PREDICTORS OF POSITIVE THALLIUM 201 SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY IN PATIENTS OF END STAGE RENAL DISEASE

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Objectives: To study coronary artery disease (CAD) risk factors predicting positive thallium-201 single photon emission computed tomography (SPECT) indicating underlying CAD among patients of end stage renal disease. **Place and Design:** This cross-sectional (analytical) study was done at Department of Cardiology, Punjab Institute of Cardiology, from April 2004 to Dec 2007. **Methods:** One hundred consecutive patients with ESRD undergoing thallium SPECT as a routine screening test before renal transplant were studied. Dipyridamole thallium SPECT was performed in patients who were unable to exercise. **Results:** Thallium SPECT was positive in 47 (47%) cases. There were significant differences in age, underlying diabetic nephropathy and total cholesterol levels among patients positive and negative on thallium SPECT. Among the risk factors age and underlying diabetic nephropathy were significantly associated ($p<0.05$) with a positive thallium SPECT in patients with ESRD. **Conclusion:** Positive thallium SPECT indicating underlying CAD was observed in a significant number of patients with ESRD awaiting renal transplant. Presence of advanced age and underlying diabetic nephropathy predict a positive thallium SPECT in this population.

Keyword: Coronary artery disease (CAD), Single photon emission computed tomography, (SPECT); End-stage renal disease(ESRD), Renal transplant.

INTRODUCTION

Cardiovascular disease remains the most common cause of mortality in chronic dialysis patients. Dialysis patients have a rate of coronary artery disease (CAD) far in excess of that of the nonuremic population.[1] Using the index of coexisting diseases for the atherosclerotic cardiovascular diseases, which defines CAD as a previous diagnosis of CAD, ischemia on electrocardiogram, or stable or exertional angina during hemodialysis patients have evidence of CAD.[2]

There is a large, but yet unknown, number of totally asymptomatic individuals, especially those with diabetes, who have severe coronary atherosclerosis but exhibit S-T segment changes during activity.[3] Conversely, several conditions in patients with chronic renal failure can mimic the symptoms of angina. These suggest that a more standardized method is necessary to evaluate the prevalence of CAD among patients with End-Stage Renal Disease undergoing Renal Transplant.

Thallium scintigraphy has been used extensively in routine clinical practice. In the detection of CAD, dipyridamole thallium scans have demonstrated sensitivities and specificities of 80–90%,[4] with one report showing a sensitivity of 97% and a specificity of 100%.[5] Dipyridamole thallium data in the renal failure population are disparate, probably due to differences in the study design, patients selection, definitions of end points, and interpretation of 'positive' thallium scans.[6] One report[7] showed the sensitivity and specificity of combined dipyridamole-exercise thallium to detect CAD in hemodialysis patients were 92 and 89%, respectively.

We performed this study to evaluate coronary artery disease (CAD) risk factors predicting positive thallium-201 single photon emission computed tomography (SPECT) indicating underlying CAD among patients of end stage renal disease.

PATIENTS AND METHODS

This cross sectional (analytical) study was conducted at the Nuclear Medicine Department of Punjab Institute of Cardiology, Lahore from April 2004 to Dec 2007. 'Purposive sampling technique' was used to collect data. All diagnosed patients of ESRD undergoing thallium SPECT as a routine screening test before renal transplant were included in the study. Patients of age <18 yr, post renal transplant status, and for whom information was not available on the outcome variables of interest were excluded from the study.

Informed consent was taken from each patient. After an overnight fast, dipyridamole (0.14 mg/kg/min) was infused over 4 min, with monitoring of symptoms by electrocardiography, heart rate, and blood pressure. This was completed with sub maximal exercise on ergometer up to 75 Watts. Pure Dipyridamole thallium SPECT was performed in patients who were unable to exercise and also those with left bundle branch block (LBBB).[8] Three minutes after infusion, 2 mCi of thallium was injected and stress images were obtained. Four hours later, redistribution images were obtained, while the patients were at rest. Both reversible and irreversible images were considered to be positive test. Reversible perfusion defects (RPD) were defined as a myocardial uptake defect after stress lesser or not evident at rest

(ischemia) while fixed perfusion defects (FPD) were the absence of radioisotope uptake at rest and stress (fibrosis/necrosis). Coronary angiography was performed in patients with a significantly positive thallium SPECT. Significant stenosis was defined as narrowing of the diameter by more than 50%.

Eight baseline covariates were selected as possible predictors of a positive thallium SPECT: age, gender, smoking, obesity ,the presence of hypertension, diabetic nephropathy, family history of CAD, and dyslipidemia. Smoking was defined as smoking cigarettes at the time of entry into the study or having a previous history of smoking. The number of cigarettes smoked was not quantified. Presence of hypertension was defined as use of antihypertensive agent(s) or a systolic blood pressure >140 mmHg. Obesity was said to be present if body mass index was more than 25.

Statistical analysis was performed using the SPSS (release 12.0; SPSS, Inc; Chicago, IL) system for Windows®. Continuous variables were expressed as Mean±SD (Standard Deviation) while categorical variables as numbers and percentages. Age, gender, smoking, obesity, hypertension, diabetes, family history of CAD, and dyslipidemia were compared between positive and negative thallium study groups. Data was analyzed both by Bivariate and Multivariate analysis approach. For Bivariate analysis Chi-Square test was used to find out the significant risk factors. While Multivariate analysis by Binary Logistic regression model (Forward Likelihood ratio) was applied to determine the predictive value of these risk factors. Associations were taken as significant if the p-value was less than 0.05.

RESULTS

After fulfilling the inclusion criteria 100 patients were studied. There were 65% males and 35% females, with a mean age of 49.99±9.6 (range 22–71) years. The underlying renal disease was diabetic nephropathy in 55 patients (55%). Table-1. A history of angina pectoris was recorded for 12% of the patients. ECG at rest revealed LBBB in two patients(2%), right bundle branch block (RBBB) in one patient (1%), left ventricular hypertrophy (LVH) in 12 patient (12%) and ST-T ischemic changes in 4 patients (4%). Echocardiography revealed left ventricular dilatation in 51(51%) patients. Seventy eight (78%) were having normal ejection.

Forty-seven patients (47%) showed a positive thallium SPECT. Of these, 40% patients were having reversible perfusion defects (RPD) and 7% patients with fixed perfusion defects (FPD) as shown in Figure-1.

The conventional risk factors for coronary artery disease (CAD) positive and negative on thallium SPECT are shown in Table-2. Comparison

of conventional risk factors for coronary artery disease by applying Bivariate analysis using Chi-Square test revealed diabetes and age as significant risk factors.

Table-1: Basic demographics of the study population

VARIABLES	NUMBERS (%) n=100
GENDER	
Male	65 (65%)
Female	35 (35%)
AGE mean years	49.99±9.6
DIABETES	55 (55%)
Hypertension	78 (78%)
Smoking	13 (13%)
Dyslipidemia	11 (11%)
Family History	17 (17%)
Obesity	8 (8%)

Table-2: Comparison of conventional risk factors for coronary artery disease by applying Bivariate analysis using Chi-Square test.

	THALLIUM SCAN		
VARIABLES	**POSITIVE n=47**	**NEGATIVE n=53**	***p*-value**
GENDER			
Male	35 (74.5%)	30 (56.6%)	0.125
Female	12 (25.5%)	23 (43.3%)	
AGE mean years	54.40±7.87	46.08±9.5	0.048*
Diabetes	32 (68.1%)	23 (43.3%)	0.016*
Hypertension	39 (83%)	39 (73.6%)	0.335
Smoking	7 (14.9%)	6 (11.3%)	0.767
Dyslipidemia	8 (17%)	3 (5.7%)	0.108
Family History	11 (23.4%)	6 (11.3%)	0.120
Obesity	4 (8.5%)	4 (7.5%)	1.00

*$p<0.05$ significant
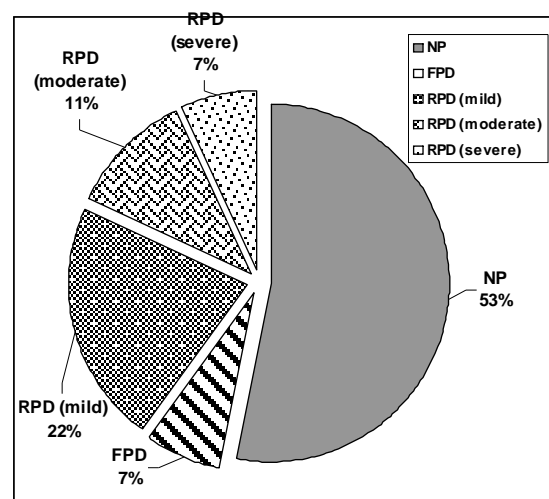
NPD=Normal perfusion, RPD=Reversible perfusion defect, FPD=Fixed perfusion defect.

Figure-1: Frequency of myocardial perfusion defects among end stage renal disease patients.

Multivariate analysis by binary logistic regression model (Forward Likelihood Ratio) identified age (40–60) years and underlying diabetes as independent predictors of a positive thallium

SPECT among all the conventional risk factors for CAD as shown in Table-3.

Table-3: Multivariate analysis by Binary Logistic regression model to determine the predictive value of conventional risk factors for positive thallium SPECT

Variables	Likelihood Ratio	*p*-Value
Age (40–60) yrs	5.612	0.022
Diabetes	3.587	0.006
Hypertension	1.068	NS
Smoking	1.015	NS
Dyslipidemia	2.635	NS
Family History	2.401	NS
Obesity	0.715	NS

Twenty patients underwent coronary angiography out of 47 patients with positive thallium SPECT. Remaining patients were lost to the follow up. Of these, 12 patients had one-vessel disease and 4 patients each had two-vessel and three vessel disease.

DISCUSSION

This study evaluates the prevalence of CAD in dialysis patients using thallium scan. We found that prevalence of CAD in our study population was 47% which is much higher than 22.5% as reported by Kim *et al* in Korean population.[9] Stack *et al*[10] reported prevalence of CAD of 38% among new dialysis patients in the United States. Similarly Bialostozky *et al*[11] found prevalence of CAD in Mexican population to be 42.7%. Since 35 of 47 patients (74%) with positive thallium SPECT had no history of CAD or anginal pain, evaluation of prevalence based only on medical history would have lowered the prevalence of CAD.

We found that age (40–60) years and underlying diabetic nephropathy were statistically significant ($p<0.05$) in patients with positive thallium SPECT. Age is an important, although non-modifiable, predictors of CAD in the general population.[12,13] Data from several renal registries have demonstrated the association of age with CAD in the univariate analysis.[14,15] Our study corroborates the observations of the other investigators with respect to the role of diabetes mellitus as a strong CAD correlate.[16,17]

Hypertension is a major risk factor for the development for the development of CAD in the general population.[18] In this study, hypertension was associated with statistically insignificant likelihood of CAD. One possible explanation for the negative association is that patients with CAD, compared with those without CAD, are more likely to have lower blood pressure resulting from coexisting heart failure. Kim *et al*[9] also reported negative association of CAD with hypertension in ESRD patients.

Although smoking is a major modifiable risk factor for the development of CAD in the general population, its role in the pathogenesis of CAD among patients initiating renal replacement therapy has been less studied. In a prospective cohort study by Parfrey *et al*[17], smoking was associated neither with the presence of CAD in baseline examinations nor with the development of new CAD during the follow up. Similarly Kim *et al*[9] and Stack *et al*[10] did not find any significant association between smoking and CAD in ESRD patients. All above findings are in accordance with our results of statistically insignificant association of smoking with CAD.

We did not find an association between dyslipidemia and CAD among patients with ESRD. Rostand *et al*[19] observed higher levels of total cholesterol, triglyceride, and HDL cholesterol and higher total cholesterol/HDL cholesterol ratio for chronic dialysis patients with significant CAD, compared with those without CAD. Similarly longitudinal studies have identified increased total serum cholesterol, LDL cholesterol and apolipoprotein B levels as predictors of atherosclerotic events among pre-ESRD and ESRD patients.[20,21] The lack of association between isolated measurements of serum lipids and CAD in our study does not exclude the possibility that lipids are, at sometime in the course of renal insufficiency, important in CAD development.

CONCLUSION

To conclude, we have shown that 47% of the patients with ESRD awaiting renal transplant had a positive thallium SPECT. Age and underlying diabetic nephropathy were statistically significant risk factors of a positive thallium SPECT.

REFERENCES

1. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32:112–19.
2. Cheung AK, Sarnak MJ, Yan G, Dwyer JT, Heyka RJ, Rocco MV, *et al*. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int 2000;58:353–62.
3. Selwyn AP, Braunwald E. Ischemic heart disease. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL: Harrison's Principles of Internal Medicine. 15th ed. New York, McGraw-Hill 2001. p 1399–414.
4. Sinusas AJ, Zaret BL. Coronary artery disease. In: Wagner HN, Szabo Z, Buchanan JW: Principles of Nuclear Medicine.2nd ed. Philadelphia, Saunders 1995. p 803–4.
5. Wackers FJ, Berman DS, Maddahi J, Watson DD, Beller GA, Strauss HW, *et al*. Technetium-99m hexakis 2-methoxyisobutyl isonitrile:Human biodistribution, dosimetry, safety, and preliminary comparison to thallium-201 for myocardial perfusion imaging. J Nucl Med 1989;30:301–11.
6. de Lemos JA, Hillis LD. Diagnosis and management of coronary artery disease in patients with end-stage renal disease on hemodialysis. J Am Soc Nephrol 1996;7:2044–54.
7. Dahan M, Viron BM, Faraggi M, Himbert DL, Lagallicier BJ, Kolta AM, *et al*. Diagnostic accuracy and prognostic value of combined dipyridamole-exercise thallium imaging in hemodialysis patients. Kidney Int 1998;54:255–62.

8. Afzal MS, Imran MB, Aslam N, Khurshid SJ, Khan MA, Irfan J, *et al*. Gated SPECT myocardial perfusion Scintigraphy for identifying septal perfusion artifacts in left bundle branch block. J Coll Physicians Surg Pak 2006;16(8):504–8.

9. Kim SB, Lee SK, Park JS, Moon DH. Prevalence of coronary artery disease using Thallium-201 single photon emission computed tomography among patients newly undergoing chronic peritoneal dialysis and its association with mortality. Am J Nephrol 2004;24:448–52.

10. Stack AG, Bloembergen WE. Prevalence and clinical correlates of coronary artery disease among new dialysis patients in the United States: A Cross-sectional study. Am Soc Nephrol 2001;12:1516–23.

11. Bialostozky D, Leyva M, Villarreal T, Casanova JM, Grovas HP, Lemus P *et al*. Myocardial perfusion and ventricular function assessed by SPECT and Gated-SPECT in End-Stage Renal Disease patients before and after renal transplant. Archives of Medical Research 2007;38:227–33.

12. Kannel WB, Dawber TR, Kagan A. Factors of risk in the development of coronary artery disease: Six-year follow-up experience: The Framingham Study. Ann Intern Med 1960;55:33–50.

13. Stampfer MJ, Malinow MR, Willett WC, Newcomer LM, Upson B, Ullmann D, *et al*. A prospective study of plasma homocysteine and the risk of myocardial infarction in US physicians. JAMA 1992;268:877–81.

14. United States Renal Data System. Patient mortality and survival in ESRD. Am J Kidney Dis 1999;34:74–86.

15. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32:112–9.

16. Rostand SG, Kirk KA, Rutsky EA. Relationship of coronary risk factors to hemodialysis-associated ischemic heart disease. Kidney Int 1982;22:304–8.

17. Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray D, Barre P. Outcome and risk factors of ischemic heart disease in chronic uremia. Kidney Int 1996;49:1428–34.

18. Kannel WB. Role of BP in cardiovascular disease: The Framingham Study. Angiology 1975;26:1–14.

19. Rostand SG, Kirk KA, Rutsky EA. The epidemiology of coronary artery disease in patients on maintenance hemodialysis: Implications for management. Contrib Nephrol 1986;52:34–41.

20. Tschope W, Koch M, Thomas B, Ritz E. Serum lipids predict cardiac death in diabetic patients on maintenance hemodialysis: Results of a prospective study. Nephron 1993;64:354–8.

21. Jungers P, Massy ZA, Khoa TN, Fumeron C, Labrunie M, Lacour B, *et al*. Incidence and risk factors of atherosclerotic cardiovascular disease in pre-dialysis chronic renal failure patients: A prospective study. Nephrol Dial Transplant1997;12:2597–602.

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