Int J Biol Med Res. 2014; 5(3): 4340-4345

BioMedSciDirect Publications

Contents lists available at BioMedSciDirect Publications

International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com

Original Article

Carotid Intima-media Thickness And Cardiovascular Risk Factors In Kidney Transplant Recipients At A South African Transplant Center

AS Muhammad, S Naidoo, MB Wambugu, R Britz, P Manga, NM Shehu, S Naicker

Consultant Physician/Nephrologist, Department of Medicine, Yariman Bakura Specialist Hospital, Gusau, Zamfar Nigeria and Division of Nephrology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.
Division of Nephrology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
Division of Nephrology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg.
Division of Vascular Surgery, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
Division of Cardiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
Division of Cardiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg.
Division of Nephrology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
Division of Nephrology, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa.

ARTICLE INFO

Keywords:
Cardiovascular risk factors
Carotid intima-media thickness
Kidney transplant recipients
South Africa.

ABSTRACT

Background: Cardiovascular diseases (CVD) are more common in kidney transplant recipients (KTRs) than in the general population. Carotid intima-media thickness (cIMT) is a marker of atherosclerosis in the general and transplant populations. We determined the prevalence and predictors of cardiovascular risk among KTRs at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and examine the relationship between cardiovascular risk factors and carotid intima media thickness. Methods: Adult recipients of kidney transplant were recruited. Patients records were assessed for information on post transplant follow up. Echocardiography and carotid Doppler were done for all patients. The Framingham Risk Score was used to categorize patients CVD risk. Appropriate inferential and modelling statistics applied as appropriate using SPSS 17, and p value of ≤ 0.05 considered significant.Results: One hundred (KTRs), 63 male (63%), were recruited with mean age of 42.2 ± 12.42 years. Thirty six percent have high cardiovascular risk. The mean ± SD cIMT of the study population was 0.62 ± 0.21 mm with a range of 0.42 to 1.45 mm; 14 patients (14%) had carotid artery plaque. Twenty five percent had cIMT of > 0.7 mm. Carotid intima-media thickness correlated with CVD risk. Multiple regression analysis showed proteinuria (p = 0.022), higher cumulative steroid dose (p = 0.028), elevated serum triglycerides (p = 0.04) and the presence of plaques in the carotid artery (p = 0.012) as predictors of high cardiovascular risk. Conclusion: KTRs in Johannesburg have high cardiovascular risk, and cIMT correlated with this high CVD risk.

1. Introduction

Kidney transplant recipients have up to a 10-fold reduced rate of cardiac death compared with dialysis patients, but still have a much higher risk in comparison with the general population [1-3].

Increased intima-media thickness in the common carotid artery is related to generalized atherosclerosis and increased risk of future MI and cerebrovascular disease [4, 5]. Over the years, clinical trials have provided outcomes that support the role of c-IMT measurements for predicting cardiovascular events [4, 5]. Holland et al found increased cIMT to be correlated with angiographically proven coronary artery disease in South African black population [6].

We determined the prevalence and predictors of cardiovascular risk among KTRs at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and examine the relationship between cardiovascular risk factors and carotid intima media thickness.

* Corresponding Author : **AS Muhammad**
Consultant Physician/Nephrologist, Department of Medicine,
Yariman Bakura Specialist Hospital,
Gusau, Zamfara State, Nigeria and Division of Nephrology,
Faculty of Health Sciences, University of the Witwatersrand,
Johannesburg, South Africa"
aminuskj@yahoo.co

MATERIALS AND METHODS

Enrollment commenced in June 2012 and was completed in October 2012 in this cross sectional study. Using a structured interview form, information on age, gender, race, physical activity, tobacco use, age at diagnosis of renal failure, cause of renal failure, prior cardiovascular event, family history of cardiovascular disease, duration on dialysis before transplant, type of dialysis, and number of transplants was collected. Physical activity was evaluated by asking patients if they engaged in regular exercises such as brisk walking, jogging, swimming or bicycling. Patients were classified into three groups based on their smoking history. They were categorized as smokers if they were current smokers, former smokers if they stopped smoking for at least six months and non smokers if they never smoked. Previous CVD event was defined as history of angina, myocardial infarction [MI], coronary artery bypass graft [CABG], percutaneous coronary intervention [PCI], stroke, peripheral vascular disease, peripheral angioplasty or amputation. The type of immunosuppression, use of BP medications, statins, number of HLA mismatches, biopsy proven rejection were all recorded. Height and weight were measured with the Detecto scale (New York) and body mass index (BMI) was calculated as ratio of weight to height squared. Waist circumference was measured using a tape rule and the point of measurement was the anterior superior iliac spine [7].

Blood pressure

Blood pressure was recorded at the time of clinic visit using an accusson mercury sphygmomanometer in the sitting position. Blood pressure average of four clinic visits was taken as the patient's actual BP (averaged over 12 months). Pulse pressure was calculated as the difference between the SBP and DBP whereas mean arterial pressure (MAP) was the sum of DBP and one third of the pulse pressure [8].

Echocardiography

Echocardiography was done at the cardiology unit of CMJAH using the Philips iE33 machine equipped with a S5-1 1-5 MHz transducer, allowing for M-mode, two dimensional and colour Doppler measurements (Philips Corporation USA).

Carotid intima-media thickness

Carotid artery IMT was measured using high resolution B-mode ultrasonography with a L3-11MHz linear array transducer (Philips Corporation USA). Patients were examined in the supine position with the neck hyper extended and the head turned 45 degrees from the side being examined. Reference point for the measurement of IMT was the beginning of the dilatation of the carotid bulb. Intima media thickness was taken as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line.

Measurements were taken on the longitudinal views of the far walls of the common carotid artery 1cm proximal to the dilatation of the carotid bulb. The linear array transducer generates a measurement of the IMT and displays it on the screen with a percentage success of the procedure, ranging from < 50% success to 100%. For this study a percentage success of >95% was used. The same procedure is done for each side and the mean of right and left common carotid IMT was calculated.

The presence of plaques was defined as localized echogenic structures encroaching into the vessel lumen, for which the distance between the media adventitia interface and the internal side of the lesion was $\geq$1.2 mm [9, 10]. Intima media thickness was measured in the plaque-free areas and measurements were carried out on both sides.

Laboratory tests

Serum creatinine, urea, lipids, complete blood count and urinary protein quantification were done at the National Health Laboratory (NHLS) as part of the routine tests for the follow up of patients at the kidney transplant clinic. All samples for serum chemistry were analyzed using ADVIAR Chemistry Systems (Siemens Healthcare Diagnostics Inc).

serum creatinine

Serum creatinine was measured using the modified Jaffe method. The normal range for males is 62-106 umol/l and for females is 44-80 umol/l at the NHLS laboratory.

serum lipids

Serum cholesterol and triglycerides were determined using enzymatic colometric methods.

The triglyceride concentration was measured based on the Fossati three-step enzymatic reaction with a trinder endpoint. High density lipoprotein (HDL) cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium, while LDL cholesterol was estimated indirectly by the use of Friedewald formula; LDL cholesterol = total cholesterol - (HDL cholesterol + triglycerides/5).

complete blood count

Complete blood count was done using automated haematology analyzer (ADVIA 2120R PHILIPS CORPORATION USA). This formed part of routine tests done at every clinic visit.

Urine protein

For 24 hour urine protein excretion, the ratio of the urinary protein excretion in mg/dl to that of urinary creatinine in mg/dl from a spot urine sample was used. Spot urine protein to creatinine ratio (UPCR) has been validated as a better test than 24 hour urinary protein quantification, it is not affected by urine volume or concentration, whereas the latter is prone to errors of collection and it is inconvenient to the patient and laboratory staff [11].

Statistics

All data obtained was analysed using the statistical package for social science (SPSS) for windows software version 17. Data were reported as mean ± SD. Differences in means for continuous variables were compared using Student's t-test, while categorical variables were compared using Chi-square or Fisher's exact tests as appropriate. The relationship between cIMT and CVD risk factors was tested by the generalized linear regression model. This model was used because the variables are both continuous and categorical. Established risk factors for CVD were analysed. P-value of 0.05 or less was taken as statistically significant and confidence intervals reported at 95% intervals.

RESULTS

Among the one hundred KTRs studied, 63% were males. The mean age of the study population was 42.2 ± 12.42 years, with a range of 19 to 70 years. The mean age of male patients was 43.59 ± 11.32 years and for females was 39.84 ± 13.93years. There were 77 (77%) black, 7 (7%) whites, 11 (11%) mixed race and 5 (5%) were Asian recipients. Ninety five (95%) had primary transplants while 5 (5%) were second transplants. The mean ± SD systolic and diastolic BP of the study populations were 132.65 ± 15.9 and 84.58 ± 12.59 respectively. Eighty seven percent were hypertensive. Ten (10%) KTRs are active smokers, 30 (30%) have quit smoking and 60 (60%) never smoked cigarettes. Smoking was associated with left ventricular hypertrophy; $\chi 2$ = 9.996, p= 0.007, and graft dysfunction $\chi 2$= 8.654, p= 0.013.

The mean serum total cholesterol and HDL cholesterol of the study population were 4.76 ± 1.31 and 1.26 ± 0.46 respectively.

Fifteen (15%) KTRs were diabetic, 8 had diabetes as the cause of their ESRD, with 7 as new onset diabetes after transplantation. Diabetes was associated with proteinuria $\chi 2$ =5.94, p=0.015, but not with graft dysfunction, CNIs or rapamycin use. The mean BMI of the study population was 26.40 ± 4.81 kg/m2, fourteen (14%) of KTRs who were obese had moderate CVD risk, 8 (8%) had high CVD risk while 6 (6%) had very high CVD risk, only 1 (1%) KTR with obesity had low CVD risk. 24 (24%) of our KTRs engage in regular physical exercise. There was no association between physical exercise and high CVD risk or increased cIMT.

There was no gender difference in CVD risk of our KTRs, $\chi 2$ = 7.443, p = 0.059. Graft dysfunction was found in 52% and proteinuria in 51% of our KTRs. Graft dysfunction was associated with LVH ($\chi 2$ = 6.58, p = 0.0181) but no association was found with CVD risk. Proteinuria was associated with high CVD risk $\chi 2$ = 12.67, p= 0.002.

Forty four patients (44%) were on tacrolimus as part of their maintenance immunosuppression protocol, 34 (34%) were on cyclosporine, nineteen (19%) were on rapamycin and 3 (3%) were on leflounamide in addition to steroids. There was statistically significant difference when all the CNIs were compared with the different CVD risk groups. Tacrolimus and high CVD risk $\chi 2$ = 12.63, p = 0.006. Cyclosporine and high CVD risk $\chi 2$ = 9.14, p = 0.027.

All but one patient were on steroids (99%) and the mean ± SD steroid dose for the study population was 11275.94 ± 12288.11 grams. There was no statistically significant difference when cumulative steroid dose was compared with different CVD risk group.

Nineteen patients (19%) were on rapamycin as part of their immunosuppression protocol. Rapamycin was associated with serum total cholesterol (p= 0.029), HDL cholesterol (p= 0.007) and serum triglycerides (p= 0.04) but had no association with LDL cholesterol (p= 0.266). When rapamycin was compared with high CVD risk group, there was no significant difference noted; $\chi 2$ = 2.74, p= 0.433.

Thirty six (36%) of the study patients have high cardiovascular risk. The mean ± SD cIMT of the study population was 0.62 ± 0.21 mm with a range of 0.42 to 1.45 mm; 14 patients (14%) had carotid artery plaque. Twenty five patients (25%) had cIMT of >0.7 mm. Table 1 shows the mean cIMT of the study population.

There was a significant difference in both measurements of the common carotid artery across the different CVD risk groups as depicted in table 1.

On univariate analysis, older age ($\chi 2$ = 6.85, p = 0.009), high systolic blood pressure ($\chi 2$ = 4.88, p = 0.027), LVH ($\chi 2$ = 7.45, p = 0.049), obesity ($\chi 2$ = 11.88, p = 0.001), and high CVD risk ($\chi 2$ = 11.34, p = 0.001) showed significant association with increased carotid intima-media thickness. When these associations were subjected to a regression model analysis, all of the significance was lost. No single factor was found to be an independent predictor of increased cIMT.

Correlation of cIMT with some CV risk variables is shown in table 2.

Risk factors for high cardiovascular risk were proteinuria (p= 0.022), high cumulative steroid dosage (p= 0.028), high serum triglycerides (p= 0.04) and the presence of plaques in the carotid artery (p= 0.012).

Table 1. cIMT of the study population according to risk profile

CVD risk group	Low risk	Moderate risk	High risk	Very high risk	P value
RIMT	0.48±0.09	0.55±0.12	0.67±0.21	0.73±0.26	<0.0001
LIMT	0.52±0.09	0.59±0.11	0.75±0.26	0.81±0.36	<0.0001
CIMT	0.50±0.09	0.58±0.11	0.71±0.23	0.78±0.31	<0.0001

RIMT; right carotid intima-media thickness, LIMT; left carotid intima-media thickness, CIMT; averaged carotid intima-media thickness for right and left; CVD, cardiovascular disease.

Table 2. Correlation of cIMT with CV risk variables

cIMT	Spearman's correlation	P value
Age	0.60	0.001
BMI	0.416	<0.0001
Waist circumference	0.567	<0.0001
SBP	0.309	0.002
DBP	0.201	0.045
Pulse pressure	0.291	0.009
MAP	0.228	0.022
UPCR	0.181	0.071 (NS)
Total cholesterol	0.179	0.075 (NS)
Haemoglobin	-0.058	0.564 (NS)
LVMI	0.511	<0.0001
GFR	-0.152	0.13 (NS)

UPCR: urine protein creatinine ratio, MAP: mean arterial pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, NS: not significant, CVD: cardiovascular disease, LVMI: left ventricular mass index, GFR: glomerular filtration rate, cIMT: carotid intima-media thickness

DISCUSSION

Cardiovascular disease among Africans has been at a low prevalence previously, epidemiological transition and increase in prevalence of risk factors has resulted in increase in atherosclerotic CVD [12, 13]. Majority of our study populations were black South Africans, constituting over 80% of patients recruited into renal replacement therapy program every year. High CVD risk was prevalent in our study population, similar to other studies [4, 14, 15].

Hypertension was highly prevalent in our study; this was also found in other studies in which prevalence ranged from 60 to 95% [16-18]. The high prevalence of hypertension could be explained by the predominantly black racial composition of our patients and the use of CNIs and steroids as part of maintenance immunosuppression [15-18].

Diabetic KTRs, by the FRS have a high CV risk, i.e. both new onset diabetes after transplant [NODAT] and those KTRs who had diabetes mellitus prior to kidney transplant. NODAT was previously reported to occur in 15.6% of patients in our unit [19]. The prevalence of NODAT reported in another study was considerably higher [20]. Diabetes was associated with proteinuria in our KTRs, but not with graft dysfunction as reported by Miles et al [20]. The use of steroids and CNIs as part of maintenance immunosuppression was not associated with NODAT in this study, in contrast to report of several other studies [19-21]. This disparity could be explained by small sample size in this study.

Cigarette smoking after kidney transplant has been associated with adverse CV outcome and graft dysfunction [7]. The prevalence of smoking was high when both active and former smokers [40%] were considered; and this was comparable to that reported in other studies [7, 22]. It was also found to be a risk factor for LVH and was associated with graft dysfunction in our study.

Lack of physical exercise is both a CV risk factor and also a risk factor for graft dysfunction with proteinuria [23]. It is inversely associated with the metabolic syndrome, a history of cardiovascular disease, fasting insulin, and triglyceride concentration, and positively associated with kidney function and 24-hour urinary creatinine excretion [23]. Twenty four percent of our KTRs were involved in regular physical exercise, with the remainder being either sedentary or involved in only mild exercise. As reported by Darien et al [23], lack of physical exercise was found to be associated with LVH. Our study did not show any association with graft dysfunction and proteinuria, probably due to the relatively small sample size.

The risk of CVD in males seen in the general population was also seen in KTRs [4, 24]. In this study however, there was no difference observed in the CVD risk profile of KTRs based on their gender. A male preponderance of high CVD risk may have been observed with a larger sample size.

An increase in cardiac death, non-cardiovascular death, all cause mortality and major adverse cardiac events were reported in KTRs with decreased graft function [25, 26]. Graft dysfunction was highly prevalent (52%) in our KTRs and similar to other reports, graft dysfunction was associated with rejection episodes and LVH [26]. Graft function was not different amongst the different CVD risk groups in this study; this finding is in contrast with reports from other studies, where it was found to be associated with higher CVD risk [19, 20].

The prevalence of proteinuria in our study was high (51%) and it was associated with high CVD risk and graft dysfunction. Similar observations were made in other studies [27, 28].

Calcineurin inhibitor based immunosuppression protocol was widely used in our study population with 44% on tacrolimus and 34% on cyclosporine. Both cyclosporine and tacrolimus were associated with high CVD risk in this study. Several studies reported higher hypertension and dyslipidaemia rates with cyclosporine than tacrolimus [29-31].

In this study, 99% of our KTRs were on steroids. We found a strong association between cumulative steroid dose and increased waist circumference, but there was no difference in cumulative steroid dose across the CVD risk strata. Our patients who had rapamycin as part of their immunosuppression protocol had a significantly higher total serum cholesterol and triglycerides and lower HDL cholesterol. Comparison of different CVD risk groups in terms of rapamycin showed no difference.

Our KTRs with higher CVD risk had a thicker mean cIMT; and this observation was similar to that reported in other studies [4-6]. Holland et al found increased cIMT to be correlated with angiographically proven coronary artery disease in a South African black population [6]. This increase in cIMT of our KTRs was seen across the different CVD risk groups.

Increased cIMT has been shown to be associated with most of the risk factors for atherosclerosis [4, 5]. In our study population, increased cIMT correlated with age, BMI and waist circumference, blood pressure, LVMI and presence of plaque in the carotid artery. The correlation of different CVD risk factors to increased cIMT was significant only on univariate analysis. When subjected to multiple regression analysis, no single risk factor was found to predict increased cIMT, suggesting a role for multiple factors. In this study, the presence of plaques in the carotid artery mirrored thickened cIMT; this observation was also made by Barbagallo et al [4].

Limitations of this study included a small sample size and its cross sectional nature. While high cardiovascular risk is traditionally more common in the white and Asian races, the relatively small number of whites (7%) and Asians (5%) against blacks (77%) in this study made such comparison inappropriate.

Conclusions

The findings from this study demonstrate that kidney transplant recipients have several factors which carry a risk for CVD and their CVD score is high.

Carotid intima-media thickness correlated with high CVD score and no single factor was found to be an independent predictor of increased carotid IMT. Predictors of higher cardiovascular risk were proteinuria, high cumulative steroid dosage, serum triglycerides and the presence of plaques.

Acknowledgement

We acknowledge the support of the staff of the transplant ward of the Charlotte Maxeke Johannesburg Academic Hospital. No funding was secured for this work.

REFERENCES

1. 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: 1662.
2. Jardine AG, Gaston RS, Fellstrom BC, Holdaas H. Prevention of cardiovascular disease in adult recipients of kidney transplants. Lancet 2011; 378:1419
3. Satayathum S, Pisoni RL, McCullough KP, Merion RM, Wikstrom B, Levin N et al. Kidney transplantation and wait-listing rates from the international dialysis outcomes and practice patterns study (DOPPS). Kidney Int. 2005; 68:330-337.
4. Barbagallo CM, Pinto A, Gallo S, Parrinello G, Caputo F, Sparacino V, et al. Carotid atherosclerosis in renal transplant recipients: relationships with cardiovascular risk factors and plasma lipoproteins. Transplantation 1999; 67: 366–371
5. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007, 115:459–467.
6. Holland Z, Lucas N, Geoffrey G, Raal F. Carotid intima-media thickness is a predictor of coronary artery disease in South African black patients. Cardiovascular Journal of Africa 2009; 20(4): 237-239.
7. Kasiske BL, Klinger D. Cigarette smoking in renal transplant recipients. J Am Soc Nephrol 2000; 11(4):753-9.
8. Opelz G, Zeier M, Laux G, Morath C, Dohler B. No improvement of patient or graft survival in transplant recipients treated with angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers: A collaborative transplant study report. J Am Soc Nephrol 2006; 17: 3257–3262
9. Wikstrand J: Methodological considerations of ultrasound measurement of carotid artery intima-media thickness and lumen diameter. Clin Physiol Funct Imaging 2007, 27:341–345.
10. Paoletti E, Amidone M, Cassottana P, Gherzi M, Marsano L, Cannella G. Effect of sirolimus on left ventricular hypertrophy in kidney transplant recipients: a 1-year non- randomized controlled trial. Am J Kidney Dis 2008; 52:324.
11. EBPG Expert Group on Renal Transplantation: European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV. 5.1. Cardiovascular risks. Cardiovascular disease after renal transplantation. Nephrol Dial Transplant; 17 [Suppl 4]: 24–25, 2002
12. Luyckx VA, Yip A, Sofianou L, Jhangri GS, Mueller TF, Naicker S. Cardiac function in an African dialysis population with a low prevalence of pre-existing cardiovascular disease. Ren Fail. 2009; 31(3):211-20.
13. Stewart S, Carrington MJ, Pretorius S, Ogah OS, Blauwet L, Antras-Ferry J, et al Elevated risk factors but low burden of heart disease in urban African primary care patients: a fundamental role for primary prevention. Int J Cardiol. 2012 Jul 12;158(2):205-10ss
14. Massy ZA. Hyperlipidaemia and cardiovascular disease after organ transplantation. Transplantation 2001; 72: S13–S15
15. Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. Transplantation 2003; 75:1291.
16. Kasiske BL, Chakkera HA, Roel J. Explained and unexplained ischemic heart disease risk after renal transplantation. J Am Soc Nephrol 2000; 11(9):1735-43
17. Marce´n R, Morales JM, Fernandez-Juarez G. Risk factors of ischemic heart disease after renal transplantation. Transplant Proc 2002; 34: 394–395

18. Matthias N, Russell GW and Nader R. Methods for measurement of LDL-cholesterol: a critical assessment of direct measurement by homogeneous assays versus calculation. Clinical chemistry 2002; 48 (2): 236-254.

19. Harrichund P, Naicker S, Frederick JR. New-onset diabetes mellitus after renal transplantation. JEMDSA 2008; 13: (3): 98-104

20. Miles AM, Sumrani N, Horowitz R, Homel P, Maursky V, Markell MS, et al. Diabetes mellitus after renal transplantation: as deleterious as non-transplant-associated diabetes? Transplantation 1998; 65: 380.

21. Lentine KL, Brennan DC, Schnitzler MA. Incidence and predictors of myocardial infarction after kidney transplantation. J Am Soc Nephrol 2005; 16: 496.

22. Cosio FG, Falkenhain ME, Pesavento TE, Yim S, Alamir A, Henry ML, et al. Patient survival after renal transplantation II. The impact of smoking. Clin Transplant 1999; 13: 336.

23. Dorien MZ, Eva C, Ronald P, de Greef MH, Gans RO, van der Heide JJ, et al. Low physical activity and risk of cardiovascular and all-cause mortality in renal transplant recipients. Clin J Am Soc Nephrol 2011; 6: 898-905

24. Lentine KL, Rocca Rey LA, Kolli S, Giuliana B, Mark AS, Kevin CA, et al. Variations in the risk for cerebrovascular events after kidney transplant compared with experience on the waiting list and after graft failure. Clin J Am Soc Nephrol 2008; 3: 1090.

25. Ojo AO: Cardiovascular complications after renal transplantation and their prevention. Transplantation 2006; 82: 603– 611,

26. Fellstrom B, Jardine AG, Soveri I, Cole E, Neumayer HH, Maes B, et al. Renal dysfunction is a strong and independent risk factor for mortality and cardiovascular complications in renal transplantation. Am J Transplant 2005; 5(8):1986-91.

27. Suhail SM, Kee TSY, Woo KT, Tan HK, Yang WS, Chan CM, et al. Impact of patterns of proteinuria on renal allograft function and survival: a prospective cohort study. Clin Transplant 2011: 25: 297-303

28. Lentine KL, Rocca-Rey LA, Bacchi G, Wasi N, Schmitz L, Salvalaggio PR, et al. Obesity and cardiac risk after kidney transplantation: experience at one center and comprehensive literature review. Transplantation 2008; 86:303

29. Solez K, Vincenti F, Filo RS. Histopathologic findings from 2-year protocol biopsies from a U.S. multicenter kidney transplant trial comparing tarolimus versus cyclosporine: a report of the FK506 Kidney Transplant Study Group. Transplantation 1998; 66: 1736.

30. Artz MA, Boots JM, Ligtenberg G, Roodnat JI, Christiaans MH, Vos PF, et al. Improved cardiovascular risk profile and renal function in renal transplant patients after randomized conversion from cyclosporine to tacrolimus. J Am Soc Nephrol 2003; 14: 1880.

31. Vincenti F, Jensik SC, Filo RS, Miller J, Pirsch J. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. Transplantation 2002; 73:775.