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FULL PAPER

Non-invasive evaluation of stable renal allograft function using point shear-wave elastography

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Objective: To investigate the feasibility of point shear-wave elastography (SWE) in evaluating patients with stable renal allograft function who underwent protocol biopsies.

Methods: 95 patients with stable renal allograft function that underwent ultrasound-guided biopsies at predefined time points (10 days or 1 year after transplantation) were enrolled. Ultrasound and point SWE examinations were performed immediately before protocol biopsies. Patients were categorized into two groups: subclinical rejection (SCR) and non-SCR. Tissue elasticity (kPa) on SWE was measured in the cortex of all renal allografts.

Results: SCR was pathologically confirmed in 34 patients. Tissue elasticity of the SCR group (31.0 kPa) was significantly greater than that of the non-SCR

group (24.5 kPa) ($p = 0.016$), while resistive index value did not show a significant difference between the two groups ($p = 0.112$). Tissue elasticity in renal allografts demonstrated significantly moderate negative correlation with estimated glomerular filtration rate (correlation coefficient = -0.604 , $p < 0.001$). Tissue elasticity was not independent factor for SCR prediction on multivariate analysis.

Conclusion: As a non-invasive tool, point SWE appears feasible in distinguishing between patients with SCR and without SCR in stable functioning renal allografts. Moreover, it may demonstrate the functional state of renal allografts.

Advances in knowledge: On point SWE, SCR has greater tissue elasticity than non-SCR.

INTRODUCTION

Renal allograft biopsy is typically performed if acute allograft dysfunction is present. However, acute rejection episodes and chronic allograft nephropathy may be subclinical without a definite measurable decrease in renal graft function.¹ Recently, protocol graft biopsy, which is performed during the first year post-transplantation regardless of graft function, has been recommended as a clinically useful tool; it allows for early identification of acute rejection or chronic allograft nephropathy, when patients may still have options for treatment.^{2,3} However, protocol biopsy is invasive procedure, although it has a low risk of complications.⁴

Subclinical rejection (SCR) is the appearance of histological signs of acute rejection in patients with stable functioning renal graft, with reported incidence of up to 30% in protocol biopsy performed in the first 6 months post-transplantation.^{1,5,6} Furthermore, persistent, unrecognized inflammatory injury of the renal allograft owing to a low-grade

rejection process may lead to long-term graft fibrosis and chronic dysfunction in the absence of episodes of overt clinical rejection.⁷ Thus, early detection of SCR using a non-invasive imaging tool may offer promising opportunity for clinical decision making, particularly for patients during outpatient follow-up.

As a non-invasive method, ultrasound has been widely used for the evaluation of renal allograft status without radiation exposure to recipients. The resistive index (RI) on colour Doppler ultrasound has been used in the early diagnosis of acute allograft rejection, but the utility of the RI is still controversial in predicting acute rejection because conflicted results have been reported.^{8,9}

Recently, ultrasound elastography that can measure tissue elasticity has been integrated into the conventional ultrasound instrument. Unlike transient elastography with a one-dimensional shear-wave technology that lack B-mode imaging, two-dimensional shear-wave elastography (SWE) based on acoustic radiation force impulse (ARFI)

quantitatively assesses tissue elasticity by allowing B-mode ultrasound guidance. Of the two-dimensional SWE techniques, point SWE as a more recent technology offer either an average shear wave speed within the tissue of region of interest (ROI) or an image.^{10,11} SWE has emerged as an important tool in the diagnosis and follow-up of liver fibrosis and cirrhosis because it is tolerable, accurate and reproducible.^{12,13} In addition, several recent studies have reported the results of SWE in evaluating renal allograft fibrosis.^{14–18} To our knowledge, no studies have reported the utility of point SWE in evaluating SCR in patients with stable functioning renal allograft. Therefore, the purpose of our study was to retrospectively investigate the feasibility of point SWE in evaluating patients with stable renal allograft function who underwent protocol biopsies.

METHODS AND MATERIALS

Patients

Our institutional review board approved this retrospective study and waived the requirement for informed consent. From March 2013 to February 2015, 95 consecutive patients (59 males and 36 females) with stable renal allograft function, who were treated with immunosuppressive drugs and underwent ultrasound-guided protocol biopsy at predefined time points (10 days or 1 year after transplantation) were enrolled in this study. All patients had received quadruple immunosuppressive therapy for kidney transplantation: induction agents (antithymocyte globulin or thymoglobulin), steroids (methylprednisolone), mycophenolate mofetil and cyclosporine or tacrolimus. The mean age was 48.3 ± 11.75 years (range, 21–73 years). Patients presenting with perirenal fluid collections with marked compression, hydronephrosis or radiologically significant renal artery stenosis were excluded in our study because they might affect RI value and tissue elasticity values on ultrasound.

Ultrasound examination and ARFI-based elastography

All ultrasound examinations were performed for each patient in the same session with ARFI-based elastography measurements by a commercial scanner using a convex C5–1 probe (ElastoPQ, iU22; Philips Healthcare, Best, Netherlands). The patients were instructed to fast for approximately 6–8 h before the biopsy. The scanning was performed with the patients in supine position. On greyscale ultrasound examination, the length, echogenicity and presence of hydronephrosis, stone or tumour in renal allografts were evaluated. On colour Doppler ultrasound examination, the RI value (peak systolic velocity–diastolic velocity/peak systolic velocity) was measured at least three times (upper pole, lower pole and midportion) at the level of the interlobar artery of the renal allograft; the average RI value was recorded.

Immediately after greyscale and colour Doppler ultrasound examinations, tissue elasticity of the renal allograft was measured using point SWE. Point SWE is a recent feature of ARFI-based imaging and has the advantage of being incorporated into high-end ultrasound equipment. It allows greyscale ultrasound guidance of elastography measurements and an integration of tissue elasticity measurements with a full evaluation of the tissue. The principle of point SWE is briefly summarized as the

following: focused acoustic radiation force “pushing” pulses of high amplitude sound energy are used to develop shear waves within the tissue of a specified ROI, and the speed of the shear waves propagating outward through the pushing location is calculated. The results can be reported as either an average value within an ROI (*i.e.* point measurement) or as an image. It is expressed as either shear wave speed (m/s) or converted to elastic modulus (kPa).

During ARFI quantification, the probe was adjusted to obtain sufficient pressure-free contact with each patient's body. The rectangular ROI (box with fixed dimensions of 1 cm length and 0.5 cm width) was positioned in the cortex of the renal allograft excluding the medulla (Figure 1). The results were expressed as the means of Young's modulus values (kPa) using an equation¹⁰: Young's modulus (E) = $3\rho c_s^2$ (ρ = density and c_s = shear wave speed (m/s)). To minimize motion artefacts, the patient was guided through breath-holding of 5 s or less during point SWE acquisition. At least six ARFI measurements were performed in each renal allograft (upper pole, midportion and lower pole) and the results were averaged. The acquisitions were performed during separate breath-holdings in the same area. All measurements were performed by one of two genitourinary radiologists (CKK and JJP, with 10 years and 2 years of experience on renal biopsy, respectively) blinded to the patients' clinical and laboratory information, except to the fact that the patients received renal transplantation.

Protocol allograft biopsy

All patients had stable renal allograft function throughout the study period and at the time of protocol biopsies. Stable allograft function was defined as serum creatinine ≤ 1.5 mg dl⁻¹ and $\leq 15\%$ increase in serum creatinine in 2 weeks before biopsy to exclude clinical rejection at the time of biopsy. The biopsy was performed at 10 days or 1 year after transplantation by one of the two genitourinary radiologists using an 18-gauge needle (SHS- 1815G, M.I.Tech, Seoul, Korea) under ultrasound guidance. Three or four cores were obtained at each biopsy. Immediately before the biopsy, all quantitative ultrasound variables were measured.

Figure 1. Ultrasound ARFI quantification measurement in renal allograft. The ROI is positioned in the cortex and measured tissue elasticity is 56.26 kPa. ARFI, acoustic radiation force impulse; ROI, region of interest.

Blood and pathological examinations

Blood samples were obtained on the day of ultrasound examination; investigations included routine blood and renal function tests. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease Study equation: $\text{eGFR} = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$, from which the result is multiplied by 0.742 for female patients.¹⁹

Histological examinations for obtained cores were performed by a renal pathologist with 13 years of experience using the Banff 2007 classification.²⁰

Statistical analysis

The results of quantitative variables in patients with stable allograft function were expressed as means $\pm$ SD. Using biopsy results, the patients were divided into two groups: patients with SCR and without SCR. The clinical and imaging variables were compared between the two groups using the Student's *t*-test or Fisher exact test.

The correlation between eGFR and several clinical or imaging variables including tissue elasticity was evaluated in all patients by Pearson or Spearman rank correlation: strong correlation, correlation coefficient > 0.75 ; moderate correlation, $0.4 \leq$ correlation coefficient ≤ 0.75 ; and poor correlation, correlation coefficient < 0.4 .

The diagnostic performance of the variables to distinguish between the two groups was evaluated using a receiver operating characteristic (ROC) curve analysis. Tissue elasticity and eGFR for each subtype of acute allograft rejection were compared using one-way analysis of variance, and acute antibody-mediated rejection was excluded in this analysis because of one case.

Univariate and multivariate logistic regression analyses were used to determine the independent predictors of SCR. The variables with *p*-value < 0.1 on univariate analysis were further analysed using multivariate analysis; tissue elasticity and RI values were dichotomized as follows: < 26.07 vs ≥ 26.07 for tissue elasticity and < 0.7 vs ≥ 0.7 for RI. The statistical analyses were performed using PASW statistical software (v. 22.0, SPSS, Inc., Chicago, IL, USA). A two-sided value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Among all 95 patients with stable allograft function, 34 had SCR and pathological characteristics of acute rejection: borderline ($n = 19$), grade IA ($n = 10$), grade IB ($n = 4$) and antibody-mediated rejection ($n = 1$). Table 1 presents the characteristics of patients with and without SCR. Tissue elasticity of renal allografts was significantly greater in patients with SCR than in patients without SCR ($p = 0.016$), while RI value of renal allografts was not significantly different between the two groups ($p = 0.112$). Among clinical variables, age, body mass index (BMI), protocol biopsy time, creatinine and eGFR showed significant differences between the two groups (all $p < 0.05$).

Regarding the relationship with eGFR (Figure 2), tissue elasticity showed significantly moderate negative correlation (correlation coefficient = -0.603 , $p < 0.001$) and was the best correlation among the variables. The RI value had significantly poor negative correlation with eGFR (correlation coefficient = -0.344 , $p = 0.001$). The renal size revealed significantly poor positive correlation with eGFR (correlation coefficient = 0.212 , $p = 0.039$). However, age, body weight, BMI and height did not show significant correlation with eGFR ($p = 0.080$, 0.266 , 0.744 and 0.061 , respectively).

At ROC curve analysis for predicting the SCR in patients with stable renal allograft function, the diagnostic performance of the variables is shown in Table 2. The areas under the ROC curve (AUC) of eGFR, tissue elasticity, BMI, age and RI were 0.728 , 0.649 , 0.644 , 0.639 and 0.605 , respectively, and there were no significant differences in pairwise comparisons (all $p > 0.05$). With an optimal cut-off value of tissue elasticity > 26.07 kPa, the sensitivity and specificity were 70.6% and 62.3% , respectively.

On univariate analysis, age, BMI, eGFR and tissue elasticity were significantly associated with SCR prediction (all $p < 0.05$). However, multivariate analysis showed that eGFR [odds ratio (OR) = 0.96 , $p = 0.020$], and BMI (OR = 1.20 , $p = 0.021$) were significantly independent predictors of SCR (Table 3). Tissue elasticity on SWE was not significantly independent predictor of SCR (OR = 1.47 , $p = 0.317$).

In each histological subtype of acute allograft rejection, no significant differences were found for tissue elasticity ($p = 0.778$) and eGFR ($p = 0.576$).

DISCUSSION

Although ARFI-based ultrasound elastography has been investigated for the evaluation of histological features of renal allograft after transplantation, published studies are scarce.^{18,21} In particular, to date, there have been no studies on the feasibility or utility of point SWE in predicting SCR in patients with stable renal allograft function followed by protocol biopsy. In our results, tissue elasticity quantified using point SWE was significantly different between SCR and non-SCR groups in patients with stable renal allograft function, followed by protocol biopsy at 10 days or 1 year after transplantation. Furthermore, quantitative measurements of tissue elasticity on point SWE demonstrated the second best diagnostic accuracy for predicting the presence of SCR in patients with stable renal allograft function. These findings indicate that point SWE, a non-invasive method, may provide the opportunity to quantify tissue elasticity in renal allograft as well as to predict SCR in patients with stable functioning allograft.

In our study, tissue elasticity of renal allograft with SCR on point SWE was significantly higher than that of renal allograft without SCR. The results were in line with several previous studies.^{18,21} These findings might be explained with the edema, interstitial fibrosis or glomerular sclerosis that are present in renal allografts with SCR, possibly resulting in increased tissue stiffness.²²

Table 1. Characteristics of patient with stable renal allograft function

Variable	SCR	Non-SCR	<i>p</i> -value ^a
Number of patients	34	61	
Sex			0.509
Male	23	36	
Female	11	25	
Age (year)	52.2 ± 11.7	46.2 ± 11.3	0.017
Weight (kg)	63.8 ± 11.9	58.7 ± 13.4	0.066
BMI (kg m ⁻²)	23.3 ± 3.5	21.6 ± 3.5	0.027
Donor			0.366
Living-related	25	38	
Cadaveric	9	23	
Post-transplantation time at ultrasound (days)	191.2 ± 198.6	66.7 ± 141.5	0.002
Protocol biopsy time			0.001
10 days	18	52	
1 year	16	9	
Histological subtype (Banff 2007)			
Acute cellular rejection, borderline	19		
Acute cellular rejection, grade IA	10		
Acute cellular rejection, grade IB	4		
Acute antibody-mediated rejection	1		
Laboratory			
BUN	20.1 ± 9.7	18.4 ± 5.5	0.262
Creatinine (mg dl ⁻¹)	1.27 ± 0.3	1.07 ± 0.3	0.003
eGFR (ml/min/1.73 m ²)	57.6 ± 13.5	71.5 ± 18.1	<0.001
Ultrasound findings			
Renal size (cm)	11.3 ± 1.2	10.8 ± 1.1	0.048
Resistive index	0.72 ± 0.06	0.69 ± 0.06	0.112
Tissue elasticity (kPa)	31.0 ± 12.8	24.5 ± 12.2	0.016

BMI, body mass index; BUN, Blood urea nitrogen; eGFR, estimated glomerular filtration rate; SCR, subclinical rejection.

Data are presented as mean ± SD.

^a*p*-value: statistical comparison between SCR and non-SCR.

A recent study reported that in enrolled 102 patients (50 with stable renal allograft function and 52 with renal allograft dysfunction) tissue elasticity on SWE had a moderate negative correlation with eGFR, with higher value than RI.¹⁷ In addition, SWE was found to have a sensitivity of 78.0% and specificity of 86.5% in the prediction of renal allograft dysfunction, which were higher than those of RI. Consistent with the previous study,¹⁷ our results demonstrated that tissue elasticity of stable functioning renal allografts on point SWE had a moderate negative correlation with eGFR, and was better value than other variables including RI value with poor negative correlation. These results might be attributed to presence of interstitial edema or fibrosis. However, further studies with radiological-pathological correlation are needed.

For predicting SCR in stable functioning renal allograft, our study demonstrated that tissue elasticity on point SWE was a

significant factor on univariate analysis. However, on multivariate analysis, significant independent predictors of SCR were eGFR and BMI. Tissue elasticity on point SWE was not a significant independent predictor of SCR. Additionally, tissue elasticity of each histological type of SCR was not significantly different. These findings indicate that although point SWE may potentially predict SCR in stable functioning renal allografts, tissue elasticity quantification on SWE cannot replace a renal-allograft biopsy at predefined time points to confirm the histological diagnosis. However, a further larger prospective study is necessary.

Until now, the intrarenal RI measurement on Doppler US is routinely performed to evaluate renal allografts, but the utility of RI measurement in renal allografts is controversial.^{8,9} A recent study reported that in 321 renal allograft recipients routinely measured RI at predefined time points after

Figure 2. Relationship between eGFR (ml/min/1.73 m²) and tissue elasticity (a) and RI (b). Tissue elasticity shows a moderate negative correlation with eGFR (correlation coefficient = -0.604 , $p < 0.001$), while RI reveals a poor negative correlation with eGFR (correlation coefficient = -0.344 , $p = 0.001$). eGFR, estimated glomerular filtration rate; RI, resistive index.

Table 2. Diagnostic performance of the variables in predicting SCR on ROC curve analysis

Variable	Cutoff value	Sensitivity (%)	Specificity (%)	AUC
eGFR (ml/min/1.73 m ²)	62.8	73.5	68.9	0.728
Tissue elasticity (kPa)	26.07	70.6	62.3	0.649
BMI (kg m ⁻²)	20.38	85.3	41.0	0.644
Age (year)	45	76.5	45.9	0.639
Resistive index	0.70	61.8	57.4	0.605

AUC, area under the curve; BMI, body mass index; eGFR, estimated glomerular filtration rate; ROC, receiveroperating characteristic; SCR, subclinalrejection.

transplantation, RI did not reflect characteristics of the graft.²³ Accordingly, RI on Doppler US cannot replace protocol biopsy performed at predefined timepoints to evaluate the histologic

results. Our results also revealed that RI was not significant in differentiating between SCR and non-SCR groups in

Table 3. Univariate and multivariate logistic regression analyses for evaluating the relationship with subclinal rejection

Variable	Univariate		Multivariate	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Sex	0.69 (0.29–1.66)	0.407		
Age	1.05 (1.01–1.09)	0.021	1.04 (0.99–1.09)	0.098
BMI	1.15 (1.01–1.30)	0.034	1.20 (1.03–1.14)	0.021
eGFR	0.95 (0.92–0.98)	0.001	0.96 (0.93–0.99)	0.020
RI (≤ 0.7 vs > 0.7)	2.16 (0.90–5.19)	0.085	1.47 (0.53–4.10)	0.465
Tissue elasticity (≤ 26.07 vs > 26.07 kPa)	3.55 (1.44–8.75)	0.006	1.75 (0.58–5.26)	0.317

BMI, body mass index; CI confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; RI, resistive index.

stable functioning allografts. Moreover, RI had poor diagnostic performance in predicting SCR on ROC curve analysis.

Although ARFI-based SWE technology is promising, several confounding factors affecting quantitative measurement should be considered¹⁰: depth of target, movement of target, area of ROI, transducer pressure, incident angle of acoustic beam and medium between target, probe machines or operator. Furthermore, tissue anisotropy, urinary tract obstruction and vascular perfusion abnormalities may affect SWE results.¹¹ However, SWE examination in renal allografts is easy and can obtain high-resolution images because most renal allografts are located in the iliac fossa with more superficial and consistent positions.

There are several limitations in our study. First, the number of patients was relatively small, with a retrospective design, which might have a potential selection bias. Second, the time point of protocol biopsy in our study was 10 days or 1 year after transplantation. Considering the results of a recent study that tissue elasticity of renal allografts on SWE increased continuously during the first 1 year after transplantation,¹⁶ a subanalysis for the variables might be needed for 10 days vs 1 year after transplantation. However, in our study, protocol biopsy was performed 1 year after transplantation in only 25 patients, which was a relatively small sample to perform the subanalysis. Thus, further studies

are needed to elucidate the potential role of SWE in patients with stable allograft function at predefined different time points. Third, intra- or interobserver variability for tissue elasticity quantification on point SWE was not obtained in our study. Locations of tissue elasticity measurement on SWE may affect inter- or intraobserver variability, which may be low (same location) or high (different location).^{17,24,25} To minimize variability according to the location of tissue elasticity in renal allografts, we measured tissue elasticity at least six times because we measured tissue elasticity on three different sites of renal allografts. Fourth, our results for tissue elasticity in renal allografts measured on point SWE might be different from other different SWE techniques. Further studies by different SWE techniques are needed in renal allografts. Finally, potential measurement error for tissue elasticity quantification in the cortex might exist because a fixed ROI box on point SWE might include some medullary portion in allografts. In conclusion, point SWE, as a non-invasive tool, appears to be feasible for distinguishing between patients with SCR and without SCR in stable functioning renal allografts. Moreover, it may demonstrate the functional state of renal allografts.

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