



RENAL TRANSPLANT RECIPIENTS; PATTERN OF LIPID ABNORMALITIES AND THEIR RELATIONSHIP TO HBA1C

Dr. Ruhina Akbar¹, Dr. Naeem Kauser², Dr. Naveed Hussain³

1. Associate Professor Pathology, Services Institute of Medical Science, Lahore
2. Professor Pathology, Ammna Anyat Medical College, Lahore
3. Lecturer (Biochemist), Department of Biochemistry, Faculty of Biotechnology & Agro-Sciences, University of South Asia, Lahore Cantt,

Correspondence Address:

Dr. Ruhina Akbar
Associate Professor Pathology,
Services Institute of Medical Science,
Lahore
ruhina_akbar@yahoo.com

Article received on:

27/01/2015

Accepted for publication:

16/03/2015

Received after proof reading:

06/05/2015

ABSTRACT... Introduction: Good glycemic control and lipid modification are potentially important intervention for improving outcome after kidney transplantation. **Objective:** To determine the frequency of dyslipidemia and its types in renal transplant recipients (RTRs), and to observe impact of hyperglycemia on their lipid profile. **Design:** Case control study. **Period:** June 2011 to May 2012. **Setting:** Kidney Dialysis Department of Jinnah Hospital Lahore, Urology Department of Mayo Hospital Lahore and Pathology Department Allama Iqbal Medical College Lahore. **Patients and Methods:** A total of 40 RTR were included in the study. An equal number of sex and age matched healthy subjects were considered as control group. The patients were on regular post transplant follow up in Kidney Dialysis Department of Jinnah Hospital Lahore and Urology Department of Mayo Hospital Lahore and had no clinical or laboratory evidence of graft rejection, post-transplant diabetes mellitus, hypertension or inter current infection. Total cholesterol (TC), triglyceride (TG), High density Lipoprotein-Cholesterol (HDL-C), and Glycohemoglobin A1c (HbA1c) were estimated in all subjects. These subjects were divided into Diabetic and non-diabetic groups, according to level of HbA1c. **Results:** The mean age of the RTR was 34.5 ± 9.02 years and the mean duration of transplant was 36.70 ± 38.07 months. RTRs showed significantly high mean levels of TG ($p < 0.002$), TC ($p < 0.00$), LDL-C ($p < 0.01$), and HDL-C ($p < 0.05$) as compared to the control subjects. Elevated TC, TG, LDL-C and low HDL was observed in 32.5%, 72.5%, 52.5%, and 60% of total RTR, respectively. The mean levels of TC, TG and HDL-C were increased in Diabetic transplant group as compared to non-diabetic RTR. Percentage of elevated TC, TG, LDL-C and decreased HDL in diabetic group of RTR versus non diabetic RTR was 43.7% Vs 25% , 81.2% Vs 66.6%, , 62.5% Vs 44.4%, and 50% Vs 66.6% respectively. There was a positive relationship between HbA1c and lipid profile (TC, TG, and LDL – C) in both Diabetic and Non Diabetic Group. A statistically significant correlation of the mean HbA1c levels with TG level was observed in Diabetic RTR. **Conclusion:** Dyslipidemia in our RTRs was observed as elevated levels of TC, TG and LDL-C. In diabetic RTR, a statistically significant positive correlation of the HbA1c levels with TG level was observed. More rigorous glycemic control and lipid modification will reduce the development of microvascular complications.

Key words: Transplantation, kidney, diabetes, dyslipidemia

Article Citation: Akbar R, Kauser N, Hussain N. Renal transplant recipients; pattern of lipid abnormalities and their relationship to hba1c. Professional Med J 2015;22(5):590-595.

INTRODUCTION

Renal transplant recipients (RTR) are at an increased risk for cardiovascular (CV) diseases and peripheral vascular diseases due to lipid abnormalities. The prevalence of post transplantation hyperlipidaemia ranges from 16–78%. Elevation of levels of both Total Cholesterol (TC), and Triglyceride (TG) are reported.¹ Observational studies in patients have demonstrated correlations between plasma lipid levels and both acute and chronic rejection.^{2,3} Decrease in the incidence of chronic rejection

of allograft may be achieved by reduction in hyperlipidaemia, and this treatment will lower the morbidity and mortality due to atherosclerotic disease.⁴

New Onset Diabetes After Transplant (NODAT) is documented as a common and severe complication of kidney transplantation.⁵ Lipid abnormalities in NODAT are described as increased serum TC, TG, VLDL– C, LDL– C and lowering of HDL– C levels.⁶ High incidence of atherosclerotic events in the renal transplantation

population, makes dyslipidemia a coronary heart disease equivalent risk. Good glycemic control and lipid modification are potentially important intervention for improving outcome after kidney transplantation.⁷ In RTR, no clear pattern of dyslipidemia is observed in different studies and it is difficult to assume whether dyslipidemia will worsen or improve over time, after kidney transplantation.⁸ This prospective study was designed to examine the pattern of serum lipids in Post Renal Transplant Patients and to observe the relationship between HbA1c and Lipid Profile.

MATERIAL AND METHOD

For this prospective study, 40 renal transplant recipients (RTR) of either sex and of age ranging from 20-60 years were selected from Jinnah Hospital and Mayo Hospital Lahore. The patients were on regular post transplant follow up and had no evidence of graft rejection, post-transplant diabetes mellitus, hypertension or intercurrent infection for at least 3 months prior to the study. Patients on antilipemic therapy were also excluded. An equal number of healthy subjects randomly selected and studied for their lipid profile, served as control for the study group. All experimental work was done at Chemical Pathology Laboratory, Allama Iqbal Medical College, Lahore.

About 5ml of fasting blood was taken from each post renal transplant patient, after 12-14 hour overnight fast. Two ml of blood was transferred into a tube (BIO-VAC, EDTA.K3) for the estimation of HbA1c. The HbA1c test was done by Fast Ion-Exchange Resin Separation Method. The serum was separated from the remaining 3ml of fasting

blood and was used for the estimation of different lipid fractions including, serum TC, TG, HDL-C and the Friedewald Equation was used to calculate low-density lipoprotein (LDL) from TC, HDL-C and TG.⁹ Hypercholesterolemia, hypertriglyceridemia and high LDL were considered if serum TC, TG and LDL- C concentrations were >6.2 mmol/l, >1.7mmol/l and >3.38mmol/l respectively. HDL- C levels less than <1.03mmol/l were considered as low HDL.¹⁰

All results were expressed, as mean \pm SD and percentages. The significance was tested by Students't test and P values \leq 0.05 were considered as statistically significant. The correlation of HbA1c and different lipid fractions was performed by Pearson's correlation test.

RESULTS

The mean age of RTR was 34.5 ± 9.02 years. The mean duration of transplant was 36.70 ± 38.07 months. Number of female subjects was small (20%), therefore mean and SDs of different parameters are given together for both sexes. RTR showed significantly high mean levels of TG ($p < 0.002$), TC ($p < 0.00$), LDL-C ($p < 0.01$), and low levels of HDL-C ($p < 0.05$) compared with age and sex matched normal subjects (Table-I). These Renal transplant recipients were divided into two groups, 16 subjects (40%) with HbA1c >6.5% (48 mmol/mol) were in Diabetic Group and 24 subjects (60%) with HbA1c <6.5 % were in Non- Diabetic Group. The mean levels of TC, TG, LDL-C and HDL-C were higher in Diabetic transplant group as compared to non diabetic RTR (Table-II).

SR. NO	Biochemical Parameters Subjects	HbA1c% Mean \pm SD Range	TC mmol/l Mean \pm SD Range	TG mmol/l Mean \pm SD Range	HDLmmol/l Mean \pm SD Range	LDL mmol/l Mean \pm SD Range
1	Study Group N=40	$5.9 \pm 1.6^{**}$ (3.2 – 11.5)	$5.57 \pm 1.2^{**}$ (3.6 – 8.0)	$2.4 \pm 1.4^{**}$ (0.8 – 7.4)	$1.0 \pm 0.3^*$ (0.6-1.7)	$3.48 \pm 1.1^{**}$ (1.8 – 6.4)
2	Control Group N=40	4.5 ± 2.1 (3.4--5.9)	4.6 ± 1.15 (2.9-7.3)	1.7 ± 0.6 (0.7-3.3)	1.17 ± 0.3 (0.7-1.8)	2.5 ± 1.1 (1.08-5.1)

Table-I. HbA1c and Lipoprotein levels in Renal transplant patients and normal subjects

Values are mean \pm SD (range in parenthesis); N= Number of patients; RTR - renal transplant recipient; TC - Total cholesterol; TG - Total triglycerides; LDL-C - Low density lipoprotein cholesterol; HDL-C - High density lipoprotein cholesterol; * $p < 0.05$, ** $p < 0.001$ versus control

SR. NO	Biochemical Parameters Subjects N=40	HbA1c% Mean ±SD Range	TC mmol/l Mean ±SD Range	TG mmol/l Mean ±SD Range	HDL mmol/l Mean ±SD Range	LDL mmol/l Mean ±SD Range
1	Non Diabetic Group N=24 (60%)	4.99 ± 0.8 (3.2 – 5.6)	5.4 ± 1.1* (3.6 – 7.1)	2.2 ± 1.1* (1.3 – 3.6)	0.97 ± 0.3 (0.6 – 1.6)	3.37 ± 1.1 (1.8 – 5.4)
2	Diabetic Group N=16 (40%)	7.5 ± 1.19 (6.5-11.5)	5.7 ± 1.3 (3.8-8.0)	2.6 ± 1.7 (0.8-7.4)	1.05 ± 0.33 (0.6 – 1.7)	3.6 ± 1.1 (1.8-6.4)

Table-II. HbA1c and Lipoprotein levels in different groups of Renal transplant patients

Values are mean ±SD (range in parenthesis); n - Number of patients; RTR-renal transplant recipient; TC - Total cholesterol; TG - Total triglycerides; LDL-C - Low density lipoprotein cholesterol; HDL-C - High density lipoprotein cholesterol; *p<0.05.

Elevated TC, TG, LDL-C and low HDL-C was observed in 32.5%, 72.5%, 52.5%, and 60% of total RTR, respectively (Table-III). Percentage of elevated TC, TG, LDL-C and decreased HDL in diabetic group of RTR versus non diabetic RTR was 43.7% Vs 25% , 81.2% Vs 66.6%, , 62.5% Vs 44.4%, and 50% Vs 66.6% respectively, as shown in Table-III. The TC and TG level were significantly higher, in patient with duration of less than 1 year

after kidney transplantation. The highest level of LDL and the lowest level of HDL were observed in patient more than 1 year after transplantation. A positive correlation was detected in HbA1c and TC, HDL – C, LDL – C in non diabetic and diabetic patients. In diabetic RTR, a statistically significant positive correlation of the HbA1c levels with TG level was observed.

Lipid Profile	Total RTR N=40	Non diabetic RTR N=24	Diabetic RTR N=16
Elevated Cholesterol ≥6.2 mmol/l	13 (32.5%)	6 (25%)	7 (43.7%)
Elevated TG ≥1.7mmmol/l	29 (72.5%)	16 (66.6%)	13 (81.2%)
Decreased HDL-C ≤1.03mmol/l	24 (60%)	16 (66.6%)	8 (50%)
Elevated LDL ≥3.38mmol/l	21 (52.5%)	11 (44.4%)	10 (62.5%)

Table-III. Pattern of Abnormal lipid levels in Renal transplant recipients

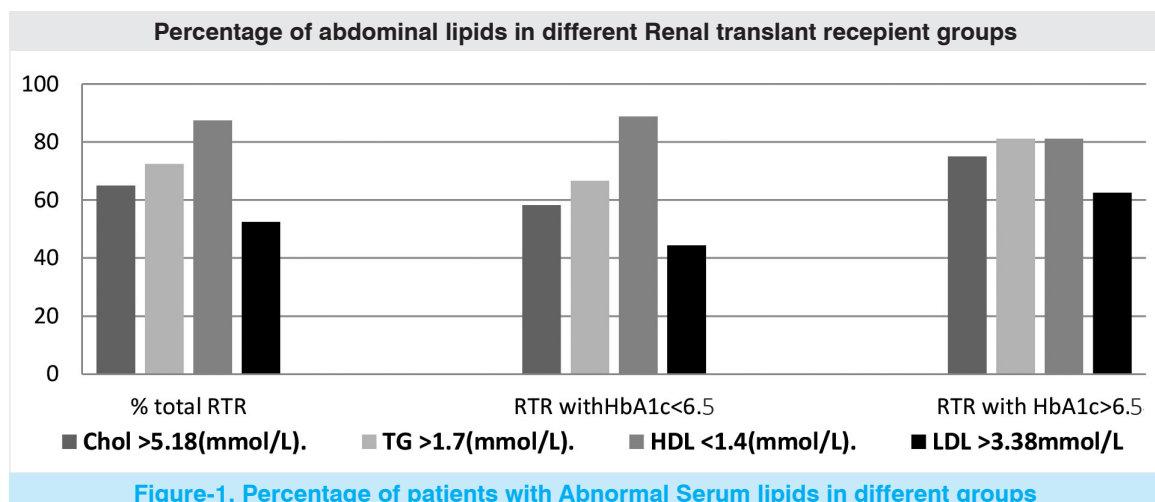


Figure-1. Percentage of patients with Abnormal Serum lipids in different groups

DISCUSSIONS

In patients with end stage renal failure, renal transplantation is a recognized method of treatment. In contrast to dialysis, it has greater possibility of long and a superior quality of life.¹¹ The current study found gender imbalance in patients undergoing transplantation, there was a noticeable *gender bias* in favour of male patients. In our study only 20% were females. The mean age of patients opting for renal transplant in India and Pakistan is lower, as compared with the developed world and renal transplant recipients are individuals in the most productive years of their lives, mostly the sole earning member of families with multiple dependents.^{12,13}

Reduction of cardio-vascular morbidity and mortality in transplant recipients can be achieved by modification of hyperlipidaemia, hypertension, and post-transplant diabetes, as these are the triple risk factors for cardiovascular accidents.⁴ Experimental studies have shown that abnormal lipoprotein patterns in kidney transplant recipients were associated with acute and chronic rejection.¹⁴ In renal transplant patients, the pattern of dyslipidemia is characterized by elevated plasma TC, LDL-C, and triglyceride (TG) in addition to markedly reduced HDL-C.^{15,16} In the present study, the mean values of serum triglycerides and cholesterol were significantly higher in RTR compared to normal controls. The incidence of post-transplant hyperlipidaemia varies from 22% to 54% in different studies, which may be due to the lack of standardization in reporting of the lipid levels.⁴ In the current study dyslipidemia prevalence is compatible with other studies, but the type of dyslipidemia is not similar in different studies.¹⁶ Hosseini et al in a study in RTR observed raised cholesterol, triglyceride, LDL and low HDL in 58.9%, 86.6%, 33.4% and 61.4% patients, respectively.¹⁷ In our study, the most common abnormality was hypertriglyceridemia, 72.5% of renal transplant patients, followed by HDL which was reduced in 60% patients. Significant post-transplant hyperlipidemia is usually acknowledged; though normal lipid profile has been reported too. No significant difference in lipid profile of post

renal transplant patients compared to control group was observed in an Indian study, although in chronic renal failure patients, triglycerides were significantly elevated as compared to controls.¹⁸ In renal transplant recipients, the pathogenesis of hyperlipidaemia is not completely understood and seems to be multifactorial. Numerous factors are associated with post transplant hyperlipidaemia including age, body weight, gender, pre-transplant lipid level, diabetes mellitus, renal dysfunction, use of diuretics or beta blockers, steroid and cyclosporin.² Lipoproteins levels were significantly high in Sudanese renal transplant patients compared to healthy controls. In this study, hyperlipidemia was noted in 62.8% of renal transplant patients with the main abnormality being hypertriglyceridemia (47.7%), but total cholesterol was reduced in 13 (17%) patients.¹

New onset diabetes mellitus after transplantation (NODAT) is a recognized complication following renal transplant and has been reported to occur in 4% to 25% of renal transplant recipients.¹⁹ This discrepancy in the reported incidence may be due to lack of a worldwide agreement on the definition of NODAT, the presence of modifiable and non-modifiable risks factors and the duration of follow-up.²⁰ In the present study, 40% of patient having HbA1c > % 6.5 were labeled as diabetic and higher percentage of patients in this group had elevated triglyceride, followed by LDL-C and Total Cholesterol levels, as compared to nondiabetic group. Studies have shown that an advanced glycosylation end-product modification of LDL could contribute to dyslipidaemia and atherosclerosis.²¹ Agrani et al reported that increased HbA1c and impaired glucose tolerance was accompanied by hypertriglyceridemia and hypercholesterolemia in hemodialysis patients and RTR, respectively.²²

Khan et al observed a linear relationship between HbA_{1c} and dyslipidaemia. The findings of this study show that HbA_{1c} is a valuable biomarker of long-term glycaemic control and a predictor of hyperlipidemia.²³ In the present study, we have evaluated the relationship of HbA1c with lipid profile in post renal transplant patients. A

significant correlation was observed between HbA1c and TG and a weak positive correlation with TC, LDL-C levels in diabetic patients, which is in agreement with the findings of several other investigators who reported significant correlation and suggested the importance of good management of diabetes in controlling dyslipidaemia.^{24,25} Reducing glycated HbA1c to about 7% (53 mmol/mol), lowers the risk of development of the microvascular complications of diabetes.²⁶ A statistically non significant correlation of the mean HbA1c levels with HDL – C level was observed in our study, which is in agreement with the observations made by Menon V, in which HDL – C levels of the patients remained the same despite the elevation in the HbA1c levels.²⁷

CONCLUSION

This study shows, a positive relationship between HbA1c and lipid profile (TC, TG, HDL – C and LDL – C) in both Diabetic and Non Diabetic Group and a highly significant relationship of HbA1c with TG and LDL – C in Diabetic Group. More rigorous glycemic control will reduce the development of microvascular complications. The assessment and treatment of dyslipidemias should be part of routine post-renal-transplant care and medication regimens should be individualized.

Copyright© 16 Mar, 2015.

REFERENCES

- Suleiman B, El Imam M, Elsabigh M, Eltahir K, Eltahir A, Miskeen E. **Lipid profile in post renal transplant patients treated with cyclosporine in Sudan.** Saudi J Kidney Dis Transpl 2009;20:312-7.
- Kasike BL. **Clinical practice guidelines for managing dyslipidemia in kidney transplant patients.** Am J Transplant. 2005; 5(6):1576.
- Jingjing Li, Meiping Guan, Chenzhong Li, Fuping Lyv, The Dipeptidyl Peptidase-4 Inhibitor Sitagliptin Protects against Dyslipidemia-Related Kidney Injury in Apolipoprotein E Knockout Mice Int. J. Mol. Sci. 2014;15: 11416-11434.
- Jindal R.M. **Post-transplant hyperlipidaemia.** Postgrad Med J. Dec 1997; 73(866): 785-793.
- Davidson J, Wilkinson A, Dantal J *et al.* **New-onset diabetes after transplant: inter-national consensus guidelines.** Transplantation 2003; 75:ss3-ss24.
- Ali A, Khem A, Syed. **Disturbance of lipoprotein metabolism in diabetes.** J Ayub Med Coll 1999; 11:3-5.
- Hami M, Mojahedi MJ, Naghibi M, Shakeri MT, Sharifipour F. **Cyclosporine trough levels and its side effects in kidney transplant recipients.** Iran J Kidney Dis. 2010;4 (2):153-7.
- Ahmed M H. **Dyslipidemia After Kidney Transplantation and Correlation With Cyclosporine Level: A Glimpse into the Future.** Nephrourol Mon. Nov 2013; 5(5): 1006-1007.
- Fukuyama N, Homma K, Wakana N *et al.* **Validation of the Friedewald Equation for Evaluation of Plasma LDL-Cholesterol.** J Clin Biochem Nutr. Jul 2008; 43(1): 1-5.
- Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Circulation. 2002 Dec 17; 106(25):3143-421.
- Jha V. **Current status of end-stage renal disease care in India and Pakistan.** Kidney International Supplements (2013) 3, 157-160.
- Modi GK, Jha V. **The incidence of end-stage renal disease in India: a population-based study.** Kidney Int 2006; 70: 2131-2133.
- Sakhuja V, Jha V, Ghosh AK *et al.* **Chronic renal failure in India.** Nephrol Dial Transplant 1994; 9: 871-872.
- Dimeny E, Fellstrom B, Larsson E, Tufveson G, Lithell H. Hyperlipoproteinemia in renal transplant recipients: is there a linkage with chronic vascular rejection. Transplant Proc 1995; 25: 2065-6.
- Dumler F, Kilates C. **Metabolic and nutritional complications of renal transplantation.** J Ren Nutr. 2007; 17(1):97-102.
- Kasike B, Cosio FG, Beto J, Bolton K, Chavers BM, Grimm R, Jr, *et al.* **Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative.** Am J Transplant. 2004;4 (7):13-53.
- Hosseini MS, Rostami Z, Einollahi B. **Dyslipidemia after Kidney Transplantation and Correlation with Cyclosporine Level.** Nephrourol Mon. 2013; 5(3): 831-

834.

18. Shah B, Nair S, Sirsat RA, Ashavaid TF, Nair K. **Dyslipidemia in patients with chronic renal failure and in renal transplant patients.** J Postgrad Med 1994;40:57-60.

19. Davidson J, Wilkinson AH, Dantal J, et al. **New-onset diabetes after transplantation: 2003 International Consensus Guidelines.** Transplantation 2003;77:SS3-24.

20. Pham T, Pham CT, Lipshutz G. **New Onset Diabetes Mellitus After Solid Organ Transplantation.** Endocrinol Metab Clin N Am 2007;36: 873-890.

21. Stem MP. **Do non-insulin-dependent diabetes mellitus and cardiovascular disease share common antecedents?** Ann Intern Med 1996; 124:110-6.

22. Argani H, Noorazarian A, Rahbaninobar M. **Comparison of glucose tolerance in renal transplant recipients and hemodialysis patients.** BMC Nephrol. 2004;5: 11.

23. Khan HA, Sobki SH, Khan SA et al. **Association between glycemc control and serum lipid profile in type 2 diabetes:HbA1c predicts dyslipidemia.** Clin Ex Med 2007; 7:24-29.

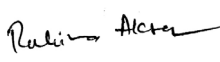

24. Ladeia A, Adan L, Couto-Silva A C, Hiltner A, Guimarães AC. **Lipid Profile Correlates With Glycemic Control in Young Patients With Type 1 Diabetes Mellitus.** Preventive Cardiology2006; 9 (2) : 82-88.

25. Faulkner MS, Chao WH, Kamth SK. **Total homocysteine, diet and lipidprofiles in type 1 and type2 diabetic and non-diabetic adolescents.** J cardiovascular Nurs. 2006; 21:47-55.

26. National Kidney Foundation. **KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease.** Am J Kidney Dis2007;49: S1-S180.

27. Menon V, Greene T, Pereira A, Wang X, Beck G, Kusek JW. **Glycosylated hemoglobin and mortality in patients with non-diabetic chronic kidney disease.** J Am Soc Nephrol 2005;16: 3413-3417.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Ruhina Akbar	Proposed topic, basic study design sampling / subject recruitment strategy and methodology, Data interpretation, Manuscript writing.	
2	Dr. Naeem Kauser	Mentor, supervision of analytical work	
3	Dr. Naveed Hussain	Data collection, data analysis literature reievew	