial evaluation facilitates CV risk assessment in kidney transplant patients. Kidney transplant patients with DM had comparable PWVs, but significantly greater AIs than their non-DM counterparts. Furthermore, two consecutive measurement with a 1-year interval demonstrated improvement in central PWV. These findings suggest a posttransplant improvement of ventricular function and large arterial stiffness shortly after transplantation, despite evidence of remained kidney-failure-induced small arterial remodelling. Yet, further prospective studies are required to investigate the above hypothesis.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. McDonald S, Excell L. The 28th Annual Report. Adelaide: Australia and New Zealand Dialysis and Transplant Registry; 2005.
2. Marcen R. Cardiovascular risk factors in renal transplantation—current controversies. *Nephrol Dial Transplant*. 2006;21 Suppl 3:iii3-8.
3. Dimeny EM. Cardiovascular disease after renal transplantation. *Kidney Int Suppl*. 2002;:78-84.
4. 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;341:1725-30.
5. Nakajima K, Ochiai T, Suzuki T, et al. Beneficial effects of renal transplantation on cardiovascular disorders in dialysis patients. *Surg Today*. 1998;28:811-5.

6. Kasiske BL, Chakkerla HA, Roel J. Explained and unexplained ischemic heart disease risk after renal transplantation. *J Am Soc Nephrol*. 2000;11:1735-43.
7. Barenbrock M, Kosch M, Joster E, Kisters K, Rahn KH, Hausberg M. Reduced arterial distensibility is a predictor of cardiovascular disease in patients after renal transplantation. *J Hypertens*. 2002;20:79-84.
8. Nyberg G, Hartso M, Mjornstedt L, Norden G. Type 2 diabetic patients with nephropathy in a Scandinavian kidney-transplant population. *Scand J Urol Nephrol*. 1996;30:317-22.
9. Schiel R, Heinrich S, Steiner T, Ott U, Stein G. Long-term prognosis of patients after kidney transplantation: a comparison of those with or without diabetes mellitus. *Nephrol Dial Transplant*. 2005;20:611-7.
10. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation*. 2002;106:2085-90.
11. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*. 2001;37:1236-41.
12. Blacher J, Guerin AP, Pannier B, et al. Impact of aortic stiffness on survival in End-Stage Renal Disease. *Circulation*. 1999;99:2434-9.
13. Meaume S, Rudnichi A, Lynch A, et al. Aortic pulse wave velocity as a marker of cardiovascular disease in subjects over 70 years old. *J Hypertens*. 2001;19:871-7.
14. Bahous SA, Stephan A, Barakat W, Blacher J, Asmar R, Safar ME. Aortic pulse wave velocity in renal transplant patients. *Kidney Int*. 2004;66:1486-92.
15. Kronson JW, Gillingham KJ, Sutherland DE, Matas AJ. Renal transplantation for type II diabetic patients compared with type I diabetic patients and patients over 50 years old: a single-center experience. *Clin Transplant*. 2000;14:226-34.
16. Mieghem AV, Fonck C, Coosemans W, et al. Outcome of cadaver kidney transplantation in 23 patients with type 2 diabetes mellitus. *Nephrol Dial Transplant*. 2001;16:1686-91.
17. Brunkhorst R, Lufft V, Dannenberg B, Kliem V, Tusch G, Pichlmayr R. Improved survival in patients with type 1 diabetes mellitus after renal transplantation compared with hemodialysis: a case-control study. *Transplantation*. 2003;76:115-9.
18. Lacy PS, O'Brien DG, Stanley AG, Dewar MM, Swales PP, Williams B. Increased pulse wave velocity is not associated with elevated augmentation index in patients with diabetes. *J Hypertens*. 2004;22:1937-44.
19. Khoshdel AR, Carney SL. Increased pulse wave velocity is not associated with elevated augmentation index in patients with diabetes. *J Hypertens*. 2005;23:669-70.
20. Khoshdel AR, S.L.Carney, Gillies A, et al. The impact of diabetes mellitus on arterial stiffness in end-stage renal disease (Abstract). *Nephrology*. 2005;10:A21.
21. Aoun S, Blacher J, Safar ME. Diabetes Mellitus and renal Failure: effects on large artery stiffness. *J Hum Hypertens*. 2001;15:693-700.

22. Shoji T, Emoto M, Shinohara K, et al. Diabetes Mellitus, Aortic Stiffness, and Cardiovascular mortality in End-Stage Renal disease. *J Am Soc Nephrol.* 2001;12: 2117-24.
23. Tamminen M, Westerbacka J, Vehkavaara S, Yki-Jarvinen H. Insulin-induced decreases in aortic wave reflection and central systolic pressure are impaired in type 2 diabetes. *Diabetes Care.* 2002;25:2314-9.
24. Dudziak M, Debska-Slizien A, Rutkowski B. Cardiovascular effects of successful renal transplantation: a 30-month study on left ventricular morphology, systolic and diastolic functions. *Transplant Proc.* 2005;37:1039-43.
25. Ferreira SR, Moises VA, Tavares A, Pacheco-Silva A. Cardiovascular effects of successful renal transplantation: a 1-year sequential study of left ventricular morphology and function, and 24-hour blood pressure profile. *Transplantation.* 2002;74:1580-7.
26. Khoshdel AR, Carney SL, Nair BR, Gillies A. Better management of cardiovascular diseases by pulse wave velocity: combining clinical practice with clinical research using evidence-based medicine. *Clin Med Res.* 2007;5:45-52.
27. Ferro CJ, Savage T, Pinder SJ, Tomson CR. Central aortic pressure augmentation in stable renal transplant recipients. *Kidney Int.* 2002;62:166-71.
28. Kocak H, Ceken K, Yavuz A, et al. Effect of renal transplantation on endothelial function in haemodialysis patients. *Nephrol Dial Transplant.* 2006;21:203-7.
29. Zoungas S, Kerr PG, Chadban S, et al. Arterial function after successful renal transplantation. *Kidney Int.* 2004;65:1882-9.

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