Can zero-hour cortical biopsy predict early graft outcomes after living donor renal transplantation?

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Abstract

Introduction: The aim of this study was to identify relevance of subclinical pathological findings in the kidneys of living donors and correlate these with early graft renal function.
Methods: This was a prospective study on 84 living donor kidney transplant recipients over a period of two years. In all the donors, cortical wedge biopsy was taken and sent for assessment of glomerular, mesangial, and tubule status. The graft function of patients with normal histology was compared with those of abnormal histological findings at one, three, and six months, and one year post-surgery.
Results: Most abnormal histological findings were of mild degree. Glomerulosclerosis (GS, 25%), interstitial fibrosis (13%), acute tubular necrosis (ATN 5%), and focal tubal atrophy (5%) were the commonly observed pathological findings in zero-hour biopsies. Only those donors who had histological changes of interstitial fibrosis and ATN showed progressive deterioration of renal function at one month, three months, six months, and one year post-transplantation. In donors with other histological changes, no significant effect on graft function was observed.
Conclusion: Zero-hour cortical biopsy gave us an idea of the general status of the donor kidney and presence or absence of subclinical pathological lesions. A mild degree of subclinical and pathological findings on zero-hour biopsy did not affect early graft renal function in living donor kidney transplantation. Zero-hour cortical biopsy could also help in discriminating donor-derived lesions from de novo alterations in the kidney that could happen subsequently**.**

Introduction

Chronic kidney disease (CKD) is a common and rapidly increasing global public health problem, both in developed and developing countries. Kidney transplantation remains the treatment of choice for ESRD as it leads to longer survival and superior quality of life[1] it is estimated that in India, 3500 patients undergo renal transplantation annually[2]

The graft recipients, their relatives and transplantation team are always eager to know how the grafted kidney will behave and how long will it survive. Several attempts had been made -to predict the early graft out come by assessing the histologic changes in "zero hour" graft biopsy; however, the issue still remains controversial[3,4,5,6] The post-revascularisation "zero hour" biopsy of renal allograft could provide useful information on subclinical renal lesions present in the healthy donors and the pathological changes which are being transmitted from the donor to recipient via grafted kidney. It might also act as a baseline biopsy for comparing morphology with subsequent graft biopsies. Lesions like Intimal fibrosis, Glomerulonephritis, Tubular Atrophy and Interstitial Fibrosis etc. may either pre-exist or may be of new onset. Majority of existing studies reported on "zero-hour" biopsy in predicting early and late graft outcome in cadaveric donors. Information on post-revascularisation renal allograft biopsies in live related donors is limited.

Methods

After getting Institutional Ethics Committee Clearance, a prospective study was conducted from March 2014 to December 2016.   Informed consent from both the donors and recipients undergoing live donor renal transplantation were obtained.

A total of 84 patients (43 males and 41 females) of the age group 13-63 years, who underwent open donor nephrectomy and renal transplantation at the institution during the above mentioned period, were enrolled in the study. Preoperative donor evaluation was done to evaluate medical, surgical, and psychosocial suitability for living donation, prior to selection of patients for transplantation.

All the recipients included in the study were given same standard immunosuppressive therapy regime consisting of Tab Tacrolimus 3 mg (once a day: OD), Tab Mycophenolate Mofetil 500 mg OD and injection Methylprednisolone 500 mg intravenously daily starting five days prior to the transplantation. Injection Basiliximab 20 mg intravenously in 100 ml normal saline stat was given to all the recipients if the donor was unrelated. Injection Methyl Prednisolone was replaced by Tab prednisolone 30 mg OD from day 3rd post operatively. Cortical wedge biopsy of the size 1x 0.5x 0.3 cm^3 of the transplanted kidney was taken immediately after revascularization after completing the vascular anastomosis. The main idea behind taking Wedge biopsy was to ensure adequate tissue (at least 20 glomeruli per core) for histopathological examination. In all the 84 cases, the wedge biopsy was taken by single transplant surgeon. Specimens were fixed immediately in 10% buffered formalin and embedded in paraffin. Three micron thick serial sections were cut and stained with H&E, Periodic acid Schiff's, Masson's Trichrome, and Periodic Schiff Silver Methylamine stain. A detailed histological examination of post revascularisation graft biopsies was performed and looked for following:

1. Glomerular Status, number of glomeruli per core, and any evidence of Glomerular Sclerosis

2. Mesangial status
3. Tubule status and number of tubules per core

In all transplant recipients, graft function was assessed by serum creatinine post transplantation. All patients had follow-up visit in their 1st, 3rd, 6th month and 1 year of operation to determine if there is any "allograft dysfunction" defined as serum Cr >15% of the baseline value or lack of response to increasing steroid dose. All the patients who developed delayed graft function had to be supported by haemodialysis post transplantation until these, renal functions normalized within one month. All those patients who needed follow up biopsies post transplantation were done percutaneously under CT guidance and by single expert radiologist.

Statistical analysis

"Pearsons Correlation" coefficient test was used for correlating serum creatinine values of patients with normal donor histology with serum creatinine values of patients who had abnormal donor histology at 1month, 3 months, and 6 months and at 1 year post transplantation.

Results

Out of 84 donors, 43 subjects were males and 41 were females. The mean age of the patients was 41 ± 9.5 years.

44 patients out of 84 patients (52%) had normal histology of the donor kidney. Only 40 patients (48%) had abnormal histological changes which include Glomerulosclerosis (GS: 25%), Interstitial fibrosis (13%), Acute Tubular Necrosis (ATN: 5%) and Focal tubal atrophy (FTA: 5%) (Table 1).

The effects of various histological changes on graft function at 1 month are given in Table 1. Only recipients with grafts having Interstitial Fibrosis and Acute Tubular Necrosis showed progressive deterioration of renal function at one month. Out of 4 patients who had ATN on biopsy, 2 developed acute rejection and 2 had delayed graft function post transplantation. Four patients of interstitial fibrosis group also had delayed graft function. Other histological changes in the graft had no effect on graft function.

Both the patients, who had acute rejection died within 3months post transplantation due to systemic infections. All the patients who had delayed graft function required haemodialysis post surgery for optimization of kidney function.

Table 2 shows Serum creatinine values in patients with normal histology and also of patients with various coexisting histological changes in donor kidneys preoperatively and at 1 month, 3 months, 6 months, and 1 year post operatively. Only Interstitial Fibrosis and ATN showed progressive increase in serum creatinine values at one month and 1 year. In cases of both the histological changes, rise in serum creatinine started at 1month post operatively and continued to rise till one year of follow up. On correlating serum creatinine values of these patients with those patients who had normal histology (Table 3), both Interstitial Fibrosis and ATN showed strong positive correlation. (p=0.0003 and p=0.0009 at 1 year post surgery). Patients with other histological changes in donor biopsy like Glomerulosclerosis and Focal Tubal Atrophy also showed marginal rise in serum creatinine obtained post operatively which was statistically insignificant.(p=0.0581and p= 0.083 at 1 year)**.**

Discussion

It is well known that, there are various donor and recipient factors which determine the function and survival of the graft after live donor renal transplantation. Donor related factors including age, organ size and quality, pre operative GFR, and co morbid conditions like diabetes, hypertension and smoking have been reported to have significant bearing on graft function post transplantation. However the role of 'Zero hour" cortical biopsy taken from donor kidney post transplantation on graft function post operatively has not been widely studied.The cortical wedge biopsy was taken as it provides adequate quantity of tissue(atleast 20 glomeruli per core) needed for histopathological examination.**[7]**   In our study "Zero hour" cortical biopsy showed that Glomerulosclerosis (25%) was the most common histological abnormality followed by, Acute Tubular necrosis (5%), Interstitial Fibrosis (13%) and Focal Tubal Atrophy (5%) which is almost similar to the histological findings noted by Lee AL at al**[8]**

        High grade of Glomerulosclerosis has been reported to be a good predictor of early graft dysfunction [8]However in our study, the grade of Glomerulosclerosis was not taken into account due difference in the number of glomeruli per core seen in different biopsy specimens. However, the presence of Interstitial Fibrosis correlated well with worst results in long-term graft survival (chi-square p = 0.029; RR = 2.23; 95% CI, 1.07-4.64). Similar results had been reported by Lopes et al [9] who found a positive correlation between IF and serum creatinine at 3 and 6 months but no correlation with TA and GS. Interestingly same authors assumed that none of the histological variables and scores provided perfect predictions and so they cautioned that results should be interpreted in the context of all available information on donor–recipients.[8, 13]

Table 4 shows comparison of our study with the standard published literature in terms of types of histological changes seen, overall survival, number of deaths, allograft dysfunction; our findings were matching with majority of the studies.

 It has been reported that Implantation Biopsy Score (IBS) 4-6 could determine an increased risk of early graft loss, especially primary nonfunction[11]

Higher IBS grades predict lower graft function until the 3[rd]postoperative year; but in this cohort we could not assess IBS because of shorter follow up period.

 Nowadays, preoperative biopsies could be considered as a graft survival prediction tool, with high specificity (despite a low sensitivity). Since the advent of cyclosporine era of immunosuppression, we have dramatically reduced the impact of allograft acute rejections, remaining with late losses due to chronic allograft dysfunction[11]

Limitations of the study

The sample size of the study was 84, which seems to be inadequate and needs further study with larger number of transplant patients so as to extrapolate the required outcomes representative of population at large. The effects of pre operative eGFR and its correlation to donor's age and comorbidities which could have effected   graft function post transplantation were not studied. Follow up of our patients was for short period and hence long term effect on graft function could not be assessed.

Conclusions

"Zero hour" cortical biopsy gave information about the general status of the donor kidney and presence or absence of subclinical pathological lesions. However it was observed that   mild degree of subclinical, pathologic findings on "zero hour" biopsy did not affect early graft renal function in living-donor kidney transplantation. Interstitial Fibrosis and Acute Tubular Necrosis were the only histological abnormalities associated with significant effect on allograft dysfunction.

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Figures and Tables

Table 1. Effect of various histological changes on graft function at 1 month		
HISTOLOGICAL CHANGES IN CORTICAL BIOPSY	**NO OF PATIENTS (OUT OF 84)**	**EFFECT ON GRAFT FUNCTION**
NORMAL HISTOLOGY	48 (58%)	NIL
GLOMERULOSCLEROSIS	21 (25%)	NIL
INTERSTITIAL FIBROSIS	11 (13%)	DELAYED GRAFT FUNCTION - 4
ACUTE TUBULAR NECROSIS	4 (5%)	ACUTE REJECTION- 2 DELAYED GRAFT FUNCTION- 2
FOCAL TUBAL ATROPHY	4 (5%)	NIL

Table 2. Comparison of serum creatinine in patients with normal histology with that of various coexisting histological changes at 1, 3, 6, and 12 months post-surgery					
	Mean serum creatinine levels (mg/dl)				
	Preop	**1 month**	**3 months**	**6 months**	**12 months**
Normal histology	0.80± 0.19	0.82± 0.18	0.83±0.18	0.83 ±0.18	0.83 ± 0.19
Glomerulosclerosis	0.83 ± 0.24	0.91± 0.23	0.92 ± 0.23	1.05 ± 0.22	0.99 ± 0.22
Interstitial fibrosis	0.87 ± 0.24	1.06 ± 0.22	1.20±0.21	1.40 ± 0.24	1.61 ± 0.28
Acute tubal necrosis	1.05 ± 0.21	1.15 ± 0.21	1.15±0.01	1.25 ± 0.07	1.30 ± 0.01
Focal tubal atrophy	0.65± 0.07	0.75 ± 0.07	0.90±0.01	1.00 ± 0.01	1.15 ± 0.07

Table 3. Comparison of p values of normal histology with various coexisting histological changes

	Preop	1 month	3 months	6 months	12 months
Normal histology vs. Glomerulosclerosis	0.8004	0.6119	0.6192	0.7233	0.0581
Normal histology vs. interstitial fibrosis	0.062	0.017	0.0024	0.0017	0.0009
Normal histology vs. acute tubal necrosis	0.0742	0.002	0.0048	0.0008	0.0003
Normal histology vs. focal tubal atrophy	0.2482	0.390	0.072	0.062	0.083

Table 4. Comparison of our study with published literature

Various studies	Histological changes seen	Overall survival at 1 year	Allograft dysfunction	Number of deaths
Our study	GS-25%, IF-13%, ATN-5%, FTA-5%	96%	7.4%	2(3.8%)
Naderi et al (2014)[12]	GS-35%, IF-16%, FTA-6%	94%	9%	3(5.5%)
Kaplan et al (1975)[13]	GS-23%, IF-6%	98%	15%	1(3%)
Chamenia et al (2004)[14]	GS-24%, FTA-15%	100%	10%	No deaths
Hashikura et al (2004)[15]	Gs-30%, HA-6%	89%	8%	No deaths