DOPPLER ULTRASONOGRAPHIC ASSESSMENT OF EARLY CHANGES IN KIDNEY GRAFT SIZE AND RESISTIVE INDEX- WHETHER RELEVANT AND PREDICTIVE ABOUT 1-YEAR POST-TRANSPLANT GRAFT FUNCTION??

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ABSTRACT

BACKGROUND

Kidney transplant (KT) is a protocolised treatment for patients with end stage renal failure with GFR <15 ml/min. Donor kidney parameters are most important in determining the success of a transplant and recipient survival outcomes. Doppler ultrasonography is a very safe, simple, non-invasive diagnostic tool for assessment and follow up studies in renal transplantation. Doppler ultrasound parameters and renal function tests especially S. Creatinine measurement are investigations commonly done post-transplant for detection of various outcomes of transplantation. We wanted to investigate the correlation between early changes in graft size and resistive index (RI) and 1- year graft function & to evaluate whether ultrasonography & its parameters of the donor kidney performed in the early stages after transplantation can be used as a predictor for long term outcome.

METHODS

Thirty recipients who underwent renal transplantation from a live related donor were studied prospectively at Institute of Nephro Urology, a Tertiary care centre at Bangalore and all patients underwent Doppler ultrasonography by a trained qualified single radiologist. Pre transplant & 1 week & 1 yr. Post-transplant graft size, Resistive Index, and serum creatinine level estimation were determined, and these parameters were assessed for the correlation between early changes in graft size and resistive index and 1-year serum creatinine.

RESULTS

Measurement tests showed a significant increase in graft size including length (initial, 98.9 +/- 4.3 mm; one week 104.4+/-3.6 mm, p< 0.0001), anterior-posterior diameter (initial, 43.2+/- 3.7 mm; one week 46.9 +/- 2.8 mm, p<0.0001) and parenchymal thickness (initial 10.6+/- 0.8 mm; one week 11.4+/- 0.6 mm p<0.001)1 week post transplantation & during the 1-year post-transplant follow up examinations the increase in graft size was not significant in contrast with 1 week post-transplant follow up values. Pearson correlations showed significant correlation between early changes in post-transplant graft size (e.g.: length, r=-0.432, p=0.045) and 1-year post-transplant serum creatinine levels.

CONCLUSIONS

There was a significant increase in kidney size (including length, anterior-posterior diameter and cortical thickness) early after transplantation. The amount of increase in size significantly correlated with serum creatinine level 1-year after transplantation. There was no correlation between RI and serum creatinine. Considering above parameters pre- and post-transplant Doppler ultrasonography is a very effective tool to evaluate the graft function at early stages and at long term follow up post kidney transplantation, which ultimately determines the long-term outcome of the graft.

KEY WORDS

KT- Kidney Transplant, USG- Ultrasonography, RI- Resistive Index, S.Cr- Serum Creatinine

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BACKGROUND

Chronic kidney disease (CKD) is a rampantly increasing public health issue worldwide, both in industrialized and developing countries.

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The worldwide prevalence of CKD is calculated to be around 8-16% as per various studies.[1] The Brunt of the Chronic Kidney disease is affected all around right from the Patient, his family, the community and the society. Hence there is a need of Definitive management in the form of Kidney allograft transplant rather than just the long-term dialysis to overcome the issue of chronic kidney disease. Kidney transplantation (KT) considered the treatment of choice for ESRD as it predicts longer survival and improved quality of life.[2] Nowadays the Post-transplant outcomes are improved because of various surgical advances and modifications and also because of post-Transplant immune suppression therapy. But what determines the ultimate success of any transplant is an area of debate and depends on various Graft related Parameters also & detecting these at the earliest

including the associated complications determines the outcomes better and predicts the survival.[3]

Ultrasound and creatinine measurement are the most important and relevant investigations for determining Renal functions post transplantation and to identify any complications. Ultrasound is an easily available bedside investigation which is termed as an extension of physical examination. Ultrasound imaging is used to detect any alterations in shape and size, the flow patterns in the renal vessels including artery and vein and also to verify on the renal parenchyma and cortical thickness and corticomedullary differentiation of the transplanted kidney. It is a very relevant, reproducible and safe modality without any associated radiation exposure or contrast related complications (As seen with a Computerized tomography), especially to identify and evaluate associated vascular complications that occur in 1–10%[3-5] of renal transplantations.[6]

Doppler indices [Pulsatility index (PI) and resistive index (RI)] are measured by Doppler Ultrasound & these indices are the parameters to quantify possible changes in kidney circulation & Kidney hemodynamic status both at the level of renal hilum and at intra lobular artery level to identify and quantify and verify the flow patterns inside the parenchyma and assess overall function of transplanted kidney.[7-9]

Rader marker et al. reported that RI was the best index to assess transplanted kidney dysfunction.[10] Various previous studies were considered as prognostic factors with respect to the association of PI and RI with long-term Renal functional outcomes post-transplant.[11] It was shown in a study that measurement of RI shortly after transplantation can be utilized as an indicator for short-term renal functional outcome and success post-transplant.[12]

Therefore, our attempt was to evaluate and correlate these immediate post-transplant ultrasound indices with the final outcome & thus we have evaluated in a prospective observational study, the pattern of changes in renal size and RI, early (1-week) post-transplant and also 1-year post-transplant and evaluated the correlation with the 1-year post-transplant Scr levels to find out if any early assessment of changes in RI and renal size have a predictive value on long-term graft function and its successful outcomes.

METHODS

A prospective observational study of thirty patients who underwent renal transplantation at institute of nephro urology Bangalore, who fulfilled the required inclusion and exclusion criteria were done. Study was conducted for a period from Oct. 2016 to Dec. 2018. IEC approval was obtained from Institutional Ethics committee and Research Review board of the Institute. Valid informed consent was taken from the donor & recipients separately and after their consent only they were considered for study. Clinical data were recorded on paper/chart during the course of hospital stay and on periodic outpatient follow-up visits serially.

Basic Demographic data of the Donor was collected which included age, sex, occupation, co morbidities, previous interventions or surgeries, recent blood and urine investigation profiles & fully explained valid consent forms. All donor patients underwent echocardiography and cardiology fitness before the surgery. They were also evaluated with USG abdomen and pelvis to look for kidneys and other abdominal organs and any incidentally detected abnormalities and also evaluated with MR angiography to know about the anatomy of the vasculature, the number of renal arteries and veins and their lengths from their origins, also any atherosclerotic changes in the vessels if any were also noted. Donors also underwent DTPA renal scan to quantify the function of the kidneys and to determine GFR of each kidney so as to appropriately select the donor kidney and counsel the donor regarding the pros and cons of the deemed procedure.

Similarly demographic data was collected from the renal allograft recipient which included age, sex, occupation, chronic kidney disease duration, basic disease responsible for the Chronic kidney disease, any Arterio venous fistulae and if any failures (primary or secondary in the past and its management if any if done), any associated co morbidities, medication history, Frequency and duration of haemodialysis if any and its complications, any history of bone disease, any history of blood transfusion, any history of treatment with erythropoietin and its frequency, history of any immunizations were accounted for, any stigmata of Chronic kidney disease and Metabolic bone disease were examined and appropriately documented. Serial measurements of renal function tests and other basic blood and urine investigations were tabulated in all recipients. All patients underwent urine culture and were treated appropriately with antibiotics if any culture positive status. All recipient patients underwent Echocardiography examination and were deemed fit from cardiologist before the planned procedure. Dental and Ophthalmologic examinations were also done in the recipient.

Also, donor and recipient cross match was done and when cross match was negative then only the planned transplant procedure was further planned after valid consents from both donors and recipients.

Once both donors and recipients of allograft donors were found fit for the transplant, Zonal Kidney Transplant board and institutional transplant review board meetings were done and appropriate clearances for the procedure taken.

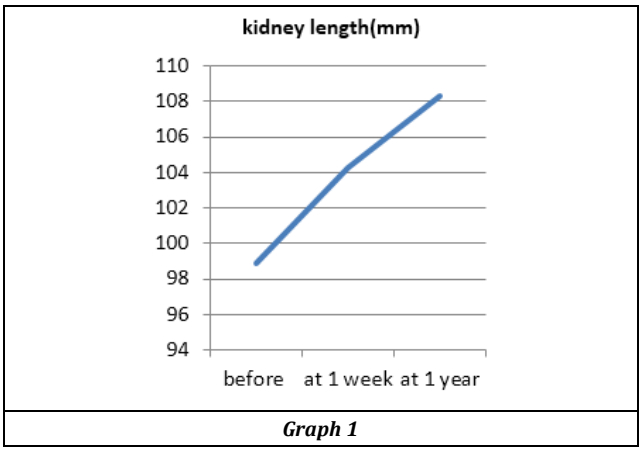
Patients underwent surgeries at our institute by a dedicated transplant team. Donor nephrectomies of the appropriate kidneys were done either laparoscopically or in an open approach. Recipient Graft placement was done only by an open approach. Anastomosis of the vein was done in all cases to external iliac vein in an end-side anastomosis and arterial anastomosis was done either to external iliac artery (In an end-side fashion) or to internal iliac arteries (In an end to end fashion). Usually the transplant kidney was placed in the Right iliac fossa area. During the procedure appropriate considerations of warm ischemia, cold ischemia and rewarm ischemia time were done, as these might also impact on the final outcome of the success of transplant.

All patients underwent ultrasonography for various graft size parameters (Including kidney length, antero-posterior diameter, and parenchyma thickness), along with RI in the pre transplant period. These parameters were recorded in all potential living kidney donors shortly before transplantation as well as 1-week and 1-year after transplantation in allograft recipients. The measurement of RI, kidney size, and parenchymal thickness were performed using a duplex Doppler apparatus (Digital colour Doppler Envisor, Philips electronic–Envisor) with a 3.5- MHz convex transducer in a supine position at the level of the Renal hilum and at level of interlobar artery in the allograft recipient.

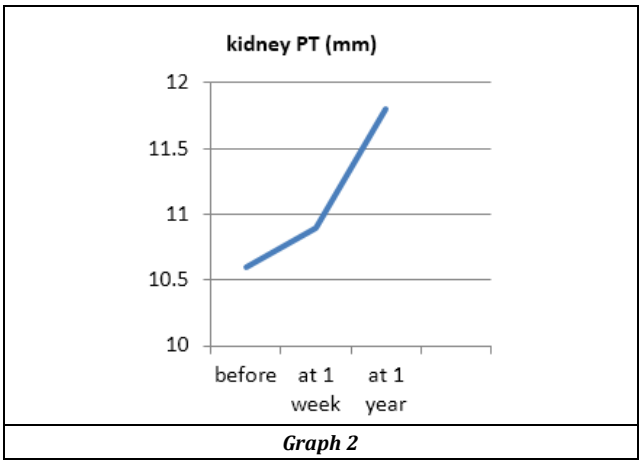
Data	Donor (D)- Pre Trans-plant	Allograft Recipient (R*) At 1 Week Post Transplant	Allograft Recipient (R**) at 1 Year Post Transplant	Difference (p-value in Repeated Measurement		
				p Value (D & R*)	p Value (D & R**)	p Value (R*& R**)
Age (yrs.)	46.77+/- 10.11	33.40+/- 7.89	33.40+/- 7.89	---	---	---
Sex (M/F)	8/22	29/1	29/1	---	---	---
Length (mm)	98.9 +/- 4.3	104.4 +/- 3.6	108.3 +/- 3.9	< 0.001	<0.0001	< 0.0001
APD (mm)	43.2 +/- 3.7	46.9 +/- 2.8	49.3 +/- 3.2	<0.001	< 0.0001	<0.0001
PT(mm)	10.6 +/- 0.8	11.4 +/- 0.6	11.8 +/- 0.7	<0.001	<0.001	0.019
RI	0.59 +/- 0.05	0.68 +/- 0.06	0.68 +/- 0.07	0.121	0.920	0.797
S creat	0.84 +/- 0.17	2.03 +/- 1.15	1.35 +/- 0.57	0.0001	0.0001	0.002

Table 1. Showing Various Demographic Parameters of Renal Doppler Ultrasonic Measurements at Three Time Points, Pre-Transplant Period (D), At 1 Week Post-Transplant (R*) and At 1 Year Post-Transplant (R**)

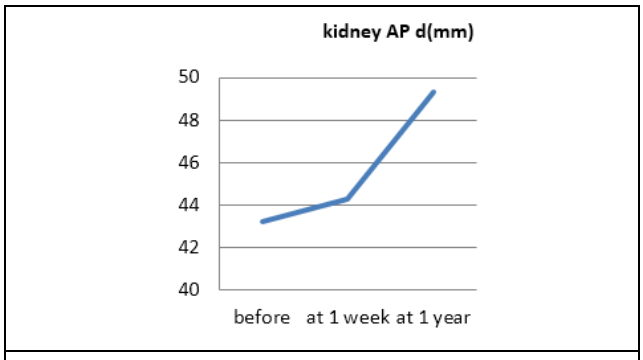
The reported values represent mean +/- SD in 30 patients,
Abbreviations: APD, anterio-posterior diameter; PT, parenchymal thickness; RI, resistive index; S.cr, serum creatinine.



Graph 1



Graph 2



Graph 3

RI was calculated using the built-in software as follows-

RI= Peak Systolic Velocity – End Diastolic Velocity/Peak Systolic Velocity

All parameters were assessed by a single radiologist, using the same equipment, without any knowledge of patient details or history. The measurements were performed in triplicate and the mean value was recorded for every component. All values that were reported represent the mean - standard deviation (SD).

All recipients received immune suppression with intravenous methyl prednisolone 500 mg on the day of surgery and 250 mg for next 2 days. Appropriate measures for prophylaxis of deep vein thrombosis were taken in both donor and recipients and both donor and recipients were advised with peri operative incentive spirometry for a better outcome of the surgery. Maintenance immune suppression following surgery included oral Prednisolone (30 mg/day tapered to 10 mg/day and continued thereafter), Mycophenolate Mofetil (MMF 1-2 g/day), and Tacrolimus (0.1 mg/kg body weight/day). Tacrolimus was replaced with Sirolimus in the event of Tacrolimus nephrotoxicity. Doses of Tacrolimus were adjusted as per their serum levels by Fluorescence Polarization Immunoassay (FPIA) technology. Tacrolimus levels were maintained around 10 ng/ml during initial 3 months of post-transplantation, between 7-9 ng/ml for a year and around 5 ng/dl thereafter. After achieving steady state levels, Tacrolimus levels were assayed once in 3 months in the first-year post-transplantation.

Levels of serum creatinine was measured on a daily basis till a stable level is reached for each patient, by automated (Jaffes) method & serum creatinine level will be considered normal if found below 1.5 mg/dl after creatinine level stability in post-transplant state in the allograft recipient.

Statistical Analysis

All statistical analyses were performed using SPSS, software version 19. Repeated measure ANOVA measurements were applied to identify the relation between kidney size, parenchymal thickness, RI, and S.cr in three time-intervals to identify how the parameters change post-transplant with respect to pre transplant status during the 1-year follow-up period.

Linear regression and Pearson correlation tests were applied to evaluate the correlation between changes in kidney size, parenchymal thickness, and RI at 1-week post transplantation and S.cr 1-year post transplantation. The correlation between RI and S.cr was also investigated. p-Value <0.05 was considered significant.

RESULTS

Various parameters that were evaluated from renal Ultrasound and Doppler in sample population are tabulated in Table 1.

The average renal length was 98.90 +/- 4.3 mm, 104.40 +/- 3.6 mm, and 108.30 +/- 3.9 mm respectively in pre transplant period, 1-week post-transplant, and 1-year post-transplant period. There was a significant increase in renal length just 1-week post-transplant (average increase, 5.50 +/- 6.1 mm, P <.0001). During the 1-year post-transplant period assessment, the renal length continued to increase, at a much slower rate 1-year after transplantation in contrast with 1-week post-transplant and the change in parameter was not significant. A similar pattern of changes was observed for anterior- posterior and parenchymal thickness parameters. The corresponding values in three intervals and their P values are tabulated in Table 1.

The average values for RI and S.Cr are tabulated in Table 1. The RI 1-week post-transplant (P = 0.121). And at 1-year post transplant, (P = 0.920) was not significant; and again, the difference between 1-week values and 1-year values was not significant (P =.797). The S.Cr levels 1-year post-transplant was significantly lower than 1-week pre transplant (P =.002, paired t-test). The 1-year S.Cr level inversely correlated with an increase in the renal length (r = - 0.432, P =.045), anterior-posterior diameter and parenchymal thickness (r = - 0.473, P =.017) of allograft recipient kidney 1-week post-transplant. No significant correlation was noted between RI (0.68 +/- 0.07) and S.Cr or RI and kidney size changes.

DISCUSSION

Successful Long-term Recipient allograft survival is predicted by multiple factors, which includes the host immune response to the allograft and represents a most important component. Other factors include, non-immune factors which affect allograft function, which include hypertension, freshly detected Diabetes mellitus post-transplant, Dyslipidaemia, and renal toxicity due to immunosuppressive drugs. One more important component that predicts renal allograft survival is the graft size (GS), which represents functional mass of allograft kidney.

In renal allograft recipients, evaluation of GS is done based on measurement of kidney length, volume or parenchymal thickness and can be done by 2-dimensional ultrasonography (US), as it is easily available bedside and easy operability by the operator with no radiations or any contrast related complications. Emamian[13] et al demonstrated that renal length in all adult volunteers predicted least observer variability as opposed to measurements of parenchymal thickness & volumetric estimations and implied that length measurement is the parameter to be considered as opposed to volume estimation.

Standard Ultrasound and Doppler examinations of the renal allograft were done to identify variations of GS over a time period and would assist the nephrologist/urologist to predict the management of renal allograft transplant recipient with an intention to determine patients at elevated risk of graft dysfunction and graft failure over a time period.

We identified a significant increase in renal size (Including length, anterior-posterior diameter, and parenchymal thickness) in (1-week) post-transplant period. This parameter correlated significantly with S.Cr 1-year post-transplant indicating that as GS increases, it translates into a better graft function outcome. Similar outcomes were noted in previous studies by various authors.[14-17] In one of the study only 2 patients had a decrease in renal size, which had higher post-transplant S.Cr (2.2 and 2.6 mg/dL, respectively at 1 week) levels & an increase in size with decrease in S.Cr at 1 year post transplant, Which finally translated to delayed allograft function. The mean RI 1-year post-transplant was 0.50 - 0.80 & findings of Mean RI values did no significantly vary between the 1 week and 1-year post transplant.

Our study correlated well with results by A Mohammadi[18] et al. we noticed significant correlation between early increase in renal allograft size immediately post transplantation and 1-year graft function which was depicted as lower serum creatinine levels after 1-year post transplant.

But, the association was not significant between renal allograft size and RI and also between RI with serum creatinine. Accordingly, in our study, increasing number of renal allo graft recipients showed near-normal graft function (S.Cr < 1.5mg/dl) at 1 year.

Radermacher[10] et al. reported that renal arterial RI -0.8 at least 3 months post-transplant was predictive of a combined endpoint including a decrease of 50% or more in creatinine clearance, allograft failure, or death. Our study implied that, 20% of the patients had an RI of 80% or more, with an unexpectedly high rates of elevated RI. Also, only 2 patients had RI -80% at 1 week and 1-year post-transplant. Saracino[19] et al showed concordant results with our results in the fact that the median RI was 63% in their study. Thus, a very high cut-off, if predictive of graft loss, is probably not relevant because it identifies only a small subset of patients. A significant change in RI can be an indicator for histologic evaluation of the transplant kidney and/or associated further therapeutic intervention. Implying, Doppler RIs can be an early marker of intra graft vascular damage.

CONCLUSIONS

There is a significant correlation between early increase in graft size at 1 week and 1-year post transplant graft function with a larger increase in graft size at 1-week post transplantation more often associated with lower S.Cr level 1-year post transplant. There was no association between kidney size and RI (range, 0.5 to 0.8) 1-week and 1-year post-transplant & between RI (range, 0.5 to 0.8) 1-week post-transplant and S.Cr (range, 0.5 to 1.5 mg/dL) 1-year post transplant. Further studies prospectively with larger sample size are needed to confirm the same. Other associated pre op and peri operative parameters are also to be considered for predicting better outcome of success of renal transplantation which are to be addressed in the future studies.

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