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Original Article

Correlation between ultrasound elastography parameters and renal function after kidney transplantation

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Abstract: Background: Conventional B-mode and Doppler ultrasound are inefficient at showing increased stiffness resulting from the fibrosis developing during kidney transplant rejection. Objectives: This study aims to assess the correlation between ultrasound elastography (UE) and renal function after kidney transplantation. Methods: Patients who underwent UE after renal allotransplantation at the First Affiliated Hospital of Xi'an Jiaotong University Medical School between October 2014 and March 2015 were grouped according to their serum creatinine levels: normal group (serum creatinine level < 134 μmol/L), acute rejection group (serum creatinine level > 134 μmol/L that recovered in three months), and chronic allograft nephropathy (CAN) group (serum creatinine level > 134 μmol/L sustained for > 3 months). UE was scored 1-5 points according to the kidney stiffness, and parameters were compared between groups. Results: All patients in the acute rejection and CAN groups scored at least 2 points, while 80% of the remaining patients scored ≥ 3 points. In the normal group, 93% of patients scored 1 point (the normal group *vs.* the acute rejection and CAN groups, $P < 0.05$). In the acute rejection group, the average relative strain value (MEAN) and the area ratio of low-strain ratio decreased with increasing serum creatinine levels. MEAN was highly predictive of postoperative renal function, with a sensitivity, specificity and area under the curve of 80%, 80% and 0.868, respectively; using a cut off value of 100. Conclusion: UE may reflect renal function and can be a non-invasive method for the evaluation of renal function after kidney transplantation.

Keywords: Ultrasonography, renal transplantation, elastography imaging technique

Introduction

Renal transplantation would eventually have to be considered for all patients with end-stage renal disease (ESRD) according to medical and surgical grounds [1]. However, the risk of acute postoperative renal allograft rejection is high, with 40-80% of patients manifesting oliguria, hyperthermia, water and sodium retention, hypertension and transplant renal enlargement/hardening/tenderness; ultimately resulting in kidney graft loss [2-4]. The prognosis may be drastically improved in > 90% of patients if the acute rejection is identified timely and treated at its early stage, but assessment methods are not optimal [5-7].

Ultrasound is one of the main imaging modalities used to monitor kidneys after transplantation [8]. B-mode ultrasound is generally used for measuring transplant renal shape, size, hydronephrosis, and perinephric effusion; while color Doppler ultrasound is used to assess transplant renal perfusion [9-11]. Both methods provide important imaging evidence for the identification of renal graft rejection [9-11]. Nevertheless, conventional ultrasound approaches fail to reflect renal stiffness subsequent to tissue enlargement during acute rejection, and clinicians have to rely on palpation of the kidney graft to assess renal function.

In contrast, ultrasound elastography (UE) provides quantitative information on tissue elasticity distribution for the assessment of renal pathological changes, enabling the indirect evaluation of renal function changes [12, 13]. Moreover, since elasticity difference is greater than acoustic impedance difference in tissues, UE also provides diagnostic information inde-

pendent of anatomical structures and blood perfusion [14]. At the present time, the advantages of UE in the assessment of renal stiffness have continuously gained recognition [15].

However, the correlation between UE and renal function after kidney transplantation in patients with ESRD still needs to be improved. Therefore, the objective of the present study was to assess the correlation between UE and renal function in patients who underwent renal transplantation.

Materials and methods

Study design

This is a prospective cross-sectional study carried out in patients who underwent UE after kidney transplantation at the First Affiliated hospital of Xi'an Jiaotong University Medical School between October 2014 and March 2015. This study was approved by the institutional review board and informed consent was obtained from all patients.

Patients

Fifty patients who underwent renal allotransplantation were examined by UE. Inclusion criteria were: (1) preoperative diagnosis of chronic renal failure, and (2) transplant renal capsule located < 2 cm below the skin (our preliminary experiments indicated that more stable and sharper UE images were acquired). Exclusion criteria were: (1) urinary tract obstruction of the renal graft; (2) local infection; (3) severe cardiac/pulmonary disease; (4) iliac or transplant renal artery stenosis, transplant renal artery, and/or vein thrombosis; or (5) any other extrarenal factors that affect transplant renal perfusion.

Grouping

Patients were followed-up once a month for six months postoperatively. Then, interval was extended to two months after six months, and regular visits were carried out every three months from the second year postoperatively. Patients were divided into three groups according to the follow-up examination at three months: normal group (serum creatinine < 134 μmol/L), acute rejection group (serum creatinine > 134 μmol/L that subsequently recovered within three months), and chronic allograft nephropathy (CAN) group (serum creatinine > 134 μmol/L sustained for > 3 months). Serum creatinine levels were detected using a Hitachi biochemistry automatic analyzer (Hitachi Ltd., Tokyo, Japan) and the manufacturer's creatinine kit, based on the creatininase-HMMPS method.

Ultrasound elastography

Ultrasound elastography was performed at 2-3 days postoperative. Patients were placed in the supine position, with the abdominal wall of the kidney graft side fully exposed. The HI VISION Preirus ultrasound system (Hitachi Ltd., Tokyo, Japan) was used for B-mode and color Doppler ultrasound using a 2.0-5.0 MHz EUP-C715 probe. UE was performed using a 5.0-13.0 MHz EUP-L74M probe.

B-mode and color Doppler ultrasound were first performed to observe transplant renal shape, size, parenchymal echo, space occupation, collecting system, ureter dilatation, and perinephric effusion. Color Doppler ultrasonography was carried out for measurements of renal parenchymal perfusion, peak systolic velocity (PV), and resistance index (RI) of interlobar artery.

Then, UE was performed with default color scales, as follows: blue, high stiffness; green, intermediate stiffness; and red, low stiffness. After a clear display of the renal cortex and pyramid, an ultrasound probe was placed on the body's surface perpendicular to the long axis of the renal pyramid. The UE imaging software was launched and the probe was manually compressed with minor vibrations to maintain the pressure guide curve in the normal range of the elastic line. Stable images were analyzed using elastography analysis software to measure the renal medulla (B) to cortex (A) strain ratio (B/A ratio), average relative strain value (MEAN), area ratio of the low-strain region (AREA%) and complexity (COMP).

Based on UE data from breast cancers [16, 17], a five-point scoring system for kidney graft was developed: 1 point, transplant renal pyramids and cortices are green or green and red; 2 points, transplant renal pyramids and most renal cortices are green with blue dots at the periphery; 3 points, transplant renal cortices are half green and half blue, and most renal pyramids are green; 4 points, most (> 80%) of the transplant renal cortices are blue, the center of renal pyramid is blue, while the periphery

Table 1. Characteristics of the patients

	Total	Normal	Acute rejection	CAN	P
Sex (male: female)	26:24	7:8	8:7	11:9	> 0.05
Age (years)	42.3±10.3	41.5±11.1	40.6±12.4	43.4±12.6	> 0.05
Course of disease (years)	10±2.8	10±2.6	9±2.7	11±2.5	> 0.05
History of hemodialysis (years)	2.4±0.8	2.5±0.7	2.3±0.7	2.5±0.7	> 0.05

CAN: chronic allograft neuropathy.

Table 2. Elastography scores in the different groups

Group	1 point	2 points	3 points	4 points	5 points
Normal	9	5	1	0	0
Acute rejection	0	3	3	6	3
CAN	0	3	8	7	2
Serum creatinine levels (μmol/L)	86.5±32.2	143.4±63.0	208.5±85.8	223.6±83.8	250.5±126.2

CAN: chronic allograft neuropathy.

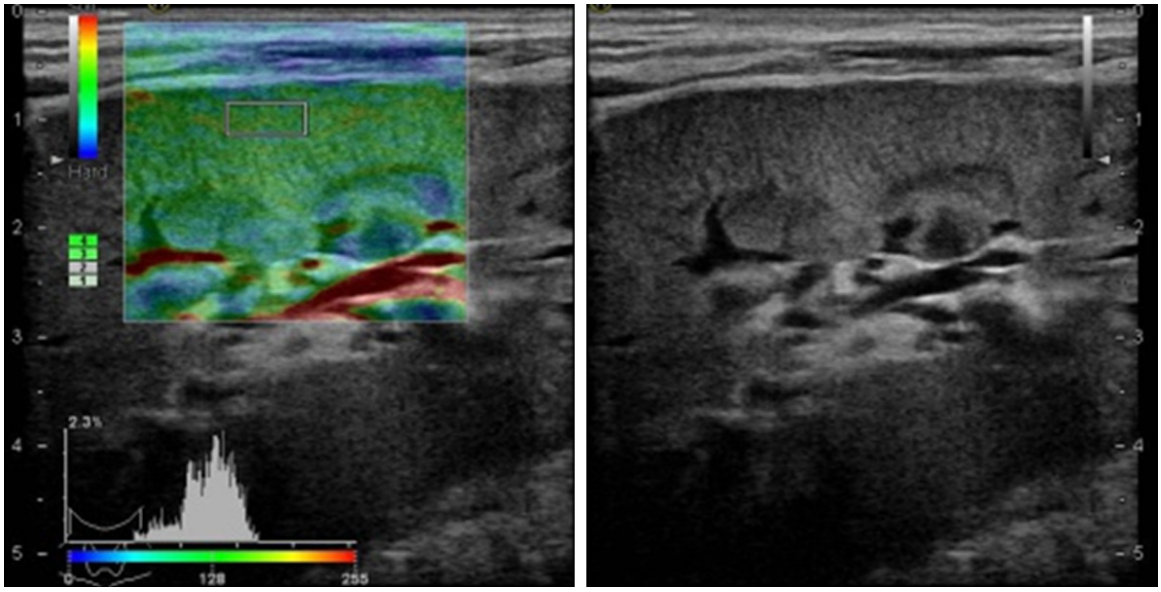

Figure 1. A representative ultrasound elastography from a patient in the normal group. Image shows that renal pyramids and cortices were uniformly green while perinephric adipose tissues and arcuate arteries were like red belts.

is green; 5 points, both transplant renal pyramids and cortices are blue. In order to avoid inter-operator difference and subjective scoring, each patient was independently scored by two radiologists who had at least five years of work experience. Discrepancies were discussed to reach a consensus.

Statistical analysis

Continuous data are expressed as mean ± standard deviation and analyzed using ANOVA with Tukey's post hoc test. Categorical variables are presented as frequencies and analyzed using the Chi-square or Fisher's exact test, as appropriate. The receiver operating characteristic (ROC) curve approach was used to determine the diagnostic value of UE. Statistical analysis was performed using SPSS 17.0 (IBM, Armonk, NY, USA). *P*-values < 0.05 were considered statistically significant.

Results

Patient characteristics

Table 1 presents the characteristics of patients. There were 26 males and 24 females, and

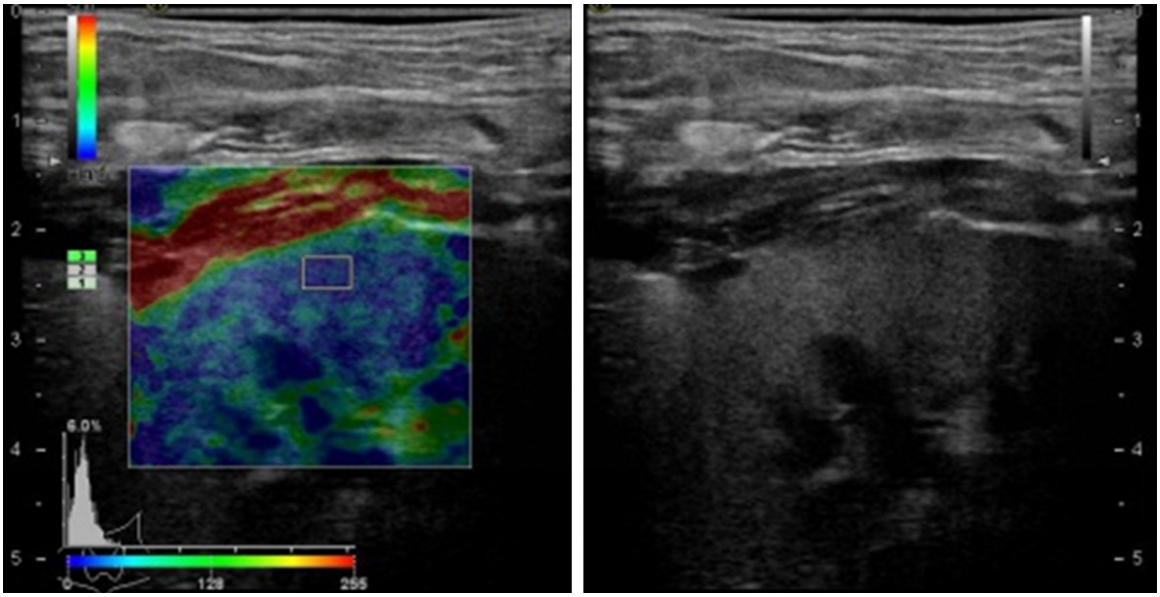

Figure 2. Representative ultrasound elastography of a patient in the CAN group. Most renal pyramids and columns are green and with blue spots scattered among them while most/all cortices are blue.

Table 3. Comparison of quantitative diffusion parameters between the different groups

	Normal	Acute rejection	CAN	*P* value
RI	0.67±0.05	0.80±0.05*	0.70±0.04#	< 0.001
B/A ratio	1.16±0.39	1.84±1.27*	2.26±1.25*	0.017
MEAN	111.1±16.0	74.5±23.4*	89.1±15.2*	< 0.001
AREA%	9.8±5.4	42.1±27.3*	24.6±13.1*,#	< 0.001
COMP	17.9±5.1	27.1±11.4*	25.7±10.1*	0.019

CAN: chronic allograft neuropathy; RI: resistance index; B/A ratio: renal to medulla to cortex strain ratio; MEAN: average relative strain; AREA%: area ratio of low-strain region; COMP: complexity. *P < 0.05 vs. the normal group. #P < 0.05 vs. the acute rejection group.

age range of the patients was 20-65 years (mean, 42.3±10.3 years). The difference in gender, age, course of disease and history of hemodialysis between these three groups was not statistically significant.

Ultrasound elastography

Table 2 presents the UE scores for each group. In the normal group, UE images revealed that renal pyramids and cortices were uniformly green, while perinephric adipose tissues and arcuate arteries were like red belts (**Figure 1**). In the acute rejection and CAN groups, most renal pyramids and columns were green with blue spots scattered among them, while most/all cortices were blue (**Figure 2**). In the acute rejection and CAN groups, all patients scored at least 2 points; and 80% of the patients scored ≥ 3 points. In the normal group, 93% of the patients scored < 2 points (the normal group *vs.* the acute rejection and CAN groups, $P < 0.05$). Serum creatinine levels increased with the score (r=0.781, $P < 0.05$).

Quantitative analysis results in the different groups are shown in **Table 3**. The acute rejection and CAN groups had significantly higher B/A ratio and cortical AREA%, but with a lower cortical MEAN value, compared with the normal group ($P < 0.05$).

Table 4 illustrates that patients in the recovery phase had lower RI, higher MEAN, lower AREA% and lower creatinine levels, than patients in the acute phase (all $P < 0.05$).

Diagnostic value of UE

Table 5 and **Figure 3** show the ROC curve analysis. Patients were presented as groups for normal *vs.* acute rejection + CAN. For a MEAN optimal cut-off value of 100, sensitivity was 80.0% and specificity was 80.0%, with an area under the curve of 0.868. For an AREA% optimal cut-off value of 19.64, sensitivity was 61.8% and specificity was 93.7%, with an area under the curve of 0.822. For a COMP optimal cut-off value of 18.25, sensitivity was 79.4% and specificity was 62.5%, with an area under the curve of 0.730.

Table 4. Comparison of resistance index, quantitative diffusion parameters, and serum creatinine levels between acute phase and recovery phase of renal graft rejection

	Acute phase	Recovery phase	*P* value
RI	0.80±0.05	0.71±0.04	< 0.001
B/A ratio	1.84±1.27	1.71±0.75	0.178
MEAN	74.53±23.44	88.78±20.61	< 0.001
%AREA	42.07±27.25	22.07±18.66	0.015
COMP	27.11±11.37	24.09±19.42	0.701
Serum creatinine level	234.13±93.66	125.09±45.11	< 0.001

RI: resistance index; B/A ratio: renal to medulla to cortex strain ratio; MEAN: average relative strain; %AREA: area ratio of low-strain region; COMP: complexity.

Table 5. ROC curve analysis of quantitative diffusion parameters

Parameter	Sensitivity (%)	Specificity (%)	Area under the curve	Cutoff
MEAN	80	80	0.868	100
AREA%	61.8	93.7	0.822	19.64
COMP	79.4	62.5	0.730	18.25

MEAN: average relative strain; AREA%: area ratio of low-strain region; COMP: complexity.

Discussion

The aim of the present study was to assess the diagnostic values of UE in the evaluation of renal function after kidney transplantation. Results revealed that all patients scored at least 2 points and 80% of the patients scored ≥ 3 points in the acute rejection and CAN groups. In the normal group, 93% of the patients scored 1 or 2 points. In the acute rejection group, MEAN and AREA% decreased with increasing serum creatinine levels. MEAN was highly predictive of postoperative renal function, with sensitivity, specificity and area under the curve of 80%, 80% and 0.868, respectively; using a cut-off value of 100.

Acute renal allograft rejection is induced by cellular immune response and manifests as transplant renal interstitial edema, bleeding and immune cell infiltration [18, 19]. If humoral immune response is subsequently activated, the patient may be further diagnosed as delayed type hypersensitivity [18, 19]. Renal cortical stiffness changes with different phases of acute rejection result in various cortical and pyramidal presentations on UE images [20, 21]. The transplant renal cortex is mainly composed of glomeruli and shows increased stiffness in response to early cellular immunity, leading to a totally/mostly blue UE image [20, 21]. The renal pyramid is mainly formed by renal tubules and interstitium, and it is not involved in early cellular immune response, but its stiffness increases in the presence of humoral immune response, displaying totally/mostly blue areas on an elastography image [20, 21].

Ultimately, the abnormal accumulation of extracellular matrices in the glomeruli and interstitium would lead to renal damage and the progressive loss of effective nephrons and renal function [18, 19]. Normally, the renal cortex has a rich blood supply, elastic vascular loop and excellent tissue compliance. Pathologically, due to atrophy of the glomerular capillary loop, thickening of the basement membrane and subsequent glomerular cirrhosis, and renal interstitial fibrosis, the kidney becomes stiff and poorly elastic [18, 19].

The present study indicated a positive correlation between serum creatinine levels and elastography scores. In other words, elastography scores indirectly reflect the renal function of patients. Since the UE score is directly derived from UE images and indicates the degree of fibrosis [20, 21], the rise in UE score might be accompanied by the transition from early cellular immune response to intermediate and late cellular and humoral immune responses. These results are supported by previous studies. Indeed, a previous study has suggested associations between serum creatinine and elasticity index [22]. Furthermore, another study has shown that the estimated glomerular filtration rate, which is calculated using creatinine levels, decreased concurrently with shear wave velocity [14]. In the present study, patients were grouped according to their serum creatinine levels, and UE images revealed uniformly green renal pyramids and cortices, as well as red-belt-like perinephric adipose tissues and arcuate arteries, in the normal group; while green and blue renal columns and cortices were observed in the acute rejection group. There-

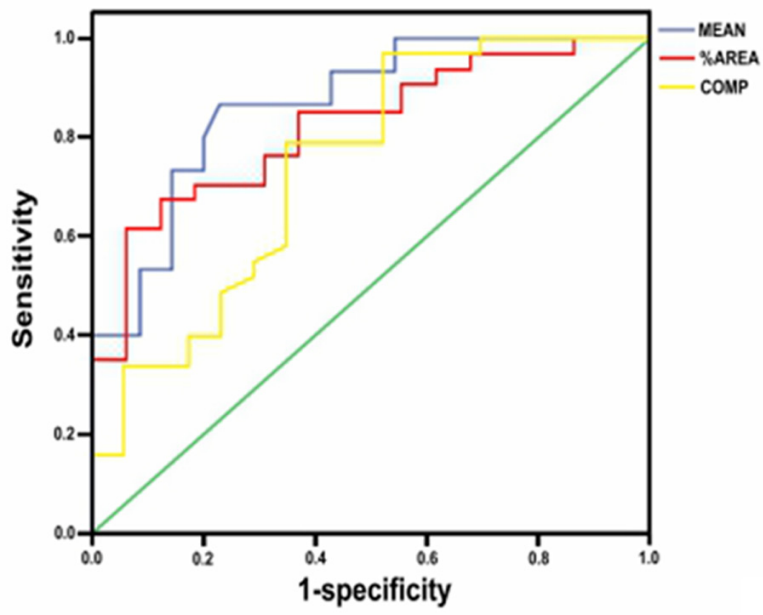

Figure 3. ROC curves for MEAN, AREA%, and COMP.

fore, transplant renal elastography scores might be related, at least to some extent, to serum creatinine levels.

Quantitative UE analysis mainly includes the 5-point semi-quantitative analysis, B/A assessment, and quantitative diffusion analysis. The 5-point method has been reported to be useful in the evaluation of solid breast lesions [17], and was adapted for kidneys in the present study. In the present study, most patients had UE scores < 2 points in the normal group, which was significantly different from the two other groups; in which the proportion of patients with ≥ 3 points was much higher. In addition, diffusion analysis of tissue stiffness displayed a lower cortical MEAN value and higher AREA% in the two other groups, compared with the normal group. The ROC curve analysis of quantitative diffusion parameters revealed that MEAN value and AREA% has high sensitivity (80%) and specificity (93.7%), respectively. However, there is a lack of study on these parameters, preventing comparisons without previous studies.

Although renal needle biopsy remains as the method of choice for the examination of renal pathologic changes, it is invasive, risky and poorly repeatable [23]. Therefore, quantitative UE analysis including the 5-point method, B/A detection and quantitative diffusion analysis may play a positive role in the evaluation of transplant renal function and may be a new simple, inexpensive and noninvasive imaging technique for the postoperative monitoring of transplant renal function.

The present study is has some limitations. Indeed, the sample size was small. In addition, UE findings were not correlated to pathological findings, since a biopsy was not performed. Multicenter studies with a larger sample size are necessary to correctly assess the diagnostic value of UE for renal function after kidney transplantation.

In conclusion, UE might reflect renal function after kidney transplantation. It could be an efficient non-invasive and inexpensive method to diagnose and monitor kidney allograft rejection.

Disclosure of conflict of interest

None.

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