Clinical Comparison of Serum Lipids between Cyclosporine and Tacrolimus Treated Renal Transplant Recipients

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ABSTRACT:

Introduction: Dyslipidemia is a common complication of renal transplantation referred to as new onset dyslipidemia. Immune suppressants, in particular cyclosporine, the calcineurin inhibitor and others are known to cause dyslipidemia through non-competitive inhibition of sterol 27-dehydroxylase (CYP27A1). On the other hand, dyslipidemia has been found to be associated with higher graft rejection due to decrease in immune suppressant activity and direct graft destruction. Hence the study was designed to analyze the effect of dyslipidemia on chronic allograft rejection. **Methods:** This retrospective observational study was carried out in the nephrology department of a multispecialty hospital for a period of two months. Clinical and biochemistry reports of 142 renal transplant recipients were collected in designed case report forms. All statistical analysis was carried out using IBM SPSS Statistics 17 and Graph pad Prism 6.0. **Results:** Higher serum lipid levels are observed in patients with cyclosporine therapy than tacrolimus. However statistical significant difference only in levels of total cholesterol, LDL-C, triglycerides was observed between cyclosporine and tacrolimus treated patients ($P<0.001$). **Conclusion:** Dyslipidemic potential of tacrolimus is comparatively lesser than cyclosporine. However, tacrolimus causes dyslipidemia to a lesser when compared to cyclosporine. Thus monoclonal antibodies such as rituximab or basiliximab should be preferred over conventional immune suppressants. However, the cost effectiveness of monoclonal antibody therapy is high. Hence we conclude that tacrolimus with dose intense therapy should be preferred as first line immunosuppressant regimen.

KEYWORDS: Renal transplant, Immunosuppressant, Metabolic Syndrome, Dyslipidemia, Graft Rejection.

INTRODUCTION:

Renal transplantation is the surgical placement and vascular integration of a human kidney from a living or cadaveric donor into a patient who has end stage renal disease (ESRD). It is the only treatment modality that restores reasonable renal function in ESRD patients[1].Though, renal function is restored to some extent, renal transplantation possesses various short term and chronic complications, the most important being cardiovascular and post-transplant metabolic syndrome (PTMS)[2,3].

Cardiovascular complications remain the major cause of morbidity and mortality in renal transplant recipients[4]. These long term complications are not direct effects of grafting but are caused due to the dose intense immunosuppressant and long term steroid therapy. The US National cholesterol education program – Adult treatment panel III defines metabolic syndrome as the presence of dyslipidemia, obesity, glucose intolerance and hypertension. Metabolic syndrome is characterized by presence of several metabolic anomalies associated with increased risk of cardiovascular mortality[5,6]. Dyslipidemia is one of the common PTMS complications and is referred as new onset [illegible]rized by an increase in total cholesterol (TC), low density lipoprotein [illegible]DL-C) and triglycerides (TGL) and/or decrease in high density lipoprot[illegible]ressants, in particular, cyclosporine used in renal transplant recipients to p[illegible]alter serum lipid levels[8]. Being metabolized by the cytochrome P450 pathway, cyclosporine non-competitively inhibits sterol 27-dehydroxylase (CYP27A1) and therefore decreases the production of 27-hydroxycholesterol which in turn is a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), the rate limiting step of cholesterol biosynthesis. In addition to CYP27A1 inhibition, cyclosporine also inhibits lipoprotein lipase and thereby increases serum triglyceride levels[9, 10]. Similar to calcineurin inhibitors, patients treated with mammalian target of rapamycin inhibitors (mTOR) such as sirolimus also display impaired lipid metabolism. However, dyslipidemia associated with sirolimus is not completely due to CYP27A1 inhibition as with cyclosporine[11]. Sirolimus, in addition to CYP27A1 inhibition also decreases LDL-C clearance by inhibiting the transcription of LDL receptor gene in hepatic cells[12]. Various studies have shown dyslipidemia to be associated with graft rejection. However, many studies have not examined the effect of immunosuppressant induced dyslipidemia on graft rejection. Hyperlipidemia can affect chronic allograft function indirectly by its effects on vessels and directly by its specific renal destructive effects. Mechanisms of hyperlipidemia induced nephrotoxicity include the following: glomerulosclerosis and chronic interstitial nephritis caused by oxidant stress put forth by generation of reactive oxygen species[13]and progressive renal damage provoked by monocyte infiltration and mesangialproliferation through

increased production of growth promoting cytokines[14]. Another interesting mechanism behind, dyslipidemia associated graft rejection is decrease in immunosuppressive activity of cyclosporine with increase in serum lipids which ultimately may lead to immune sensitization. Dyslipidemia decreases the availability of intracellular cyclosporine concentration available to inhibit the immune activation process and thereby contributes to chronic allograft loss[15]. Thus dyslipidemia induced by immune suppressants tends to decrease the effect of immunosuppressant by decreasing its availability and leading to graft loss. In this study efforts have been made to comparatively analyze the dyslipidemia between cyclosporine and tacrolimus treated patients.

MATERIALS AND METHODS:

This retrospective observational study was carried out in the nephrology department of a multispecialty hospital for a period of 2 months from January 2015-March 2015. Consent from the hospital authorities and nephrologists were obtained before accessing patient medical records. The study protocol was approved by the institutional ethics committee of Vels University (Approval no: IEC/DOP/2015/04). Clinical and biochemistry reports of 142 renal transplant recipients who visited the hospital in the past one year for any of the following reason was recorded: hemodialysis, routine checkup as instructed by the nephrologist, transplant kidney biopsy and for other comorbidities. Clinical data was recorded from the patient case sheets stored in medical records whereas biochemical parameters were recorded from the laboratory database. A case report form was designed for recording clinical and biochemistry data of renal transplant recipients as per study requirements.

Inclusion Criterion:

The study included chronic kidney disease or ESRD patients of both gender who have undergone unilateral or bilateral renal transplantation.

Exclusion Criterion:

Chronic kidney disease or ESRD patients on renal replacement therapies other than transplantation were excluded from the study. Patient case sheets with incomplete clinical data were not considered for inclusion in the study.

Statistical Analysis:

Comparison between two groups was analyzed by means of student t test to determine the presence or absence of statistically significant difference. Wherever computed, a P value of less than 0.05 was considered significant, since the confidence interval was maintained at 95%.

RESULTS:

The study population for the retrospective analysis included Chronic Kidney Disease patients (CKD) who had undergone unilateral or bilateral renal transplantation, receiving immunosuppressant and are on regular visit to the hospital for either of the following reasons: hemodialysis, routine checkup at regular intervals as instructed by the nephrologist, biopsy of transplanted kidney and for any other co-morbidity. Age wise distribution of patients considered for the study is shown in **Table 1.**

Renal transplant recipients of both genders were included for the study. Gender wise distribution of patients included in the study is shown in **Table 2.**

The incidence of single and combined immunosuppressant usage between genders was found to be almost similar with no statistically significant difference (P value = 0.1671, odds ratio=0.2148) (**Table 3).** The patients received concomitant steroid therapy with prednisolone, methyl prednisolone and hydrocortisone. Distribution of patients on the basis of long term steroid they received is as shown in **Table 4.**

Table 1. Age Wise Distribution of Renal Transplant Recipients

Age (Years)	No. of patients (n=142)	Percentage (%)	Mean	SD	Age Quartiles	Median age
11-20	9	6.34	16.6	2.21	13-20	17
21-30	12	8.45				
31-40	27	19.01				
41-50	28	19.72				
51-60	46	32.39				
61-70	16	11.27				
71-80	4	2.82				

Mean age = 46.01±14.02, Median age=49

Table 2. Gender wise Distribution of Patients

Gender	No. of Patients (n=142)	Percentage (%)	Mean Age	SD	Age Quartile	Median
Male	96	67.61	47.01	14.67	13-75	50.5
Female	46	32.39	43.93	12.28	17-63	44.5

P value = 0.2242

Table 3. Distribution of Patients based on Immunosuppressive Regimen

Immunosuppressive Regimen	No.of Patients			Percentage	Statistical Parameters
	Male	Female	Total		
Mono-Immunosuppressive therapy	87	45	132	92.96	P value = 0.1671
Combined Immunosuppressant therapy	9	1	10	7.04	Odds ratio=0.2148

Table 4. Distribution based on Long Term Steroid Received

S. No	Steroid	Brand	ROA	No. of Patients (n=142)	Percentage (%)
1	Prednisolone	Wysolone, Omnacortil	P/O	114	80.28
2	Methyl Prednisolone	Medrol, Solumedrol	P/O, IV	17	11.9
3	Hydrocortisone	Effcorlin	IV	2	1.4
4	None	N/A*	N/A	9	6.3

* N/A = Not applicable

Table 5. Distribution of Patients Based on the Immunosuppressant

S. No	Immunosuppressant	No.of Patients	Percentage	Median Dose	Daily Dose Quartile
1	Cyclosporine	87	61.27	100mg	25-300mg
2	Tacrolimus	48	33.80	2.5mg	0.5-20mg
3	Sirolimus	8	5.63	1mg	0.5-1.5mg
4	Azathioprine	2	1.41	62.5mg	50-75mg
5	Rituximab	6	4.23	500mg	100-500mg

Table 6. Incidence of Choice of Immunosuppressant between Genders

S. NO	Immunosuppressant	Odds Ratio*	P value	Relative Risk
1	mTOR inhibitor	0.4947	0.0703	0.7760
2	Antimetabolites	0.3254	0.5281	0.9643
3	Monoclonal Antibodies	0.3273	0.4098	0.943

*Odds ratio was calculated between calcineurin inhibitor and other immunosuppressant usage

Out of the 142 patients studied, 109 (76.7%) patients received immunosuppressive antimetabolite therapy with mycophenolate mofetil whereas 33 (23.2%) patients did not. Distribution of patients on the basis of immunosuppressants received and values of incidence rate of immunosuppressant usage between genders are shown in **Table 5** and **6** respectively.

The glomerular filtration rate is an endogenous marker of renal function that requires 24 hours urine collection. However, GFR can theoretically be estimated using the modification of diet in renal disease (MDRD) formula from serum creatinine and age of the patient. Renal transplant recipients in the study have been segregated into different GFR quartiles (**Table 7)**.

Table 7. Distribution of Patients Based on Estimated Glomerular Filtration Rate

GFR (mL/min/1.73m^2)	No. of Patients (n=142)	Percentage (%)	Mean observede GFR (mL/min/1.73m^2)	SD	Median observed GFR (mL/min/1.73m^2)
≤15	44	30.9	10.5	2.8	10.6
15-29	42	29.5	20.7	3.7	20.3
30-59	39	27.4	41.3	7.6	40.9
60-89	11	7.7	70.9	6.4	72.1
≥90	6	4.2	104.2	13.7	100.5

Mean ± SD GFR = 30.6 ± 23.9 mL/min/1.73m^2, Median GFR = 21.59 mL/min/1.73m^2

The dyslipidemic potential of cyclosporine and tacrolimus vary to great extent, though being calcineurin inhibitors. Hence a comparison of the lipid parameters between cyclosporine and tacrolimus receiving patients was made using unpaired student t-test at a confidence interval of 95%.The mean serum lipid level of cyclosporine and tacrolimus treated patients is as shown in **Table 8**.

Table 8. Comparison of Serum Lipids in Cyclosporine and Tacrolimus Groups

Parameters (mg/dl)	Patients on Cyclosporine (n= 87)		Patients on Tacrolimus (n=48)		P Value
	Mean ± SD	Median	Mean ± SD	Median	
Total Cholesterol	204.1 ± 2.486	203	186.2 ± 3.474	184	<0.0001*
LDL	136.9 ± 2.284	137	119.6 ± 3.025	117	< 0.0001*
VLDL	31.97 ± 1.554	32	34.90 ± 1.647	37	0.2264
HDL	34.74 ± 1.692	39	31.71 ± 1.882	30	0.2583
Triglycerides	244.0 ± 9.244	249	194.6 ± 11.22	178	0.0012*

*Statistically significant difference at 95% confidence interval

DISCUSSION:

The study population included renal transplant recipients in the age range of 13-75 years with a mean age of 46.01±14.02 and a median age of 49 years. The studied population was ith unequal distributions. The percentage of patients in the age interval clas f 54.8±2.55 and median age of 54 while number of patients between 71 ean age of 74.5±0.86 and median age of 75 years.

Renal transplant recipients of both genders were included of which 67.6% patients were male and 32.3% patients were female. The median age was significantly higher in males (50.5 years) with a mean age of 47.01±14.6 while 44.5 years was the median age in female patients with a mean age of 43.9±12.2 with no significant difference in age distribution between genders of renal transplant recipients(P value = 0.2242). 97.2% had renal transplantation done due to progressive CKD or end stage renal disease (ESRD) while 2.09% had undergone renal transplantation for renal cell carcinoma and congenital single and dysplastic kidneys. 93.6% patients received concomitant long term steroid therapy including prednisolone or methyl prednisolone or hydrocortisone whereas 6.3% patients were not on steroid therapy. Out of the 93.6% patients who received steroids, 12.7% patients received methyl prednisolone, 85.7% patients received prednisolone whereas 1.5% patients received hydrocortisone. However, no statistically significant difference was observed in development of post-transplant metabolic syndromes and dyslipidemia between the two groups but steroids are known to provoke metabolic syndromes (P value >0.05)[16].The dyslipidemic potential of cyclosporine and tacrolimus vary to great extent. Various studies have comparatively assessed the extent of dyslipidemia associated with cyclosporine and tacrolimus and have shown cyclosporine to predominantly cause dyslipidemia than tacrolimus[17,18]. Cyclosporine induced dyslipidemia is due to a direct non-competetive inhibition of sterol 27-dehydroxylase (CYP27A1) and decrease in production of 27-hydroxycholesterol which

in turn is a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), the rate limiting step of cholesterol biosynthesis. In addition to CYP27A1 inhibition, cyclosporine also inhibits lipoprotein lipase and thereby increases serum triglyceride levels[9]. Similar to calcineurin inhibitors, patients treated with mammalian target of rapamycin inhibitors (mTOR) such as sirolimus also display impaired lipid metabolism. However, dyslipidemia associated with sirolimus is not completely due to CYP27A1 inhibition as with cyclosporine[11]. Sirolimus, in addition to CYP27A1 inhibition also decreases LDL-C clearance by inhibiting the transcription of LDL receptor gene in hepatic cells[12].

The mean TC and LDL levels are significantly higher in the cyclosporine group (p value <0.0001) whereas HDL was high in the cyclosporine group. However, low HDL levels are reported in Cyclosporine treated patients. Decrease in HDL levels predisposes the patient to atherogenic risk[19]. Elevated HDL levels in our study could be attributed to concomitant steroid usage. No significant difference was found between HDL and VLDL of the two groups (p value >0.05). Triglycerides was found to be significantly high in the cyclosporine treated group (p value =0.0012).

CONCLUSION:

Dyslipidemia was found in patients receiving both cyclosporine and tacrolimus. However, tacrolimus causes dyslipidemia to a lesser when compared to cyclosporine. Thus monoclonal antibodies such as rituximab or basiliximab should be preferred over conventional immune suppressants. However, the cost effectiveness of monoclonal antibody therapy is high. Hence we conclude that tacrolimus with dose intense therapy should be preferred as first line immunosuppressant regimen.

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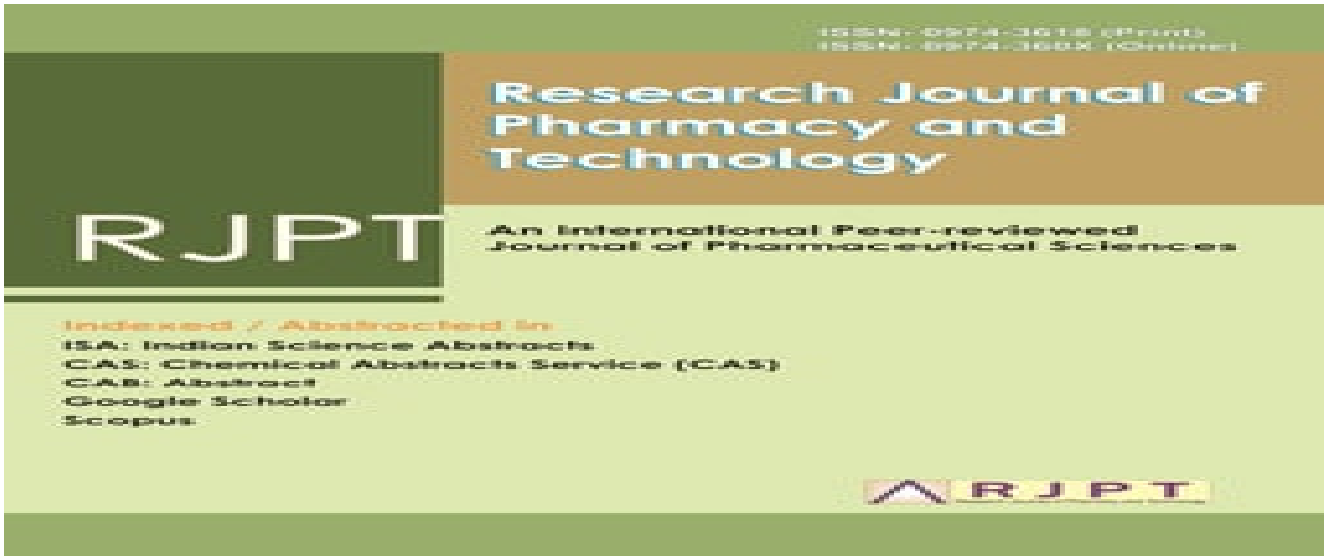

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