Correlation between Sonoelastography and Histopathological Findings in Evaluation of Chronic Renal Allograft Disease

Bhandari RM,[1] Suwal S,[2] Chataut D,[2] Ansari MA[2]

[1]Department of Radiology,

Post Graduate Institute of Medical Education and Research,

Chandigarh, India.

[2]Department of Radiology and Imaging,

Tribhuvan University Teaching Hospital,

Kathmandu, Nepal.

Corresponding Author

Sundar Suwal

Department of Radiology and Imaging,

Tribhuvan University Teaching Hospital,

Institute of Medicine, Maharajgunj,

Kathmandu, Nepal

E-mail: sundarsuwal@iom.edu.np

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ABSTRACT

Background

Non-invasive evaluation tool for allograft kidney is important to predict chronic allograft dysfunction as it can be alternative to the invasive biopsy which is prone to so many complications. Sonoelastography can assess the stiffness of the allograft renal parenchyma, which is prone to undergo interstitial fibrosis.

Objective

To correlate sonoelastography with histopathology findings in the renal allografts.

Method

Sonoelastography was done in 60 renal allograft recipients prior to their biopsy for various indications. Estimated glomerular filtration rate (eGFR) of the patient were also obtained. Histopathology reports were collected to determine Banff score of interstitial fibrosis. Descriptive measurements (Mean ± standard deviation, Frequencies, Proportions) were calculated. Correlations among the variables were measured using Pearson's correlation, independent sample t-test, and ANOVA.

Result

The mean strain index (SI) was lower in higher grades of fibrosis. There was significant difference in mean SI ($F=18.264$; $df= 2,57$; $p < 0.001$) among the histological grades of fibrosis. Also a significant difference in SI among mild and moderate (S.E. 0.27, p value < 0.001), mild and severe (S.E. 0.213, p value < 0.001) as well as moderate and severe fibrosis (S.E. 0.244, p value < 0.001) was seen. Significant correlation of eGFR with SI ($p < 0.001$) was also seen.

Conclusion

Strain index, measured with sonoelastography, significantly correlated with different grades of tissue fibrosis. Thus it can be used as alternative method for evaluation of renal allograft patients to avoid complications of biopsy.

KEY WORDS

Allograft biopsy, Complications, Interstitial fibrosis, Renal allograft, Strain index

INTRODUCTION

Chronic allograft dysfunction, previously named chronic allograft nephropathy, is a multifactorial process associated with progressive interstitial fibrosis and tubular atrophy and fibrosis is the final outcome of various types of injury.[1] Interstitial fibrosis and arteriolar hyalinosis lead to progressive glomerular sclerosis which causes a decline in glomerular filtration rate. Biochemical changes usually occurs late in the course of chronic allograft dysfunction. Thus, relying solely on biochemical parameters for identification of at risk renal allografts can delay the measures to prevent the graft loss. Histopathology is the gold standard for diagnosis of chronic allograft dysfunction, however, it is an invasive procedure prone to significant complications.[2] A reliable non-invasive method of diagnosis of the allograft dysfunction, which can early predict the deteriorating renal function, can be helpful in avoiding the complications associated with the invasive allograft renal biopsy.

Sonoelastography, a technique that can render the tissue as elastic or stiff, is a safe and non-invasive method for evaluation of the renal allograft. Since, tissue fibrosis is the pathologic endpoint of any chronic disease process, it will make the tissue more stiff, which can be evaluated with sonoelastography.[3,4] The aim of this study was to find role of sonoelastography in predicting grade of fibrosis in the renal allograft.

METHODS

Hospital based prospective quantitative study done in 60 patients referred for renal allograft biopsy (protocol biopsies and for other indications) between November 2018 to November 2019 after obtaining ethical clearance from Institutional Review Board of Institute of Medicine. Patients with ascites and under dialysis were excluded from the study. An informed consent was taken from all the study participants who met the inclusion criteria. Patient's demographics and estimated glomerular filtration rate (eGFR) were collected. Then they underwent routine ultrasonographic evaluation of the allograft kidney with 1-5 MHz curved transducer. Subsequently a high frequency 5-13 MHz linear transducer was used for the assessment of elastographic strain index (SI) of the allograft.

Gray scale sonographic morphology of the graft kidney (length, cortical thickness, parenchymal echotexture and corticomedullary differentiation) were recorded.

For the elastographic evaluation the transducer was positioned over the region of interest. Three different sites were evaluated with elastography box (medium, lower and upper pole). Three samplings were performed one each for upper, middle and lower pole of the kidney for a total of three measurements. A numerical value of elasticity strain index from each measurement was obtained and the average value recorded.

Following diagnostic evaluation including elastography, the renal biopsy was performed under ultrasound guidance. The final histopathological report of the biopsy sample was collected and the Banff grading of the allograft interstitial fibrosis was recorded.

All the collected data were entered in Microsoft Excel and Statistical Package of Social Services (SPSS) IBM version 23 for data analysis. The quantitative data were reported using mean and standard deviation (Mean ± SD) and categorical variables in frequency and proportions. Analytical statistics was performed using independent sample "t" test, Analysis of Variance (ANOVA) and Pearson's Correlation (r), and chi-square. P value < 0.05 was considered statistically significant.

RESULTS

A total of 60 patients with age range of 18 years to 59 years were included in the study who met the inclusion criteria. Mean eGFR was 75.23 ± 25.45 ml/min/1.73 m^2, with eight patients having eGFR of < 50 ml/min/1.73 m^2.

Increased renal parenchymal echotexture was seen in 36 patients, among them 10 had Grade II and four had Grade III increased parenchymal echotexture. Corticomedullary differentiation was poorly maintained in 11 patients and not maintained in three patients. Mean allograft renal length was 10.12 ± 0.88 cm with range of 8.2 cm to 11.7 cm. Cortical thickness ranged from 6.4 mm to 15.2 mm with mean cortical thickness of 9.3 ± 1.87 mm (Table 1).

Table 1. Distribution of patients by grades of renal parenchymal echotexture, corticomedullary differentiation and fibrosis (histopathology) (n=60)

		Frequency	Percentage
Renal parenchymal echotexture	Grade 0	24	40.0
	Grade I	22	36.7
	Grade II	10	16.7
	Grade III	4	6.7
CMD	Grade I (maintained)	46	76.7
	Grade II (poorly maintained)	11	18.3
	Grade III (not maintained)	3	5.0
Fibrosis (Banff Grade)	Grade I	43	71.7
	Grade II	13	21.7
	Grade III	4	6.7

The mean strain index of the sample was found to be 3.08 ± 1.33. The mean SI in the two eGFR categories > 50 ml/min/1.73 m^2 and < 50 ml/min/1.73 m^2 were 3.33 ± 1.22 and 1.45 ± 0.78 respectively. There was a significant difference in SI among the eGFR categories > 50 and < 50

Table 2. Correlation between Strain index and eGFR (n=60)

	EGFR (ml/min/1.73 m²)	N	Mean	SD	t	df	Sig. (2-tailed)	95% CI	
								Lower	Upper
Strain Index	< 50	8	1.4513	0.7881				-2.7856	-0.9857
	> 50	52	3.3369	1.2282	-4.194	58	0.000	-2.7856	-0.9857

ml/min/1.73 m² (t= 4.194, df=58, p=0.000) (Table 2). There was a significant moderate correlation between eGFR and SI (r=0.416, p=0.001).

Pearson correlation between Mean SI and Mean Cortical thickness was observed to be r = -0.026 with p value of 0.841. There was almost no correlation between SI and both cortical thickness (p= 0.841) and renal length (p= 0.098) of the allografts (Table 3).

All the renal allografts biopsied had at least some grade of fibrosis, however most (43) had mild degree of fibrosis (< 25%). Four patients had severe (> 50%) fibrosis (Table 4).

There was a significant difference in mean SI among the histological grades of fibrosis (F=18.264; df=2,57; p < 0.001) (Table 4). Among the histological grades of fibrosis, there was a significant difference in SI among mild and moderate (S.E. 0.27, p value < 0.001), mild and severe (S.E. 0.213, p value < 0.001) as well as moderate and severe (S.E. 0.244, p value < 0.001). The mean SI was found to be lower in higher grades of fibrosis.

Table 3. Correlation between mean SI, mean RL and mean CT (n=60)

	Variables	SI	RI	RL (cm)	CT (mm)
SI	Pearson correlation	1	-.533**	.215	-.026
	Sig. (2-tailed)		.000	.098	.841
	N	60	60	60	60
RL (cm)	Pearson Correlation	.215	-.397**	1	.090
	Sig. (2-tailed)	.098	.002		.496
	N	60	60	60	60
CT (mm)	Pearson Correlation	-.026	.033	.090	1
	Sig. (2-tailed)	.841	.799	.496	
	N	60	60	60	60

Table 4. Correlation between Histological grade of fibrosis and SI (n=60)

Histological grades	N	Mean SI	Std. Deviation	Variance	Sum of squares	df	F	Sig.
Mild fibrosis (< 25%)	43	3.5751	1.16731	Between Grades of Fibrosis	41.375	2	18.264	0.000
Moderate fibrosis (25-50%)	13	2.1477	.77288	Within Grades of fibrosis	64.563	57		
Severe fibrosis (> 50%)	4	.8700	.23495					
Total	60	3.0855	1.33999		105.938			

DISCUSSION

Ultrasonography has been the most common imaging modality for the evaluation of renal allograft recipients. Sonoelastography is now available in several commercially available ultrasound systems which is showing its promise to be clinically valuable for many organs. It provides an estimation of tissue stiffness by measuring the degree of distortion under the application of an external force.[5] Elastographic estimates of renal elasticity are lower in patients with chronic allograft nephropathy.[6] Renal fibrosis is a plausible explanation for the observed difference in elasticity index.[7]

In our study, the mean SI in the two eGFR categories > 50 ml/min/1.73 m² and < 50 ml/min/1.73 m² were 3.33 ± 1.22 and 1.45 ± 0.78 respectively. There was a significant difference in SI among the eGFR categories > 50 and < 50 ml/min/1.73 m² (t= 4.194, df=58, p < 0.01). The elasticity was found to be decreased and thus the stiffness increased with decrease in eGFR, which suggests allograft renal parenchymal elasticity can reflect the renal function. This was in concordance with the results of the separate studies done by Arndt et al., He et al., Lukenda et al. and Ghonge et al.[8-11] Arndt et al. found the stiffness values of patients with an eGFR > 50 ml/min significantly lower than in patients with an eGFR ≤ 50 ml/min (22.2 ± 11.0 vs. 37.1 ± 14.2 kPa, P = 0.0005).[8] He et al. found elasticity index more strongly correlated with eGFR than was RI (r = –0.657 vs. r = –0.429, both p < 0.0001).[9] Lukenda et al. found that the renal allograft stiffness was highly negatively correlated with eGFR (r = -0.640; p < 0.0001).[10] Also, they found that the renal allograft stiffness showed a statistically significant difference between patients who had an eGFR > 50 ml/ min per 1.73 m² and patients with eGFR < 50 ml/min per 1.73 m² (28 ± 2.7 vs. 33.9 ± 5.5 kPa; p = 0.0003).[10] The study done by Ghonge et al. in 60 allograft renal transplant patient found the inverse correlation of parenchymal stiffness with eGFR (r = −0.725; P < .001).[11] However, the study done by

Ozkan et al. did not show a significant correlation between parenchymal stiffness and eGFR (r: –0.12, p = 0.42).[12]

There was no correlation between SI with CT and RL of the renal allograft in our study (r = -0.026, p = 0.841; and r-0.215, p= 0.098 respectively). No literature was available comparing the SI with CT in renal allograft. No statistically significant differences were observed between correlations of kidney volume and stiffness as well in a study done by He et al., however this study compared kidney volume rather than renal length with stiffness.[9]

There was a significant difference in mean SI among the histological grades of fibrosis (p < 0.001) as well as a significant difference in SI among mild with moderate and severe fibrosis (p value < 0.001); and moderate with severe fibrosis (p value <0.001). The mean SI was found to be lower in higher grades of fibrosis, which suggests higher the percentage of renal interstitial fibrosis the more stiffer will be the renal parenchyma. Arndt et al. found similar correlation between the degree of interstitial fibrosis and stiffness (r= 0.67, p= 0.002).[8] Also the stiffness values of CAI Banff grades 0–1 differed significantly from grade 2 (p= 0.008) and grade 3 (p= 0.046).[8] Gao et al. found the renal cortical strain to be strongly correlated to the grade of renal cortical fibrosis and elasticity to be decreasing with increasing renal cortical fibrosis.[13] Lukenda et al. found there was a highly positive correlation between renal allograft stiffness and extent of interstitial fibrosis on renal biopsy (r= 0.727; p < 0.001).[10] Orlacchio et al. showed inverse correlation between Tissue Mean Elasticity (TME) values and the degree of fibrosis (p < 0.05).[6] Patients with grade 1 fibrosis had mean TME values significantly higher compared with TME in patients with grade 2 fibrosis (p = 0.005) and grade 3 fibrosis (p = 0.004).[6] All the studies mentioned above showed concordance with the findings of our study.

We didn't include acute allograft dysfunction in our study. Interstitial fibrosis and tissue stiffness changes may not be same in acute and chronic allograft dysfunction. The skin and subcutaneous tissue thickness is known to increase the error of the elastographic measurement of the renal allograft which was not considered in our case and this could be one of the limitations of our study. Again the ultrasonography including sonoelastography was done in single setting by single person, thus intra-observer and inter-observer variation could not be determined.

CONCLUSION

Tissue stiffness, as shown by the sonoelastography, was more in patients with the renal allograft dysfunction. Even, there was significant difference in tissue stiffness in different grades of fibrosis in these patients. Thus, Sonoelastography is a reliable non-invasive imaging modality for predicting chronic allograft dysfunction, which can help clinicians for opting preventive measures in at risk allograft kidneys. This can be even more helpful in renal allograft patients needing frequent evaluation as frequent invasive biopsy may not be feasible in them.

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