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FULL PAPER

Strain wave elastography for evaluation of renal parenchyma in chronic kidney disease

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Objective: Chronic kidney disease (CKD) is an important and costly health problem in developed countries and has a tendency to progress to end-stage renal disease regardless of the aetiology. This progress ends in interstitial fibrosis, which decreases the elasticity of tissue. Elastography is a developing technique to assess tissue elasticity. The aim of this study was to determine the difference of strain index (SI) value of renal parenchyma between patients with CKD and healthy individuals. In addition, SI differences of inter-stages were studied.

Methods: Toshiba (Toshiba Medical Systems Corporation, Otawara, Japan) Aplio™ 500 ultrasound device and 3.5- to 5.0-MHz convex probe were used for the elastography examinations.

Results: A total of 58 patients with CKD from nephrology and endocrinology clinics (30 males and 28 females; mean age, 56.14 ± 11.60 years) and 40 normal healthy

individuals (19 males and 21 females; mean age, 51.70 ± 11.71 years) were included in this prospective study. The mean SI of normal healthy individuals and patients with CKD (regardless of stages) was 0.42 ± 0.30 and 1.81 ± 0.88 , respectively ($p < 0.001$). SI values were not statistically significant among the CKD stages (except CKD Stages 1 and 3). The area under the receiver operating characteristic curve was 0.956 for SI. The optimal cut-off value for the prediction of CKD was 0.935 (sensitivity, 88% and specificity, 95%).

Conclusion: SI value of sonoelastography can be used to differentiate patients with CKD and healthy individuals. Sonoelastography is an acceptable technique to approach patients with CKD, but we have not shown that it can reliably differentiate different stages.

Advances in knowledge: Determining a cut-off SI value between normal and diseased renal parenchyma can help in the diagnosis of CKD.

Chronic kidney disease (CKD) is an important and costly health problem in developed countries.^{1–3} The survival rates of patients treated with dialysis for 1, 2, 5 and 10 years are 80%, 67%, 40% and 18%, respectively.^{4,5}

CKD is defined as kidney damage of a duration of 3 months or more caused by structural or functional abnormalities with or without a decreased glomerular filtration rate (GFR) by The Kidney Disease Outcomes Quality Initiative™ (KDOQI) guidelines.⁴ CKD is categorized into five stages (Stages 1–5) according to the GFR based on the US National Kidney Foundation and the KDOQI guidelines.^{3,4}

CKD has a tendency to end-stage renal disease (ESRD) regardless of the aetiology. CKD progresses to some histological

changes such as progressive glomerulosclerosis, vascular sclerosis and tubulointerstitial injury, which encompass tubular atrophy and interstitial fibrosis.¹ Fibrosis decreases the elasticity of tissue.⁶ If we can detect the elasticity difference between normal parenchyma and CKD parenchyma, this may support the diagnosis of CKD.

Elastography is a developing technique to assess tissue elasticity. It is a software that can be integrated to the ultrasonography machines.^{1,7,8} There are different elastography techniques.^{8,9} Strain wave elastography, acoustic radiation force impulse (ARFI) imaging, shear wave elastography (SWE) and transient elastography are the different techniques. Strain wave elastography was introduced to clinical use earlier than other image-based elastography techniques, and there are studies in the literature

concerning its use in different areas such as the breast, prostate, liver, pancreas, thyroid, lymph nodes and kidney.

ARFI technique is a variant of strain wave elastography, which is stimulated by an internal ultrasound pulse rather than applying external pressure to the tissue, supplying quantitative data about the stiffness of the tissue.¹⁰ A limitation of this technique is that it cannot be used in the presence of ascites.

SWE is a technique that does not require external pressure on the tissue and supplies quantitative data. On the other hand, the production of shear waves needs a particular deepness, and the use of SWE is limited in superficial tissue.¹⁰ Also, it cannot be used in the presence of ascites.

Transient elastography, also known as vibration elastography, is a type of SWE that uses equipment applying external pressure on the tissue and is mostly used in the liver.¹⁰ However, it cannot supply sonographic image and thus cannot be used in focal liver lesions.⁹

Significant results on studies related to renal parenchymal evaluation have been obtained by using ultrasonography–elastography. However, further studies using all these ultrasonography–elastography techniques are required in order to demonstrate whether they display different results or which technique is better on the kidneys. To highlight this topic, in this study we used strain wave elastography that had already been integrated into the ultrasonography machine in our clinic.

The aim of this study was to determine the difference in strain index (SI) values of renal parenchyma between patients with CKD and healthy individuals, and SI values of CKD inter-stages were also studied.

METHODS AND MATERIALS

Informed consent form was obtained from all patients, and the study was performed in accordance with the ethical guidelines of the Helsinki Declaration and approved by the local ethics committee. No financial support was received for the present study.

In this prospective study, patients who were referred to radiology clinic from nephrology and endocrinology clinics were randomly selected. Individual healthy volunteers were selected from the hospital staff.

Toshiba (Toshiba Medical Systems Corporation, Otawara, Japan) Aplio 500 ultrasound device and 3.5- to 5.0-MHz convex probe was used for ultrasonography, colour Doppler ultrasonography (CDUS) and ultrasonography–elastography examinations.

Demographic data (age and sex), blood glucose, urine, creatinine, creatinine clearance, cholesterol, high density lipoprotein, low density lipoprotein, triglyceride, albumin, calcium, phosphorus, uric acid, Hb, haematocrit, parathormone, creatinine in urine and proteinuria (grams per day) of the patients were recorded in nephrology and endocrinology clinics.

Sonoelastography examination

After greyscale B-mode and CDUS, we activated the elastography system using “Elastography” button. We used strain wave elastography, a software that was integrated into our ultrasonography machine.

This technique is semi-static and semi-quantitative. In this technique, the operator performs compression to the adjacent area of examination. Owing to the compression, the lesion shows displacement and deformation. The software calculates the elasticity score of the lesion based on the displacement.⁹ The data unit of this technique is SI.⁹ The “strain” means the contraction or expansion of the tissue towards the direction of the compression. The operator performs compression and decompression to the tissue. The compression and decompression phases cause a sinusoidal wave. The wave and the lesion can be observed in the ultrasonography monitor. The monitor divides into three windows. The right window is greyscale ultrasonography image, the left window is colour-coded ultrasonography–elastography image and the bottom window is sinusoidal wave of compression and decompression (Figure 1).^{9,11} The measurement should be performed in the decompression phase. In this phase, there is no pressure from outside, so the measurement contains only the own internal dynamics.^{9,11} SI values were performed from the axial axis of the kidney. Orientation of the region of interest (ROI) with its main axis lying as parallel as possible to the main axis of pyramids was managed to reduce the effect of anisotropy. 7–12 light repetitive compressions were performed to obtain elastography images using a free-hand technique. Repetitive compressions cause sinusoidal waves. If the pressure of compression and decompression is periodic and regular, symmetric sinusoidal wave can be obtained. If the symmetric sinusoidal wave could not be obtained, compression and decompression should be performed again. The compression phase was observed above the baseline and the decompression phase was observed below the baseline. The measurements were performed during the decompression phase. We used two ROIs. One was placed on the renal parenchyma and the other was placed on the renal sinus (reference ROI). The elastography software automatically calculated the SI unit. We took care that two ROIs were placed at the same depth level because changes in the distance of control ROI to the ultrasonography probe would significantly influence strain ratio values both *in vitro* and *in vivo*.^{12,13}

SI values were calculated from the upper, mid and lower poles of bilateral renal parenchyma and sinus, and the mean of three measurements was used for statistical analysis. Only one value was measured for each pole, and if the measurement was incorrect or the sinusoidal wave was irregular, the measurement was repeated.

Statistical analysis

IBM SPSS® programme v. 21 (IBM Corporation, Armonk, NY) was used for statistical analysis. Descriptive statistics were used for demographic data. One-sample Kolmogorov–Smirnov test was performed to analyse the distribution of the data. Student's *t*-test was used to analyse the difference between the normal healthy individual volunteers and the CKD groups (data were

Figure 1. The elastography-ultrasonography image of the kidney. The monitor is divided into three windows. The right window is greyscale ultrasonography image, left window is colour-coded ultrasonography-elastography image and the bottom window is sinusoidal wave of compression and decompression. The circles indicate the region of interests (ROIs). The upper ROI is on the parenchyma and the lower ROI is on the sinus echogenicity. The vertical white line on the sinusoidal wave indicates the point of measurement.

parametric) for values. Pearson correlation coefficient was used to see the correlation between CKD stages (Stages 1–5) and values. One-way analysis of variance (ANOVA) and *post hoc* Tukey honest significant difference tests were used to see the changes of SI values according to the CKD stages. Receiver operating characteristic (ROC) curve was also used to find the cut-off point of SI in normal individuals and patients with CKD.

The mean value [(left kidney + right kidney)/2] of SI values of both kidneys were used in statistical analysis.

Continuous variables were expressed as arithmetical mean $\pm$ standard deviation, categorical variables were expressed as percentages. Level of significance was set at $p \leq 0.05$.

RESULTS

A total of 58 patients with CKD (30 males and 28 females) and 40 healthy individuals (19 males and 21 females) were included in this study. The mean age of the patients was 56.14 ± 11.60 years (18–83 years) and that of healthy individuals was 51.70 ± 11.71 years (22–76 years). There was no statistically significant difference between the ages of the patients and the control groups ($p > 0.05$). CKD was classified into five stages (Stages 1–5) according to the GFR.^{3,4} A total of 10 patients were in both Stages 1 and 2; 19 patients were in Stage 3; 11 patients were in Stage 4; and 8 patients were in Stage 5 (Table 1).

The mean SI values of normal healthy individuals and patients with CKD (regardless of stages) were 0.52 ± 0.30 and 1.81 ± 0.88 , respectively. The difference was statistically significant ($p < 0.001$).

The numerical mean SI values according to stages are seen in Table 1, and the box plot chart is seen in Figure 2.

In ANOVA and *post hoc* Tukey test, SI values were statistically significant between healthy individuals and all CKD inter-stages. But there was no significant difference among inter-stages except CKD Stages 1 and 3 ($p = 0.02$). There was statistically significant difference between the RI values of healthy volunteers and CKD inter-stages.

The Pearson correlation coefficient between CKD stages and the SI values was 0.680.

The area under the ROC curve was 0.956 for SI (Figure 3). The optimal cut-off value (in which the sum of sensitivity and specificity

Table 1. Indicates the mean strain index (SI) values of chronic kidney disease (CKD) stages

CKD stage (n)	SI (mean $\pm$ standard deviation)
0 (40)	0.52 ± 0.30
1 (10)	1.24 ± 0.34
2 (10)	1.49 ± 0.84
3 (19)	2.08 ± 0.93
4 (11)	1.97 ± 1.19
5 (8)	2.07 ± 0.42

0, normal individual healthy volunteers.

was the highest) for the prediction of CKD was 0.935. For this cut-off value, sensitivity was 88%, specificity was 95%, positive likelihood ratio was 17.95, negative likelihood ratio was 0.17, positive-predictive value was 96.23% and negative-predictive value was 84.44%. A total of 51 of 58 patients (88%) and 2 of 40 normal individuals (5%) exceeded this cut-off point.

DISCUSSION

In our study, the elastography examinations of the patient and control groups were performed by one radiologist who was completely blinded to the clinical information. We found statistically significant difference for SI values between normal individuals and patients with CKD (regardless of stages). The cut-off value was 0.935 for SI to differentiate normal individuals and patients with CKD regardless of stages. There was no significant difference among stages for SI (except CKD inter-stages 1 and 3). We think that the variation of SI values among the CKD stages is mainly just owing to our low patient numbers and perhaps owing to the renal parenchymal component.

CKD ends its own progression as ESRD with fibrosis.¹ Generally, fibrosis tends to increase tissue stiffness regardless of tissue and organ.⁶ For example, Kirscheis et al¹⁴ and Bota et al¹⁵ reported increased stiffness in fibrosis in the liver. Kirscheis et al¹⁴ made a study about hepatic fibrosis and cirrhosis, and reported that the strain of the tissue increased significantly with the stage of hepatic fibrosis. The cut-off values were 1.09 ± 0.13 , 1.46 ± 0.27 and $2.55 \pm 0.77 \text{ m s}^{-1}$ for “no significant fibrosis, significant liver fibrosis and liver cirrhosis”, respectively. Bota et al¹⁵ reported similar

results in their study. They calculated cut-off values for fibrosis, severe fibrosis and liver cirrhosis, being 1.34, 1.55 and 1.80 m s^{-1} , respectively. In our study, we determined that the SI value of CKD was higher than those of the normal healthy population. In CKD stages, the SI values were increasing, but these were not regular and there was no cut-off value among the stages.

Guo et al¹ performed a study about renal parenchymal stiffness in patients with CKD. They used ARFI elastography technique unlike us. Their study contained 327 healthy volunteers and 64 patients with CKD. In conclusion, they reported that ARFI elastography technique could not differentiate stages of CKD as we reported.¹ They also performed ROC curve and defined a cut-off value for shear wave velocity (SWV), which was 1.88 m s^{-1} with 71.9% sensitivity and 69.7% specificity.¹ We used strain wave elastography in our study. Although these two techniques were different, the results were similar. Guo et al¹ reported significant difference between the healthy control group and patients with CKD for SWV. Thus, we can presume that fibrosis tends to increase tissue stiffness, and the elastography technique does not change the result. We think that the following studies with different elastography techniques and machines will support our results.

We found positive-sided moderate correlation between SI values and CKD stages (Pearson correlation coefficient was 0.680). But there was a mismatch between SI values and CKD stages. The SI values were showing an increase except for Stage 4. We detected non-significant and slight decreased in SI values in Stage 4. In the study of Guo et al,¹ we see an irregular change in SWV for CKD stages. The irregularity

Figure 2. Clustered box plot chart of the strain index values according to chronic kidney disease (CKD) stages. The top and bottom of the boxes indicate 75 and 25 percentiles, respectively. The line through the middle of each box represents the mean. The error bars show the minimum and maximum values (range). The circles indicate the extreme values. In the x-axis, “0” indicates normal individual healthy volunteers.

Figure 3. Receiver operating characteristic (ROC) curve estimates the diagnostic performance of strain elastography: for a cut-off value of 0.835, the area under curve was 0.958 (95% confidence interval, 0.901-1.000) and standard error was 0.029. For this cut-off value, the sensitivity was 93.5% and the specificity was 88.2%. A total of 43 of 46 patients (93.5%) and 2 of 17 healthy individuals (11.8%) exceeded this cut-off point.

of SI in CKD stages may be owing to the parenchymal component and anisotropy. Renal parenchyma consists of cortex and medulla. Cortex is highly vascularized and the degree of vascular pressure influences elasticity values.^{8,16} Anisotropy is an effect of distribution of Henle's loop and vasa recta within medulla and the collecting ducts within the cortex. The measured values differ when ultrasound beams are sent parallel or perpendicular.⁸ Gennisson et al¹⁶ reported that anisotropy influenced the SWE. Therefore, when emission of the ultrasound beam is sent parallel to these structures, the shear wave propagates perpendicular to these, creating multiple vascular and tubular interfaces, thus decreasing its speed of propagation and resulting in lower elasticity values. Conversely, when emission of the ultrasound beam is sent perpendicular to these structures, the shear wave propagates at a higher speed, without interfaces, resulting in higher elasticity values.¹⁷ Maybe factors such as these also influenced our results. To decrease the effect of anisotropy, the operator should perform the pressure in the axial axis of the kidney.

In our study, we defined a cut-off SI value for the diagnosis of CKD, which was 0.935 (Figure 2), with a sensitivity of 88% and a specificity of 95%. A total of 51 of 58 patients (88%) and 2 of

40 normal individuals (5%) exceeded this cut-off point. We hope that this cut-off value is useful and provides enough sensitivity and specificity.

Ultrasonography-elastography is more complex in the kidney than in the liver owing to its heterogeneous parenchymal context,¹⁷ which may be responsible for the differences in SI values among CKD stages in our study. Further studies comparing different techniques of ultrasonography-elastography may supply more information in this topic.

The major limitation of our study was the small sample size. We suppose that this resulted from the location where the study was performed, which had a small population, not allowing the number of patients to increase during the study period. The second limitation was the inequality of subgroups.

In conclusion, strain wave elastography is a useful technique in the evaluation of patients with CKD, and we think that it would be better to perform further studies including increased number of patients and different elastography techniques.

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