

Original Research Article

Etiology of graft dysfunction in renal transplant recipients

S. Thirumavalavan¹, Krishna Kumar^{2*}, S. A. K. Noor Mohamed³, R Vijaya Kumar⁴


¹Assistant Professor, Department of Nephrology, Government Kilpauk Medical College Hospital, Chennai, Tamil Nadu, India

²Assistant Professor, Department of Nephrology, SRM Medical College and Hospital, Chennai, Tamil Nadu, India

³Associate Professor, Department of Nephrology, Government Mohan Kumaramangalam Medical College Hospital, Salem, Tamil Nadu, India

⁴Retired Professor of Nephrology, Government Stanley Medical College Hospital, Chennai, Tamil Nadu, India

*Corresponding author email: krishmahalaxmi@hotmail.com

	International Archives of Integrated Medicine, Vol. 6, Issue 3, March, 2019. Copy right © 2019, IAIM, All Rights Reserved. Available online at http://iaimjournal.com/	
	ISSN: 2394-0026 (P)	ISSN: 2394-0034 (O)
	Received on: 04-03-2019	Accepted on: 09-03-2019
	Source of support: Nil	Conflict of interest: None declared.
How to cite this article: S. Thirumavalavan, Krishna Kumar, S. A. K. Noor Mohamed, R Vijaya Kumar. Etiology of graft dysfunction in renal transplant recipients. IAIM, 2019; 6(3): 313-318.		

Abstract

Background: Kidney transplantation is the preferred mode of renal replacement therapy for the end-stage renal disease, with dramatic improvements in patient and graft survival over the last 50 years. In the modern era of immunosuppression, 1-year patient survival is close to 98%, and 1-year allograft survival rates have improved to 90% for deceased donor kidney transplants and 95 % for living donor kidney transplants with some inter-center variability.

The aim of the study: To elucidate the etiology of graft dysfunction among renal transplant recipients.

Materials and methods: A retrospective study was conducted among 155 patients who underwent both cadavers and live donor transplant from October 2009 to March 2011 at a tertiary care center in Chennai, South India. All the transplant recipients were regularly followed with serum urea and creatinine, urine routine, calcineurin inhibitor drug levels in the serum, USG Abdomen, urine culture depending on the graft status. Graft dysfunction defined by a rise in the creatinine more than 25% or 0.3 to 0.5 mg per dl from the baseline. Those who developed graft dysfunction were presented for graft biopsy and managed based on the report accordingly.

Results: Among the 155 transplant recipient patients, 66 (44%) patients developed graft dysfunction and underwent renal biopsy. The graft dysfunction was due to chronic allograft dysfunction (interstitial fibrosis and tubular atrophy) in 24 (15.4%) patients, acute cellular rejection in 13 (8.4%) patients, acute antibody-mediated rejection in 2 (1.3%) patients, acute tubular necrosis in 9 (5.8%) patients, calcineurin toxicity in 6 (3.9%) patients, thrombotic microangiopathy in 6 (3.9%) patients, IgA nephropathy in 3 (1.9%) patients and transplant renal artery stenosis in 1(0.6%) patient.

Conclusion: Among the various causes, acute cellular, acute antibody rejection and chronic allograft nephropathy holds nearly 25% of the incidence of graft dysfunction. It indicates appropriate immunological evaluation, appropriate immunosuppression, use of induction agents in high-risk patients and protocol renal biopsy to identify early rejection in high-risk patient and appropriate early intervention is important to improve long-term term graft and patient survival.

Key words

CNI-calcineurin inhibitors, ACR-acute cellular rejection, AMBR – acute antibody-mediated rejection, IFTA -interstitial fibrosis and tubular atrophy, ATN-acute tubular necrosis.

Introduction

Chronic Kidney Disease (CKD) is a global public health problem with a rising trend in prevalence. In India, the projected number of deaths due to chronic kidney disease was around 5.21 million in 2008 and is expected to rise to 7.63 million by 2020 (66.7% of all deaths) [1]. Indeed, it has been recently estimated that the age-adjusted incidence rate of ESRD in India to be 229 per million population [2]. More than 100,000 new patients enter renal replacement programs annually in India [3]. In view of the shortage of organs, early identification of graft dysfunction and appropriate intervention is important to increase long term patient and graft survival [4]. Renal biopsy is the gold standard for the diagnosis of graft dysfunction. Biopsy results can change the clinical diagnosis in 36% and therapy in 59% of patients [5]. Many pathological and morphological studies have focused on graft dysfunction based on biopsy. Allograft dysfunction is classified into early (within weeks), immediate (1 to 6 months), late (more than 6 months) following post-transplant period. Any factors like immunologic, non-immunologic, recipient, and donor factors can contribute to graft dysfunction [6]. With the advent of new Immunosuppressive agent, advancement in renal biopsy studies, early identification of graft dysfunction, appropriate rescue therapy leads to graft survival 95% in

living donor allograft and 91% in deceased donor transplant [7].

Materials and methods

All the patients who underwent a renal transplant at Stanley Medical College and were on regular follow-up in the outpatient Department of Nephrology between October 2009 to March 2011 were enrolled in the study. All the patients enrolled in the study belonged to different periods of follow-up. All transplant recipients were fully evaluated prior to transplant for HLA, crossmatch, ABO compatibility, an aorta-iliac angiogram of the recipient, viral serology, chronic infection, native kidney disease for the recurrence and graft loss. Both live related, spousal and deceased donor transplant recipients are included in the study. All the grafts were perfused with HTK solution. All patients were started on triple Immunosuppression either tacrolimus or cyclosporin based regimen [16]. No induction agent was given to any of these patients. Patients were followed postoperatively with serum urea and creatinine, urine output, urine routine, ultrasonogram of graft, serum drug level, complete blood count, depending on their period of post-transplant. Those patients who are developed graft dysfunction were presented for renal biopsy. The biopsy reports of the patients were studied in detail for the etiology of graft dysfunction.

Operational Definition: Graft dysfunction is defined as a rising serum creatinine of more than 25% or 0.3 to 0.5mg per dl from the baseline.

Statistical analysis: The data collected were entered in Microsoft Excel 2013 version and double-checked for errors. The data was analyzed using Statistical Package for Software Solutions (SPSS) version 21. The categorical variables were expressed in frequencies and percentages and pictorially represented in bar and pie charts.

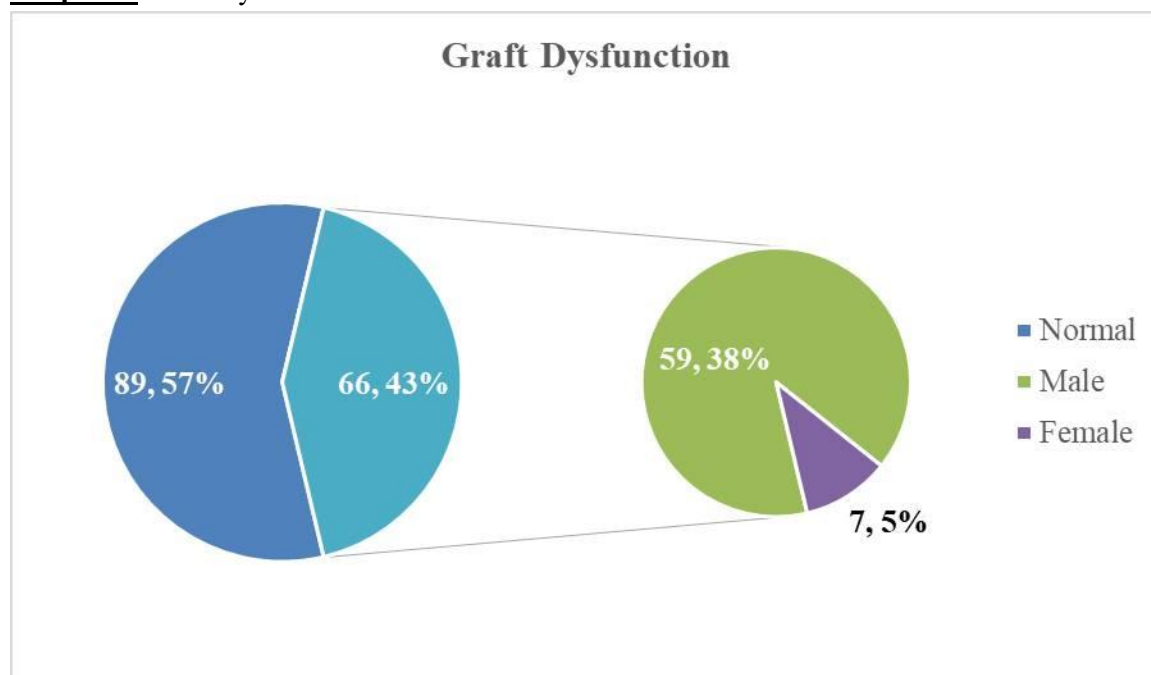
Results

There were totally about 155 subjects, who were transplanted during the study period. Out of 155 patients, 123 were males and 32 were females. Considering the distribution of donors among the

transplant recipients, 114 patients had live donor recipients, 6 had the spousal transplant and 35 had cadaver transplants. Only in 35 transplant recipients, native kidney disease was known.

Among the study population, the chronic allograft dysfunction (interstitial fibrosis and tubular atrophy) was seen in 24 (15.4%) patients, acute cellular rejection in 13 (8.4%) patients, acute antibody mediated rejection in 2 (1.3%) patients, acute tubular necrosis in 9 (5.8%) patients, calcinuerin toxicity in 6 (3.9%) patients, thrombotic micro-angiopathy in 6 (3.9%) patients, recurrence IgA nephropathy in 3 (1.9%) patients, graft pyelonephritis in 2 (1.3%) patients and transplant renal artery stenosis in 1(0.6%) patient (**Graph – 1**).

Graph – 1: Graft dysfunction.



Among the total recipients in the study population, 66 (42.6%) had graft dysfunction based on serum creatinine levels. Among the graft dysfunction subjects, 59 were male and 7 were female recipients. About 21 (31.8%) patients had a serum creatinine of more than 2.0 mg/dl, 42 (63.6%) patients had creatinine around 1.5 to 2.0 mg/dl and 3 (4.5%) patients had

creatinine less than 1.5 at the time of biopsy (**Table – 1**).

Among the biopsy timing, 4 were done in less than one month, 18 were done at two to six months, 26 patients were biopsied after 12 months after transplant. No induction therapy was given (**Table – 2**).

Table – 1: Biopsy creatinine group.

Biopsy creatinine group	N	%
< 1.50	3	4.5
1.51 - 2.00	42	63.6
> 2.00	21	31.8
Total	66	100.0

Table – 2: Month vs Biopsy.

Month Group	N	%
1 month	4	6.3
2 - 6 months	18	27.0
7 - 12 months	18	28.6
> 12 months	26	38.1
Total	66	100.0

Table – 3: Etiology of graft dysfunction.

Parameter	N	%
Antibody mediated rejection	2	1.3%
Acute cellular rejection	13	8.4%
Infection	2	1.3%
Acute tubular necrosis	9	5.8%
Thrombotic microangiopathy	6	3.9%
Chronic allograft nephropathy	24	15.5%
Drug Toxicity	6	3.9%
Transplant renal artery stenosis	1	0.6%
Recurrence (IGA)	3	1.9%
No graft dysfunction	89	57.4%

Among the 66 graft dysfunction patients, 54 were cyclosporine and 12 were tacrolimus-based regimen. All the graft dysfunction patients had a negative cross-match of less than 10%. Among the total 155 recipients, delayed graft function (required hemodialysis in the post-operative period) was seen in 7 patients and 12 had slow graft function (**Table – 3**).

Discussion

Biopsy proved acute cellular rejection was seen in 13 patients who were treated with methylprednisone pulse therapy. The incidence of acute rejection in our study is 8.4% compared to that of 8% reported by the Organ Procurement and Transplantation Network (OPTN) in 2013 - 2014 [8]. This is mainly due to more number of live donor transplants and better matching and

lesser cold ischemic time. Overall acute rejection episodes are generally associated with a reduction in long-term allograft survival. If the renal function returns to baseline, acute rejection does not necessarily cause irreparable damage or impact long-term graft survival [9]. Antibody-Mediated Rejection (ABMR) is caused by the binding of circulating antibodies to donor alloantigens on graft endothelial cells, which results in inflammation, cell damage, and, ultimately, graft dysfunction [10]. The acute antibody-mediated rejection was seen in 2 (1.8%) recipients. None of them recovered even after plasmapheresis, hemodialysis and ATG. A multicentre study by Wolf et al observed an incidence of ABMR of 2% among 551 protocol biopsies and 12.2% among 377 indication biopsies [18]. The lowest incidence in our study was due to more number of live donor transplants (HLA, ABO and immunologically compatible pairs) [11]. Acute tubular necrosis (ATN) was observed in 9 (5.8%) patients in the study population. Among those, six patients had ATN within 3 months, remaining three within 6 months. 8 patients had recovered completely [12]. A study done by Gaber, et al. showed a prevalence of acute tubular necrosis in Protocol biopsy was 40% (6 weeks), 34% (3 months) and 37% (6 months), and 46% in indication biopsy [13]. The lower prevalence of ATN in our study may be due to more live donor transplant, less cold ischemic time, less number of delayed graft function patients, smaller sample size [14].

Thrombotic microangiopathy (TMA) was seen in 6 (3.9%) recipients, out of them two were on tacrolimus-based and four were on the cyclosporine-based regimen. All of them were denovo TMA on the graft [15]. Our incidence correlated well with a study done by Shapiro et al which showed 4 – 15% in renal transplant patients treated with cyclosporine with 43% graft survival. Twenty four recipients (15.5 %) had severe interstitial fibrosis and tubular atrophy suggestive of chronic allograft nephropathy (CAN) [16]. Among those 24 recipients, three patients had permanent graft loss and started on hemodialysis. A study done by Madden et al

(showed 24.7% of recipient had CAN at one-year post-transplant and 89.8% of recipients in 10 years [17]. Our study had lesser incidence may be due to smaller sample size, more no of live donor transplant. Biopsy proven calcineurin toxicity was observed in 6 patients (4%). Among them 4 were on cyclosporine-based, 2 were on the tacrolimus-based regimen. A study done by Mengal, et al. [18] showed the incidence of calcineurin toxicity of 12.1% among renal transplant recipients. The present study showed less incidence of toxicity which may be due to frequent monitoring of drug level and smaller sample size [18]. One patient developed transplant renal artery stenosis after three months and underwent stenting but the renal function had not recovered even after stenting. In the present study, 3 (2%) had biopsy-proven IgA and among them, one was de novo & two were due to recurrence of the disease in the graft. A study on recurrence of glomerular disease after kidney transplantation by Noris, et al. showed the incidence of 10% to 20% IgA recurrence rate depending on diseases. Since our study sample was comparatively smaller the incidence was lower in this study population [19].

Conclusion

Among the various causes, acute cellular, acute antibody rejection and chronic allograft nephropathy holds nearly 25% of graft dysfunction. It indicates the need for more immunological evaluation, appropriate Immunosuppression, use of induction agents in high-risk patients and protocol renal biopsy to identify early rejection in high-risk patient and appropriate early intervention is important to improve long-term term graft and patient survival.

References

1. Veerappan I, Abraham G. Chronic Kidney Disease: Current Status, Challenges, and Management in India. http://www.apiindia.org/medicine_update_2013/chap130.pdf

2. Modi GK, Jha V. The incidence of end-stage renal disease in India: a population-based study. *Kidney Int.*, 2006 Dec; 70(12): 2131–3.
3. Kher V. End-stage renal disease in developing countries. *Kidney Int.*, 2002 Jul 1; 62(1): 350–62.
4. Gjertson DW. Impact of delayed graft function and acute rejection of kidney graft survival. *Clin Transpl.*, 2000; 467–80.
5. Nankivell BJ, Alexander SI. Rejection of the Kidney Allograft. *N Engl J Med.*, 2010 Oct 7; 363(15): 1451–62.
6. Zeier M, Döhler B, Opelz G, Ritz E. The Effect of Donor Gender on Graft Survival. *J Am Soc Nephrol.*, 2002 Oct 1; 13(10): 2570–6.
7. Ojo AO. Expanded criteria donors: process and outcomes. *Semin Dial.*, 2005 Dec; 18(6): 463–8.
8. Cooper JT, Chin LT, Krieger NR, Fernandez LA, Foley DP, Becker YT, et al. Donation after cardiac death: the University of Wisconsin experience with renal transplantation. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg.*, 2004 Sep; 4(9): 1490–4.
9. Magee CC. Transplantation across previously incompatible immunological barriers. *Transpl Int.*, 2006; 19(2): 87–97.
10. Gore JL, Pham PT, Danovitch GM, Wilkinson AH, Rosenthal JT, Lipshutz GS, et al. Obesity and outcome following renal transplantation. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg.*, 2006 Feb; 6(2): 357–63.
11. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med.*, 1999 Dec 2; 341(23): 1725–30.
12. Gaber AO, First MR, Tesi RJ, Gaston RS, Mendez R, Mulloy LL, et al. Results

- of the double-blind, randomized, multicenter, phase III clinical trial of Thymoglobulin versus Atgam in the treatment of acute graft rejection episodes after renal transplantation. *Transplantation*, 1998 Jul 15; 66(1): 29–37.
13. Rush D, Nickerson P, Gough J, McKenna R, Grimm P, Cheang M, et al. Beneficial effects of treatment of early subclinical rejection: a randomized study. *J Am Soc Nephrol JASN*, 1998 Nov; 9(11): 2129–34.
 14. Goggins WC, Pascual MA, Powelson JA, Magee C, Tolkoff-Rubin N, Farrell ML, et al. A prospective, randomized, clinical trial of intraoperative versus postoperative Thymoglobulin in adult cadaveric renal transplant recipients. *Transplantation*, 2003 Sep 15; 76(5): 798–802.
 15. Shapiro RL, Young JB, Milford EL, Trotter JF, Bustami RT, Leichtman A. Immunosuppression: evolution in practice and trends, 1993-2003. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg.*, 2005; 5(4): 874–86.
 16. Madden RL, Mulhern JG, Benedetto BJ, O’Shea MH, Germain MJ, Braden GL, et al. Completely reversed acute rejection is not a significant risk factor for the development of chronic rejection in renal allograft recipients. *Transpl Int Off J Eur Soc Organ Transplant.*, 2000; 13(5): 344–50.
 17. Mengel M, Rogers J, Bosmans J-L, Serón D, Moreso F, Carrera M, et al. Incidence of C4d stain in protocol biopsies from renal allografts: results from a multicenter trial. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg.*, 2005 May; 5(5): 1050–6.
 18. Gwinner W, Hinzmann K, Erdbruegger U, Schaffner I, Broecker V, Vaske B, et al. Acute tubular injury in protocol biopsies of renal grafts: prevalence, associated factors, and effect on long-term function. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg.*, 2008 Aug; 8(8): 1684–93.
 19. Noris M, Remuzzi G. Thrombotic Microangiopathy After Kidney Transplantation. *Am J Transplant.*, 2010; 10(7): 1517–23.