Journal of Transplantation Technologies & Research

Fadel et al., J Transplant Technol Res 2016, 6:4
DOI: 10.4172/2161-0991.1000167

Research Article Open Access

Endothelial Dysfunction in Pediatric Renal Transplant Recipients

Fatina Fadel[1], **Hafez Bazaraa**[1], **Rania Hachem**[2], **Doaa M Salah**[1] **and Hesham Safouh**[1*]

[1]*Center for Pediatric Nephrology and Transplantation, Cairo University, Egypt*

[2]*Department of Radiodiagnosis, Cairo University, Egypt*

[*]**Corresponding author**: Hesham Safouh, Center for Pediatric Nephrology and Transplantation, New Children Hospital, Faculty of Medicine, Cairo University, P O Box 98, Orman 12612, Giza, Egypt, Tel: + 201222477081; E-mail: heshamsafouh@kasralainy.edu.eg

Received date: June 13, 2016; **Accepted date**: July 12, 2016; **Published date**: July 20, 2016

Abstract

Background: Cardiovascular disease is a major cause of morbidity and mortality after kidney transplantation. Endothelial dysfunction was shown to constitute an independent predictor of cardiovascular events. This study aimed at detecting endothelial dysfunction in pediatric renal transplant recipients.

Methods: This was a prospective cohort study of 36 pediatric renal transplant recipients during their first post-transplantation year (transplantation group), 30 patients with end stage renal disease (ESRD) on regular hemodialysis (HD) (dialysis group) and 30 normal subjects (control group). Doppler ultrasound was performed for assessment carotid artery intima-media thickness (IMT) and brachial artery flow-mediated dilatation (FMD).

Results: Carotid artery IMT measurements in the transplantation group (mean ± SD = 0.43 ± 0.08 mm) were significantly (p=0.001) lower than the dialysis group (0.5 ± 0.1mm) and insignificantly higher than the control group (0.41 ± 0.07mm). FMD was significantly impaired in the dialysis group. The median (IQR) FMD of the transplantation group, 8.7% (2.5-20.4), tended to be higher than that of the dialysis group, 4.4% (2.6-10.8) and lower than that of normal controls, 14% (8.5-19.7); p=0.055 and 0.12 respectively.

Conclusion: Pediatric renal transplant recipients tend to show evidence of endothelial dysfunction at an apparently lesser extent than those on regular hemodialysis.

Keywords: Atherosclerosis; Doppler ultrasound; End stage renal disease (ESRD); Flow-mediated dilatation (FMD); Hemodialysis; Intima-media thickness (IMT); Renal replacement therapy (RRT).

Introduction

Chronic kidney disease (CKD) is an increasingly common, worldwide, health problem and is now known to be associated with an increased risk of cardiovascular disease [1]. Recent studies suggest that pediatric patients with even moderately impaired kidney function may be afflicted with significant early cardiac and vascular abnormalities [2].

Although there have been many advances in dialytic therapy, renal transplantation is the best treatment for children with end stage renal disease (ESRD) [3]. The outcome of pediatric renal transplant recipients has improved dramatically in the past 3 decades, as a result of the use of more potent immunosuppression and a decline in the mortality from infection. However the expected life span is still shorter than an age - matched normal population, mostly as a result of accelerated cardiovascular disease (CVD). CVD is the second most common cause of death in children after infection, and the leading cause of death in young adults, who have undergone renal transplantation [4].

Some of the known risk factors for CVD and death such as hypertension, obesity, left ventricular hypertrophy and dyslipidemia are commonly seen in renal transplant recipients. They may be contributed to, or aggravated, by the adverse effect of steroids and other immunosuppressive medications [5].

It is now generally accepted that the first reversible step in atherosclerosis is endothelial dysfunction (ED) [6]. ED appears to be useful in the prediction of morbidity and mortality in cardiovascular risk groups [7]. Doppler based measurement of intima media thickness (IMT) of the carotid artery and quantification of flow mediated, endothelium dependent, dilatation (FMD) of the brachial artery are the most frequently used methods of non-invasive assessment of ED in the pediatric population. ED, evidenced by impaired FMD, has been previously documented in children with CKD [8].

The aim of this study was to detect ED in pediatric renal transplant recipients through measurement of brachial artery FMD and carotid artery IMT after the first post-transplantation year, and to study the different potential risk factors for post-transplant ED.

Patients and Methods

This was a prospective cohort study that included 96 subjects divided into three groups.

Transplant group

Thirty six renal transplant recipients, being followed-up after their first transplantation year at the Center of Pediatric Nephrology and Transplantation (CPNT), Faculty of Medicine, Cairo University, Egypt, as of June, 2012.

Dialysis group

Thirty HD patients, on regular chronic HD for at least one year at the CPNT. Both groups were 4-18 years of age, had ESRD and those with evidence of primary cardiovascular diseases such as congenital heart disease, rheumatic heart disease or active vasculitis were excluded from the study.

Control group

Thirty normal age-matched subjects who were used as a reference group for Doppler measurements.

This sample size was sufficiently powered for a difference in IMT of 0.1 mm (at SD of 0.1 mm) and a 5% difference in FMD (at SD of 6%), with a minimum required sample size per group, to achieve 80% power, of 16 and 28 subjects respectively. The study protocol was approved by the Research Committee of the Department of Pediatrics, Faculty of Medicine, Cairo University.

Following informed parental consent, all cases were subjected to full history taking, complete physical examination and routine laboratory investigations. The report of the Second Taskforce on Blood Pressure Control in Children [9] was used to determine blood pressure (BP) percentiles and BP was classified into: Normal (BP <90th percentile with no antihypertensive medications), borderline hypertension (BP between 90th-95th percentiles without antihypertensives), controlled hypertension (BP<95th percentile on treatment) and uncontrolled hypertension (BP ≥ 95th percentile).

Non-invasive assessment of endothelial function was done using measurement of the IMT of the carotid arteries and FMD of the brachial artery. Procedures were explained to the subjects for obtaining consent prior to starting the assessment.

Carotid artery IMT

Measurements were performed in both common carotid arteries on frozen, magnified images obtained 10 mm below the bifurcation. IMT was analyzed on the "far wall", measuring the maximum distance between the leading edge of the luminal echo to the leading edge of the media-adventitia echo [10]. The mean for both arteries was calculated.

Brachial artery FMD

It was measured by comparison of the vessel diameter at rest with that during reactive hyperemia [8]. Subjects were fasting for 6 hours before the test and were examined in a quiet, temperature-controlled room by the same physician, who was guided by the methods described by Hussein et al. [8] and Peretz et al. [11].

The diameter of the brachial artery was measured from B mode ultrasound images using a C 5.2 MHz linear array transducer attached to a Sony Endisor (Sony Corporation, 6-7-35 Kitashinagawa, Shinagawa-ku, Tokyo, 141, JP). The artery was imaged above the antecubital fossa in the longitudinal plane, using a segment with clear anterior and posterior intimal surfaces between the lumen and the vessel wall. Arterial flow velocity was measured with a pulsed Doppler signal at a 90˚ angle to the vessel.

A baseline scan was taken after the patient had an initial rest period of 15 min in the supine position. To induce increased flow, pneumatic tourniquet was applied to the forearm and inflated to a pressure above the systolic BP for 5 minutes, then released. A second scan for reactive hyperemia was taken continuously from 30 seconds before to 90 seconds after cuff deflation, with flow velocity recording for the first 30 seconds following cuff deflation.

The child's arm was marked to help maintain the same image of the artery throughout the study. Resting and peak flow volumes (ml/min) were measured. Reactive hyperemia (RH) was calculated as follows:

$$RH = (\text{Peak Flow} / \text{Resting Flow}) \times 100$$

Flow-mediated dilatation represented the difference between the vessel diameter at rest (D1) and during reactive hyperemia (D2). Percent FMD was calculated as follows:

$$FMD = (D2 - D1) / D1 \times 100$$

A percent FMD less than 5% was considered impaired [8].

Data Analysis

Data were tabulated and subjected to computer-assisted statistical analysis using Statistical Package for the Social Sciences (SPSS) version 16.0. Nominal data were described as frequency and percentage and compared using the chi-squared test. Numerical data were described as mean and standard deviation and compared using t tests. Non-parametric data were described as median and interquartile range and were compared using Mann-Whitney test. Numerical associations were tested using Pearson correlations. A p-value less than 0.05 was considered significant.

Results

Table 1 demonstrates the basic data of the study subjects. Causes of ESRD included various urological causes in 31% of cases, nephronophthisis in 20%, primary glomerulopathies in 11%, while 24% had ESRD of undetermined etiology. The median (interquartile range) for dialysis duration was 45 (24-74) months in the HD group and 17 (4-24) months in the transplant recipients, who were enrolled 15 (12-24) months post-transplantation.

	Transplant recipients (n=36)	Hemodialysis patients (n=30)	p-value
Boys; no (%)	20 (55.6%)	12 (40%)	0.1
Girls; no (%)	16 (44.4%)	18 (60%)	
	(mean ± SD)	(mean ± SD)	
Age (years)	11.5 ± 3.48	11.4 ± 3.34	0.93
Weight (kg)	32.83 ± 14.77	24.54 ± 9.43	0.008
Height (cm)	123.25 ± 14.03	117.03 ± 13.99	0.08
SBP (mmHg)	109 ± 10.5	113 ± 13.3	0.13
DBP (mmHg)	70.28 ± 8.45	72.63 ± 7.52	0.24
BMI (kg/m^2)	20.76 ± 6.26	17.50 ± 4.11	0.014
SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index			

Table 1: Clinical data of transplant recipients and HD patients.

Uncontrolled hypertension was present in 23% of dialysis patients and 11% of transplant recipients (p=0.09), while 13% and 19% respectively had hypertension which was controlled by medications

(p=0.3). In addition, 23% of dialysis patients and 11% of transplant recipients had borderline hypertension (p=0.07)

In the dialysis group, Kt/V (urea) ranged from 1.23 to 2.56 (mean ± SD = 1.85 ± 0.37), while in the transplanted cases, the mean (± SD) serum creatinine at hospital discharge was 0.61 ± 0.13 mg/dl (range 0.4-0.9). Other laboratory data are summarized in Table 2.

	Transplant recipients (n=36)		Hemodialysis patients (n=30)		p-value
	Mean	SD	Mean	SD	
HB (g/dl)	10.89	1.37	10.1	1.64	0.042
TLC (×10^3/mm^3)	7.49	2.42	6.34	1.85	0.045
PLT (×10^3/mm^3)	294.63	96.55	205.68	52.95	<0.001
BUN (mg/dl)	20.06	7.64	63.03	15.75	<0.001
Creatinine (mg/dl)	0.79	0.2	6.48	1.39	<0.001
Na (mmol/L)	138.33	3.61	135.5	1.96	<0.001
K (mmol/L)	4.54	0.53	5.56	0.94	<0.001
Calcium (mg/dl)	9.72	0.75	8.99	1.1	0.003
Phosphorus (mg/dl)	4.3	0.89	4.9	1.74	0.1
Ca × P product*	41.28	34.9-46	38.66	27.6-62	0.9
ALP (IU/L)*	214	152-306	538	313-927	<0.001
ALT (IU/L)*	19	14-34.5	19.5	14.8-22	0.49
Albumin (g/dl)	3.87	0.31	3.6	0.36	0.008
Cholesterol (mg/dl)	171.08	37.54	170.63	45.52	0.97
TG (mg/dl)*	82.5	63.8-124	133.5	74-201	0.09
LDLc (mg/dl)	105.22	31.78	104.25	35.94	0.92
HDLc (mg/dl)	48.25	9.99	42.25	15.91	0.1
LDL/HDL (mg/mg ratio)	2.29	0.93	2.71	1.082	0.16
Data are expressed as mean and SD					
*Non-parametric data expressed as median and interquartile range (IQR)					
HB: hemoglobin; TLC: total leucocytic count; PLT: platelet count; BUN: blood urea nitrogen; ALP: alkaline phosphatase; ALT: alanine transferase; TG: triglycerides; LDLc: low density lipoprotein cholesterol; HDLc: high density lipoprotein cholesterol.					

Table 2: Laboratory data of transplant recipients and hemodialysis patients.

In the transplanted group, 29 patients (81%) had received antibody induction (polyclonal antithymocyte globulin in 20 and basiliximab in 9); calcineurin inhibitors (tacrolimus in 22 and cyclosporine in 13 cases) were received in all but one patient on sirolimus-mycophenolate. All others received mycophenolate mofetil or mycophenolic acid sodium and low dose corticosteroids. Biopsy-proven acute rejections occurred in 11 cases (30%), of whom five required depleting antibody therapy and one with antibody-mediated rejection required plasma exchange. All acute events were not present at the time of assessment for ED. Regarding cardiovascular medications in transplant recipients, 10 cases (28%) received antihypertensives (calcium channel blockers in 10, beta blockers in 3 and methyldopa in one case). In addition, 4 patients received acetylsalicylic acid (11%) and one (3%) received clopidogrel; the latter following graft renal angioplasty for late renal artery stenosis.

As shown in Figure 1, the mean carotid artery IMT in normal controls (± SD) was 0.41 ± 0.07 mm. HD patients had significantly increased IMT (0.5 ± 0.1 mm, p < 0.001), while transplant recipients had a mean ± SD of 0.43 ± 0.08 mm, significantly lower than dialysis patients (p=0.001) and insignificantly higher than controls (p=0.31).

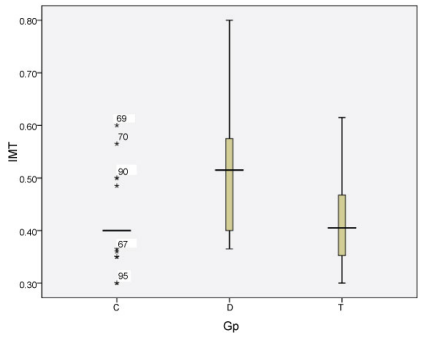

Figure 1: Carotid artery intima-media thickness (mm) in the study groups. C: normal controls; D: hemodialysis patients; T: transplant recipients; IMT: intima-media thickness.

The results of measurement of FMD are shown in Table 3. There was no significant difference in reactive hyperemia between the groups (Figure 1). The median FMD in normal subjects was 14% (IQR 8.5-19.7%). Patients on HD had a significantly impaired FMD (median 4.4%, p < 0.001), while transplanted patients had a median FMD of 8.7%; higher than dialysis patients with a near-significant difference (p=0.055). Transplant recipients had insignificantly lower FMD than normal subjects (p=0.12) (Figure 2). As shown in Figure 3, one-third of transplanted cases had impaired FMD (<5%), compared to 16 (53.3%) of dialysis patients (p = 0.05).

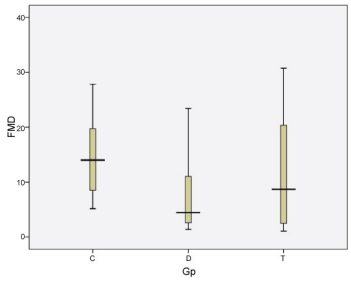

Figure 2: Flow-mediated dilatation (%) in transplant recipients (T), hemodialysis patients (D) and control subjects (C).

	Transplant recipients (n=36)		Hemodialysis patients (n=30)		Normal controls (n=30)	p-value (transplant vs. HD)
		p†		p†		
Resting flow (ml/min)	80.4 ± 25.7	0.19	73.06 ± 21.3	0.008	88.4 ± 21.9	0.22
Peak flow (ml/min)	268 ± 91.9	0.2	248.4 ± 74.8	0.03	299.8 ± 101.8	0.35
D1 (mm)	2.35 ± 0.6	0.01	2.26 ± 0.5	0.039	2.1 ± 0.26	0.53
D2 (mm)	2.6 ± 0.6	0.04	2.42 ± 0.4	0.59	2.4 ± 0.24	0.15
RH (%)	337.1 ± 62.3	0.8	345 ± 57.8	0.42	333 ± 55.2	0.6
FMD (mm)*	0.21 (0.07 -0.41)	0.16	0.11 (0.06 - 0.2)	<0.001	0.33 (0.17 - 0.44)	0.15
FMD %*	8.7 (2.5 - 20.4)	0.12	4.43 (2.6 - 10.8)	<0.001	14 (8.5 - 19.7)	0.055
FMD/RH (ratio)*	4.15 (1.09 -8.04)	0.12	2.14 (1.2 - 4.58)	<0.001	6.46 (4.01 - 8.02)	0.18

Data are expressed as mean and SD. *Non-parametric data expressed as median and interquartile range (IQR) P† (p - value versus control group) HD: hemodialysis; D1: vessel diameter at rest; D2: vessel diameter during reactive hyperemia; RH: reactive hyperemia; FMD: flow-mediated dilatation

Table 3: Flow-mediated dilatation of transplanted and dialysis groups versus control group.

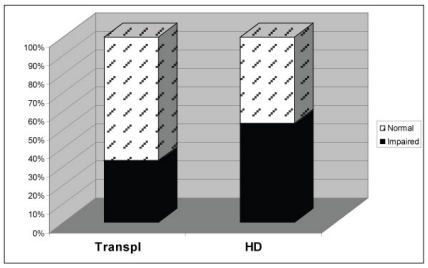

Figure 3: Impaired flow-mediated dilatation (<5%) in transplanted and hemodialysis groups.

There was a modest negative correlation of borderline statistical significance (r = -0.247, p = 0.051) between FMD and IMT (Figure 4). There was no significant correlation between dialysis duration and either FMD (r = -0.2, p = 0.12) or IMT (r = 0.088, p = 0.49). Blood pressure and lipid profile were also not significantly correlated to either FMD or IMT.

There was no significant difference between patients receiving cyclosporine (CsA) and those receiving tacrolimus in FMD% (10.44 ± 9.71 vs 12.65 ± 9.6, p=0.53) or IMT, although IMT tended to be somewhat higher with CsA (0.46 ± 0.09 vs 0.41 ± 0.07, p=0.07).

Discussion

As kidney transplantation is the treatment of choice for patients with ESRD [12] and CVD is a major cause of morbidity and mortality after kidney transplantation, effective prevention and management of CVD in kidney transplant recipients are integral to increasing patient longevity and quality of life, in addition to improving graft survival [13]. ED was shown to constitute an independent predictor of cardiovascular events, providing valuable prognostic information in addition to that derived from conventional risk factor assessment [14].

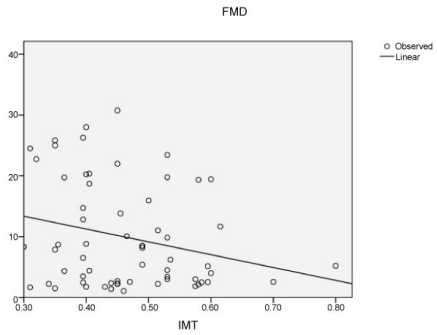

Figure 4: Correlation between carotid artery intima-media thickness (IMT) and brachial artery flow-mediated dilatation in all study subjects. R2= 0.6, r=-0.247, p=0.051

Carotid artery IMT has been previously reported to be an early marker of atherosclerosis and a predictor of cardiovascular events [15,16]. We found significantly lower carotid IMT in the transplantation group as compared with dialysis group (p=0.001), while values of the transplantation group were insignificantly higher than those of the control group (p=0.31). The finding of increased IMT in dialysis patients is in agreement with other studies showing that, as compared with control subjects, patients with uremia (including pre-dialysis uremic patients) had high carotid IMT values reflecting atherosclerosis [17,18]; however, our findings, furthermore, show that transplant recipients had better IMT.

As regards brachial artery FMD, reactive hyperemia was similar in transplant recipients, HD patients and normal controls. Because reactive hyperemia represents the stimulus for FMD, a difference in FMD would represent ED. The median FMD in dialysis patients was 4.4%, significantly lower than normal subjects (14%; p < 0.001). This denotes that children with ESRD on HD have ED manifested as impaired endothelium-dependent vasodilatation (EDV). This

coincides with previous reports showing impaired FMD in adults [19] and children [8] with chronic kidney disease. In those on renal replacement therapy, Prasad et al. [20] observed a similar result of lower FMD and brachial artery compliance in children on continuous ambulatory peritoneal dialysis and a small study comparing ten HD patients with ten healthy controls demonstrated reduced FMD in children on HD [21].

While reports exist in the literature regarding ED in adult and recently, pediatric patients with CKD, data from pediatric transplant recipients are relatively lacking. Results of the present study show that transplant recipients had insignificantly lower FMD than normal subjects (p=0.12) (median FMD of transplanted population and normal subjects were 8.7% and 14% respectively).

Lilien et al. [22] however, previously reported significantly less FMD (7.7% ± 5.4%) in 20 pediatric renal transplant recipients than healthy controls (15.0% ± 7.1%; P < 0.001), indicating ED in pediatric kidney recipients.

ED observed in renal transplant children and adolescents were investigated by Andrade et al. [23]. They found that even with only moderately decreased renal function, disturbances in the methylation cycle and arginine-creatine pathway present in these population which lead to elevated plasma values of homocysteine (Hcys), S-adenosylhomocysteine (SAH) and asymmetric dimethylarginine (ADMA) that inhibits nitric oxide synthesis contributing to ED observed in renal transplanted patients.

In the current study, FMD of the transplanted group tended to be higher than the dialysis group (p=0.055) and lower than controls (p=0.12). These findings denote that transplantation is associated with less ED, although still present, than ESRD on HD. To the same effect, 53% of dialysis patients had impaired FMD (<5%) compared to only 33% of transplant recipients. Our results regarding IMT also support the same notion. The tendency to a correlation between IMT and FMD is also interesting since both are markers of ED.

No significant correlation was found between BP of the studied group and FMD or IMT. This was in agreement with Hussein et al. [8] and Annuk et al. [24]. Cross et al. [25] also reported that the relation between ED and short term changes of BP was unclear. On the other hand, Lilien et al. [22] reported that Impairment of FMD was found predominantly in transplant recipients being treated for hypertension but they could not rule out the possibility that the antihypertensive medication used by the transplant recipients in itself some way influenced FMD.

Since only 4 of our transplanted patients (11%) and 11 of all cases (17%) had uncontrolled hypertension with elevated BP values, the lack of correlation between ED and BP values in the normal range would not necessarily exclude the possibility that those with uncontrolled hypertension would have more ED. In addition, it has been reported that calcium channel blockers and ACE inhibitors, used in many of our cases, can achieve a demonstrable improvement of EDV in hypertensive patients [26], probably in relation to antioxidant activity through the protection of endothelial cells against free radical injury and diminishing oxidative breakdown of nitric oxide [27]. This effect could have mitigated the effect of hypertension on ED.

Dyslipidemia is an established risk factor for atherosclerosis in uremic and non-uremic patients [20]. Triglycerides, cholesterol, LDL and LDL/HDL ratio were not significantly different between our two groups. This is despite the fact that drugs such as steroids and cyclosporine are known to cause dyslipidemia [28]. There was no relation between any of the lipids and FMD or IMT in our study, but the fact that lipid levels and LDL/HDL ratio were not elevated in transplant recipients and that the vascular effects of dyslipidemia may require a longer time than the duration of the present study, the association of dyslipidemia with ED cannot be ruled out based on our results.

Conclusion

Children with ESRD on HD have impaired FMD and increased IMT denoting vascular dysfunction, a marker of increased cardiovascular risk and a possible early reversible phase of atherosclerosis. Transplantation is associated with a better risk profile, manifesting as lower IMT and higher FMD, although not reaching that of the normal population. Pediatric renal transplant recipients are still at increased cardiovascular risk, to an apparently lesser extent than those on dialysis. The follow up of the long term implications of vascular dysfunction should be the subject of further research, and so should the effect of therapies targeting ED and cardiovascular risk modification since the outcome of pediatric renal transplantation is not only the consequence of graft function, but also involves many other factors of which cardiovascular outcome is of high importance.

References

1. Choi AL, Rodriguez RA, Baccchetti P, Bertenthal D, Hernandez GT, et al. (2009) White/black racial differences in risk of end stage renal disease and death. Am J Med 122: 672-678.
2. Querfeld U, Anarat A, Bayazit AK, Bakkaloglu AS, Bilginer Y, et al. (2010) The Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) study: objectives, design and methodology. Clin J Am Soc Nephrol 5: 1642-1648.
3. McDonald SP, Craig JC (2004) Long-term survival of children with end-stage renal disease. N Engl J Med 350: 2654-2662.
4. Becker RC, Nir A, Rinat C, Feinstein S, Algur N, et al. (2006) Risk Factors for Cardiovascular Disease in Children and Young Adults after Renal Transplantation. Clin J Am Soc Nephrol 6: 1284-1292.
5. Jardine AG, Fellstrom B, Logan JO, Cole E, Nyberg G, et al. (2005) Cardiovascular risk and renal transplantation: Post-hoc analyses of the Assessment of Lescol in Renal Transplantation (ALERT) study. Am J Kidney Dis 46: 529-536.
6. Pawlak K, Pawlak D, Mysliwies M (2005) Method of dialysis therapy and selected markers of oxidative stress and endothelial injury in patients with chronic renal failure. Pol Arch Med Wewn 113: 21-26.
7. Cross J (2002) Endothelial dysfunction in uremia. Blood Purif 20: 459-461.
8. Hussein G, Bughdady Y, Kandil ME, Bazaraa HM, Taher H, et al. (2008) Doppler assessement of brachial artery flow as a measure of endothelial dysfunction in pediatric chronic renal failure. Pediatr Nephrol 23: 2025-2030.
9. Report of the Second Task Force on Blood Pressure Control in Children--1987. Task force on Blood Pressure control in children. National Heart, Lung and Blood Institute, Bethesda, Maryland. (1987) Pediatrics 79:1-25.
10. Vicenzini E, Ricciardi MC, Puccinelli F, Altieri M, Vanacore N, et al. (2007) Common carotid artery intima-media thickness determinants in a population study. J Ultrasound Med 26: 427-432.
11. Peretz A, Leotta DF, Sullivan JH, Trenga CA, Sands FN, et al. (2007) Flow mediated dilation of the brachial artery: an investigation of methods requiring further standardization. BMC Cardiovasc Disord 7: 11.
12. Djamali A, Samaniego M, Muth B, Muehrer R, Hofmann RM, et al. (2006) Medical Care of Kidney transplant recipients after the First Post-transplant Year. Clin J Am Soc Nephrol 1: 623-640.

13. Kiberd BA (2007) cardiovascular diseases in kidney transplant recipients. Adv Stud Med 7: 169-178.
14. Bonetti PO, Lerman LO, Lerman A (2003) Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler, Thromb Vasc Biol 23: 168-175.
15. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE, et al. (1997) Common carotid intimamedia thickness and risk of stroke and myocardial infarction: the Rotterdam study. Circulation 96: 1432-1437.
16. Burke GL, Evans GW, Riley WA, Sharrett AR, Howard G, et al. (1995) Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) Study. Stroke 26: 386-391.
17. Ishimura E, Shoji T, Emoto M, Motoyama K, Shinohara K, et al. (2001) Renal insufficiency accelerates atherosclerosis in patients with type 2 diabetes mellitus. Am J Kidney Dis 38: 186-190.
18. Shoji T, Emoto M, Tabata T, Kimoto E, Shinohara K, et al. (2002) Advanced atherosclerosis in predialysis patients with chronic renal failure. Kidney Int 61: 2187-2192.
19. Ghiadoni L, CupistI A, Huang Y, Mattei P, Cardinal H, et al. (2004) Endothelium dependent and oxidative stress in chronic renal failure. J Nephrol 17: 512-519.
20. Prasad N, Kumar S, Singh A, Sinha A, Chawla K, et al. (2009) Carotid intimal thickness and flow mediated dilatation in diabetic and non-diabetic continuous ambulatory peritoneal dialysis patients. Perit Dial Int 29: 96-101.
21. Lilien MR, Koomans HA, Schroder CH (2005) Hemodialysis acutely impairs endothelial function in children. Pediatr Nephrol 20: 200-204.
22. Lilien MR, Stroes ES, Roodt JO, Saskia de Jongh NR, Cornelis H, et al. (2003) vascular function in children after renal transplantation. Am J Kidney Dis 41: 684-691.
23. Andrade F, Rodríguez-Soriano J, Prieto JA, Aguirre M, Ariceta G, et al. (2010) Methylation cycle, arginine-creatine pathway and asymmetric dimethylarginine in paediatric renal transplant. Nephrol Dial Transplant 26: 328-336.
24. Annuk M, Soveri I, Zilmer M, Lind L, Hulthe J, et al. (2005) Endothelial function, CRP and oxidative stress in chronic kidney disease. J Nephrol 18: 721-726.
25. Cross JM, Donald A, Vallance PJ, Deanfield JE, Woolfson RG, et al. (2001) Dialysis improves endothelial function in humans. Nephrol Dial transplant 16: 1823-1829.
26. On YK, Kim CH, Oh BH, Lee MM, Park YB, et al. (2002) Effects of angiotensin converting enzyme inhibitor and calcium antagonist on endothelial function in patients with essential hypertension. Hypertens Res 25: 365-371.
27. Taddei S, Virdis A, Ghiadoni L, Magagna A, Favilla S, et al. (2001) A Restoration of nitric oxide availability after calcium antagonist treatment in essential hypertension. Hypertension 37: 943-948.
28. Boots JM, Christiaans MH, van Hooff JP (2004) Effect of immunosuppressive agents on long-term survival of renal transplant recipients: focus on the cardiovascular risk. Drugs 64: 2047-2073.