Renal shear wave velocity by acoustic radiation force impulse did not reflect advanced renal impairment

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Abstract

Aim: Acoustic radiation force impulse is a noninvasive method for evaluating tissue elasticity on ultrasound. Renal shear wave velocity measured by this technique has not been fully investigated in patients with renal disease. The aim of the present study was to compare renal shear wave velocity in end-stage renal disease patients and that in patients without chronic kidney disease and to investigate influencing factors.

Methods: Renal shear wave velocities were measured in 59 healthy young subjects (control group), 31 subjects without chronic kidney disease (non-CKD group), and 39 end-stage renal disease patients (ESRD group). Each measurement was performed ten times at both kidneys, and the mean value of eight of ten measurements, excluding the maximum and minimum values, was compared.

Results: Renal shear wave velocity could be measured in all subjects. Renal shear wave velocity in the control group was higher than in the non-CKD group and in the ESRD group, and no difference was found between the non-CKD group and the ESRD group. Age and depth were negatively correlated to the renal shear wave velocity. In multiple regression analysis, age and depth were independent factors for renal shear wave velocity, while renal impairment was not. There was no difference between the non-CKD group and the ESRD group, even when ages were matched and depth was adjusted.

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Conclusion: Renal shear wave velocity was not associated with advanced renal impairment. However, it reflected alteration of renal aging, and this technique may be useful to detect renal impairment in the earlier stages.

Key words: aging, elasticity, end-stage renal disease, ultrasonography

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Introduction

Patients with chronic kidney disease (CKD) show a progressive decline in renal function with time, which leads to end-stage renal disease (ESRD). Glomerular sclerosis and interstitial fibrosis are the principal processes underlying the progression of CKD. However, they are elucidated only by renal biopsy. These pathological findings may be related to tissue elasticity.

A new non-invasive method for the evaluation of tissue elasticity has received a great deal of attention as an alternative to needle biopsy. Acoustic radiation force impulse (ARFI) imaging is a recently developed non-invasive method for evaluating tissue elasticity using B-mode ultrasound.[1,2]

In ARFI imaging, a mechanical excitation of tissue by short-duration acoustic pulses produces shear waves that spread away from the tissue. By recording the shear wave front and measuring the elapsed time, the shear wave velocity (SWV) can be quantified.[3] Generally, the stiffer the tissue is, the faster the SWV will be.[2]

In recent studies, hepatic SWV using ARFI has shown good correlation with the stage of hepatic fibrosis.[3,4] There were only a few reports using this technique for renal tissues in CKD patients, and its feasibility in the diagnosis of renal fibrosis has yet to be elucidated. The aim of the present study was to compare the renal SWVs assessed by ARFI elastography in ESRD patients with those in non-CKD subjects, and to investigate factors influencing renal SWV in ARFI elastography.

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Patients and Methods

Study population

Between April 2013 and November 2014, we enrolled the following three groups: 59 healthy young volunteers (control group; 59 men; median age, 23.0 years; range, 20-35 years) without any medical history or present illness; 31 non-CKD subjects (non-CKD group; 24 men and 7 women; median age, 59.0 years; range, 17-94 years) without past history of renal disease or renal dysfunction, whose estimated glomerular filtration rate was more than 60 mL/min/1.73m^2; and 39 ESRD patients (ESRD group; 25 men and 14 women; median age, 72.0 years; range, 38-86 years) who were admitted to our hospital and underwent maintenance hemodialysis or peritoneal dialysis. This study was conducted in accordance with the Declaration of Helsinki and with approval from the ethics committee of our hospital (approval number; 2316).

Measurement of SWVs by ARFI elastography

All examinations were performed using a Siemens Acuson S2000 ultrasound system (Siemens, Erlangen, Germany), with convex probes (4C1, frequency range: 1-4 MHz) and a mechanical index of 1.7.

Measurement was performed with the preliminary identification of a target region of interest (ROI; box with fixed dimension of 1 × 0.5 cm) on a conventional ultrasound image. The ROI was placed perpendicular to a renal parenchyma that did not include a renal sinus, capsule, or cyst, and the distance

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from the surface to the ROI was limited to less than 8 cm (Fig. 1). The applied transducer pressure was minimized as much as possible during imaging to avoid mechanical compression on the kidney. Then, with the patients holding their breath, an acoustic push pulse was transmitted immediately on the right side of the ROI, where the SWVs were calculated and expressed with a numerical value (m/s) as a result of multiple measurements made for the same spatial location.

Measurements were performed ten times for each kidney. Excluding the maximum and minimum values, the mean of the remaining 8 measurements was used. In the event of a non-valid measurement (expressed as X.XX m/s), a repeat measurement was carried out. All measurements were performed by one experienced ultrasound physician (T.T).

Statistical analysis

For statistical data analysis, Statflex Version 6.0 for Windows (Artec, Osaka, Japan) was used. All descriptive results are presented as median vales with the range. A statistical comparison of all data was performed using the Mann-Whitney U test with Bonferroni correction. The relationship between variables was investigated using Spearman's correlation coefficient (r). A two-tailed p value of less than 0.05 was considered statistically significant. Multiple linear regression analysis, in which age, depth of ROI and presence or absence of CKD were included, was performed to investigate factors influencing renal SWV.

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Results

Patient characteristics

Table 1 summarizes the major demographic and clinical characteristics. The most common etiology of ESRD was diabetic nephropathy (16/39, 41.0%) followed by nephrosclerosis (8/39, 20.5%). Both kidneys were significantly more atrophic in the ESRD group compared to the control group ($p < 0.001$ at the right kidney, $p < 0.001$ at the left kidney, respectively).

Renal SWV

The coefficient of variance of five sets of measurement repeated in the same healthy subject was 8.2%. SWV for all subjects could be measured by ARFI elastography.

The SWVs in the control group were 2.87 (m/s) (range, 1.63 – 3.81) at the left kidney, 3.01 (m/s) (range, 1.99 – 4.05) at the right kidney. There was no significant difference between the left and right kidneys. The SWVs in the non-CKD group were 2.26 (m/s) (range, 0.76 – 3.58) at the left kidney, 2.23 (m/s) (range, 1.08 – 3.89) at the right kidney. There was no significant difference between both kidneys. The SWVs in the ESRD group were 1.87 (m/s) (range, 1.01 – 3.44) at the left kidney, 2.19 (m/s) (range, 0.96 – 3.60) at the right kidney. Similarly, no significant difference in SWVs was observed between both kidneys in the ESRD group. The SWV in the control group was significantly higher than in the non-CKD group ($p < 0.001$ at bilateral kidneys) and in the ESRD group ($p < 0.001$ at bilateral kidneys). However, there was no significant difference in SWVs between the non-CKD group and the ESRD group at both

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kidneys (Fig. 2).

Association between renal SWV and clinical parameters

In the control group and the non-CKD group, age was negatively correlated with the SWV ($r = -0.44$, $p < 0.001$ at the left and $r = -0.38$, $p < 0.001$ at the right kidney) (Fig. 3). In the control group, the SWV and the depth set for SWV measurement showed a negative correlation ($r = -0.35$, $p < 0.01$ at the left and $r = -0.34$, $p < 0.05$ at the right kidney). There were similar correlations between the SWV and the depth in the non-CKD group ($r = -0.49$, $p < 0.01$ at the left and $r = -0.63$, $p < 0.001$ at the right kidney) and ESRD group ($r = -0.39$, $p < 0.05$ at the left and $r = -0.39$, $p < 0.05$ at the right kidney) (Fig. 4).

In order to investigate the factors influencing SWV, we performed multiple linear regression analysis applying the SWV as a dependent variable and the depth, age, and the presence or absence of CKD as independent variables. The depth and age were independent factors affecting the SWV ($p < 0.001$ at both kidneys); however, renal impairment was not. Because the depth greatly affected SWV measurement, we compared SWVs among the three groups (37 subjects in the control group, 21 in the non-CKD group and 21 in the ESRD group for the left kidney, 43 in the control group, 17 in the non-CKD group and 23 in the ESRD group for the right kidney) in subjects in whom depth could be measured from 2.0 cm to 4.0 cm. The SWVs in the ESRD group and in the non-CKD group were significantly lower than those in the control group ($p < 0.01$, $p < 0.001$ at the left kidney and $p < 0.01$, $p < 0.001$ at the right kidney, respectively) as analyzed in all subjects (Fig. 5). However, there was no difference between SWVs in the

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ESRD group and those in the non-CKD group.

To exclude the effects of age and depth on the measurement of SWV, we chose age-matched patients over 40 years of age from both the non-CKD group and the ESRD group and compared SWVs (Table 2). The SWV was adjusted for the depth using a regression formula obtained from the control group:

Adjusted SWV (left) = 3.52857 - 0.197 × depth

Adjusted SWV (right) = 3.64024 - 0.1925 × depth

As a result, there was also no difference in adjusted SWV between the non-CKD group and the ESRD group at both kidneys (Fig. 6).

Discussion

In the present study, we obtained three important findings. First, renal SWV with ARFI could be measured, even in atrophied kidneys in ESRD patients. Second, renal SWV depended on age and the depth of ROI. Third, renal SWV was not associated with renal impairment in the advanced stage; however, it is useful for detection of renal impairment in earlier stages.

Renal SWV using ARFI has been investigated in healthy subjects[5-7] and in transplanted kidneys,[8,9] but it has not been fully investigated in CKD patients and has rarely been applied to ESRD patients. In the present study, renal SWV with ARFI could be measured in all subjects, even in atrophied

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kidneys in ESRD patients. Furthermore, because the coefficient variance of SWV measurements was low, the measurement of SWV had enough reproducibility.

Second, the present study revealed that SWV was inversely correlated with age in subjects without renal disease. This result is consistent with previous reports,[7,10] while Goertz[6] reported no significant correlation was observed between age and the SWV in healthy adults. Structural changes with aging include glomerular sclerosis, interstitial fibrosis, and cyst formation.[11] The ischemic changes seen in aging kidneys first cause cortical glomerular sclerosis and consequent juxtamedullary hypertrophy, followed by juxtamedullary glomerular sclerosis.[11] These changes increase renal SWV. However, the aging kidney also shows the dilatation of afferent arteries and glomerular capillary lumens.[11] In addition, according to the decreased number of glomeruli in the superficial cortex, shift perfusion of the blood supply of the superficial cortex promotes enlargement of the remaining glomeruli.[11] These changes decrease renal SWV. In our study, SWVs decreased with age and may **have been influenced** more by the glomerular enlargement and dilated arteries than by interstitial fibrosis.

The depth of ROI strongly affected the SWV value. In fact, the depth was inversely correlated with the renal SWV and was an independent factor for renal SWV. Although ROI in the SWV measurement should be set at the constant depth, it is difficult to measure SWV at a constant depth due to body size or obesity. Because the regression lines between the depth and renal SWV in each group were similar as shown in Figure 4, SWV may be adjusted by the measurement depth with a regression formula. Further investigation should correct for variations due to the depth of ROI.

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Third, renal SWV was not associated with renal impairment in the advanced stage; however, it is useful to detect renal impairment in earlier stages. Although we compared renal SWVs in between the non-CKD group and the ESRD group, which were measured at a depth of ROI of 2 to 4 cm, no significant difference was found. Furthermore, no difference was found in age-matched and depth-adjusted renal SWVs between both groups.

Wang[12] revealed that renal elasticity was not related to either CKD stage or pathological fibrosis. In CKD patients who underwent renal biopsy, another report found no difference in renal elasticity among different stages of CKD except for stage 5.[7] Asano[13] found a positive correlation between the SWV and estimated glomerular filtration rate, and reported that the hemodynamics of the kidney have an influence on renal elasticity with ARFI, but the report did not indicated the extent of the influence of the hemodynamics. In principle, however, blood flow through the ROI could be ignored because the acoustic pulse from the transducer takes a very short time to reach the target.[14] Renal elasticity has been reported to increase with the progression of renal fibrosis in patients with nephropathy.[15] The alteration of renal elasticity in ESRD remains controversial.

The histologic changes with the progression of CKD include not only glomerular sclerosis, tubular atrophy, and interstitial fibrosis, but also tubular dilatation and cyst formation. Acquired cystic kidney disease, which is characterized by small cysts distributed throughout the renal cortex and medulla,[16] is often found in patients with CKD with or without hemodialysis.[17] The origin of the cysts is considered to be both fusiform dilatation of tubule segments and multiple small tubule diverticula.[16] In fact, glomerular

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cysts are frequently seen in ESRD patients.[18] In an autopsy case series of hemodialysis patients, several subjects had multiple small cysts that had not been diagnosed clinically by imaging modalities.[19] Because ESRD patients had both fibrosis as a factor increasing the risk for renal SWV and undetectable small cysts as a factor decreasing their risk, their SWVs may have been counterbalanced by both effects.

There are several limitations in our study. First, only male subjects were included in the control group. Our study did not take gender into consideration because there was no difference due to gender in the non-CKD and the ESRD groups. Second, pathological validation was investigated in neither aging kidneys nor end-stage kidneys. Further study is required in order to confirm the relationship between renal SWV and pathological findings.

In conclusion, renal SWV was not associated with renal impairment in the advanced stage. However, it reflected alteration of renal aging, and this technique may be useful in the detection of renal impairment in earlier stages.

All the authors declare no conflict to interest.

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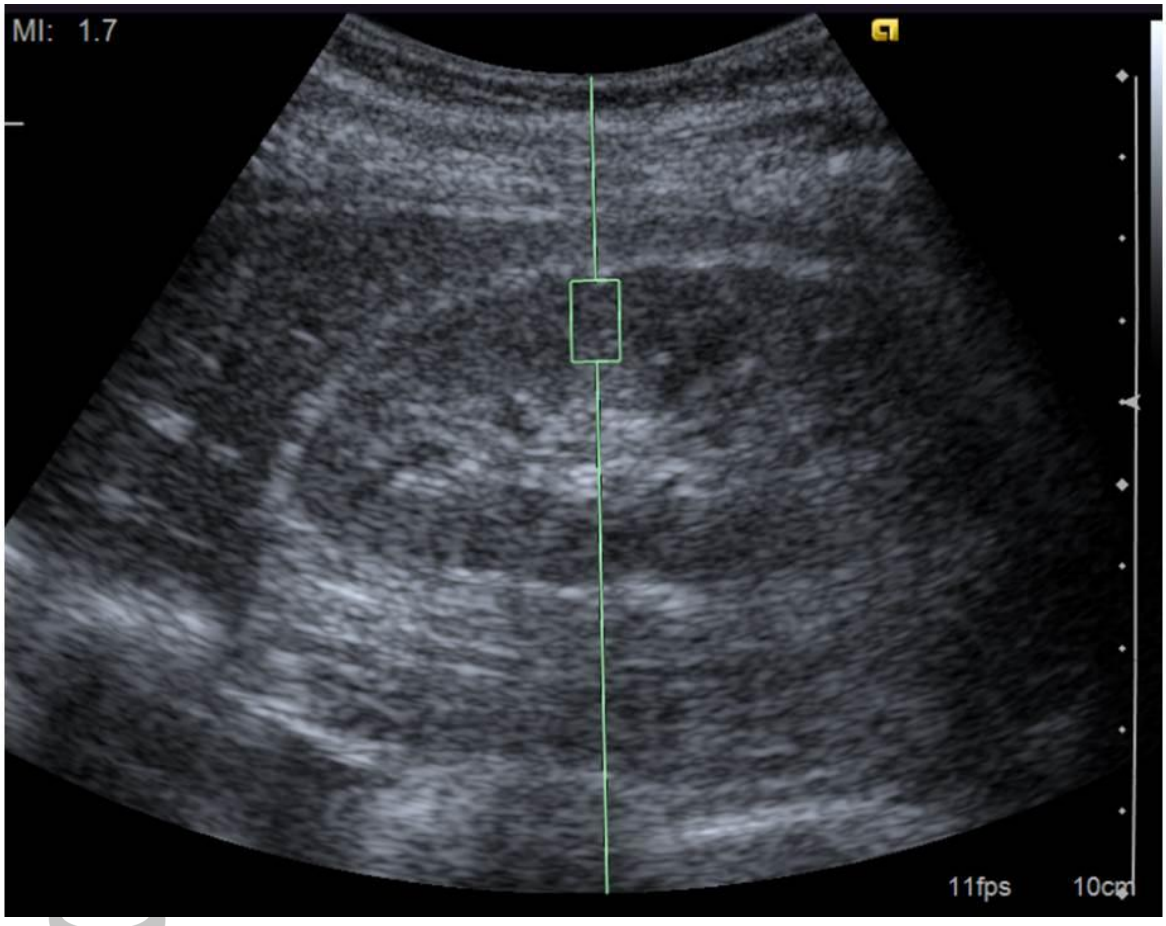

Figure 1. Measurement of SWVs. The region of interest was placed perpendicular to a renal parenchyma that did not include a renal sinus, capsule, or cysts.

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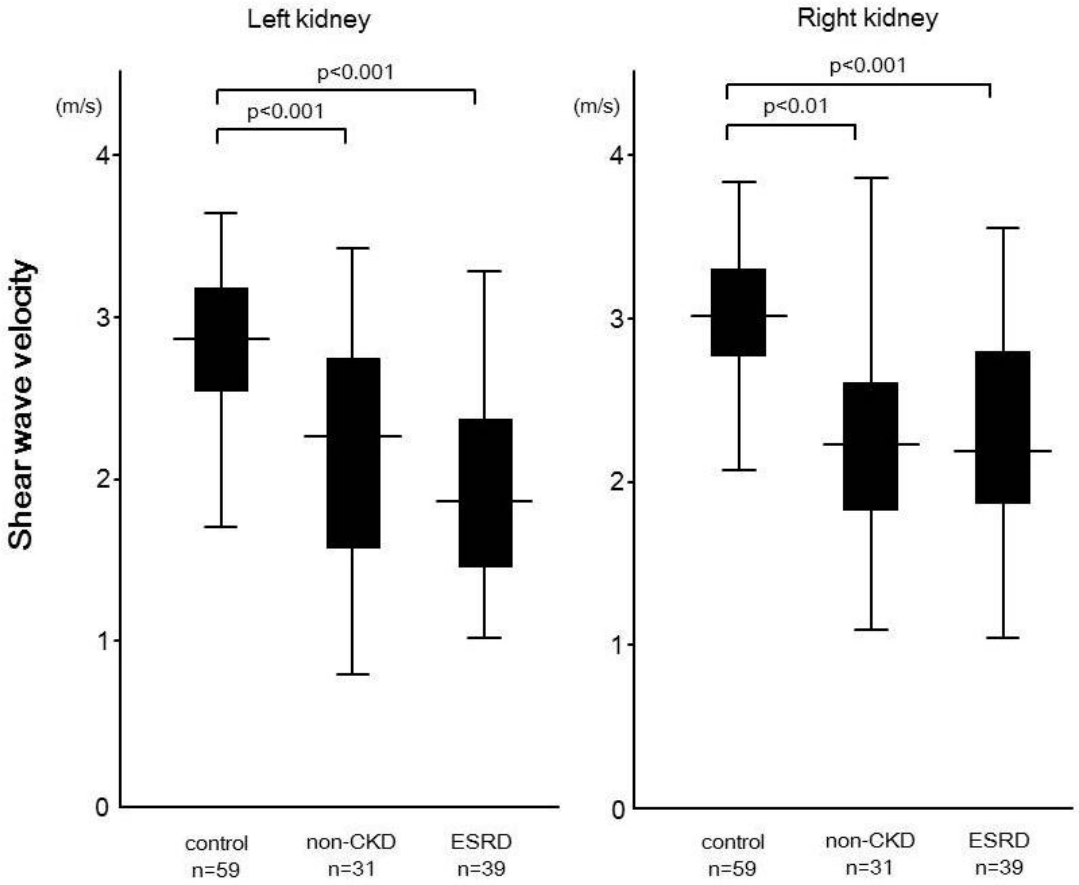

Figure 2. SWV at the left kidney among three groups. The SWV in the control group was significantly higher than in the non-CKD group and in the ESRD group ($p < 0.001$, $p < 0.001$, respectively); however, there was no significant difference between the non-CKD group and the ESRD group. The top of the bottom of the boxes are the first and third quartile, respectively. The length of the box represents therefore the interquartile range including 50% of the values. The line through the middle of each box represents the median. The error bar shows the minimum and maximum values (range).

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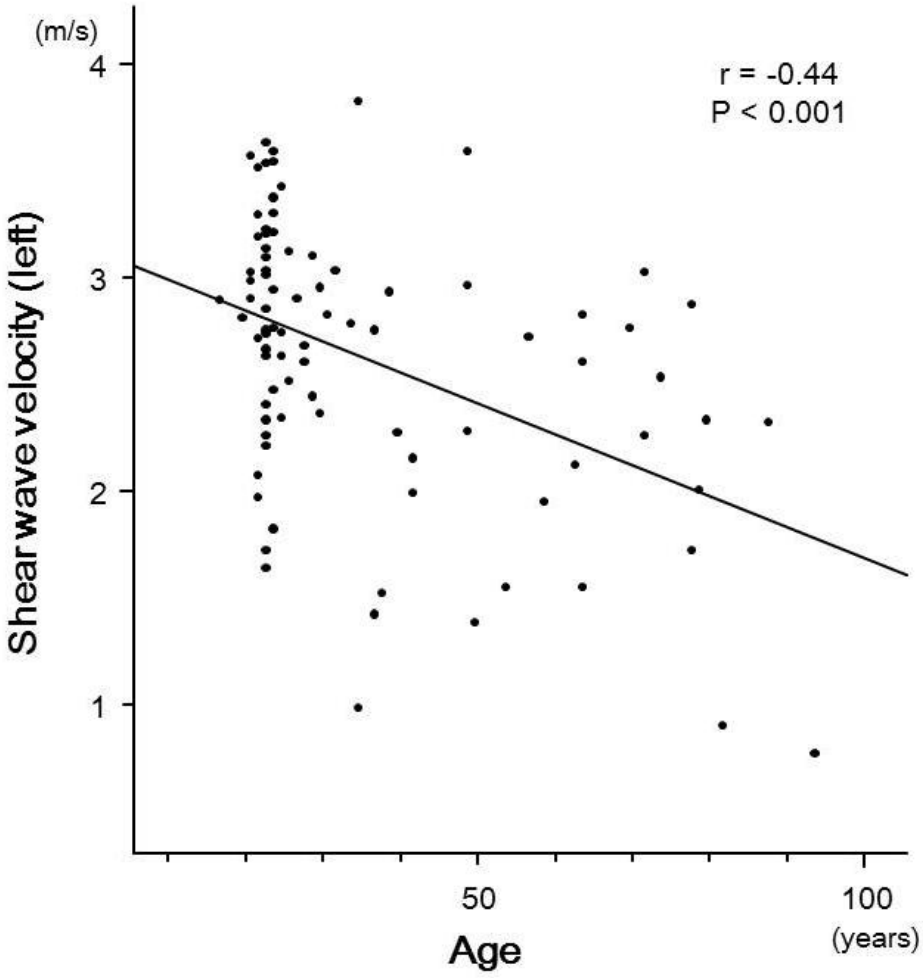

Figure 3. Correlation between age and the SWV at the left kidney among control and non-CKD groups. Renal SWV was negatively correlated to age among the control and the non-CKD groups ($r = -0.44$, $p < 0.001$).

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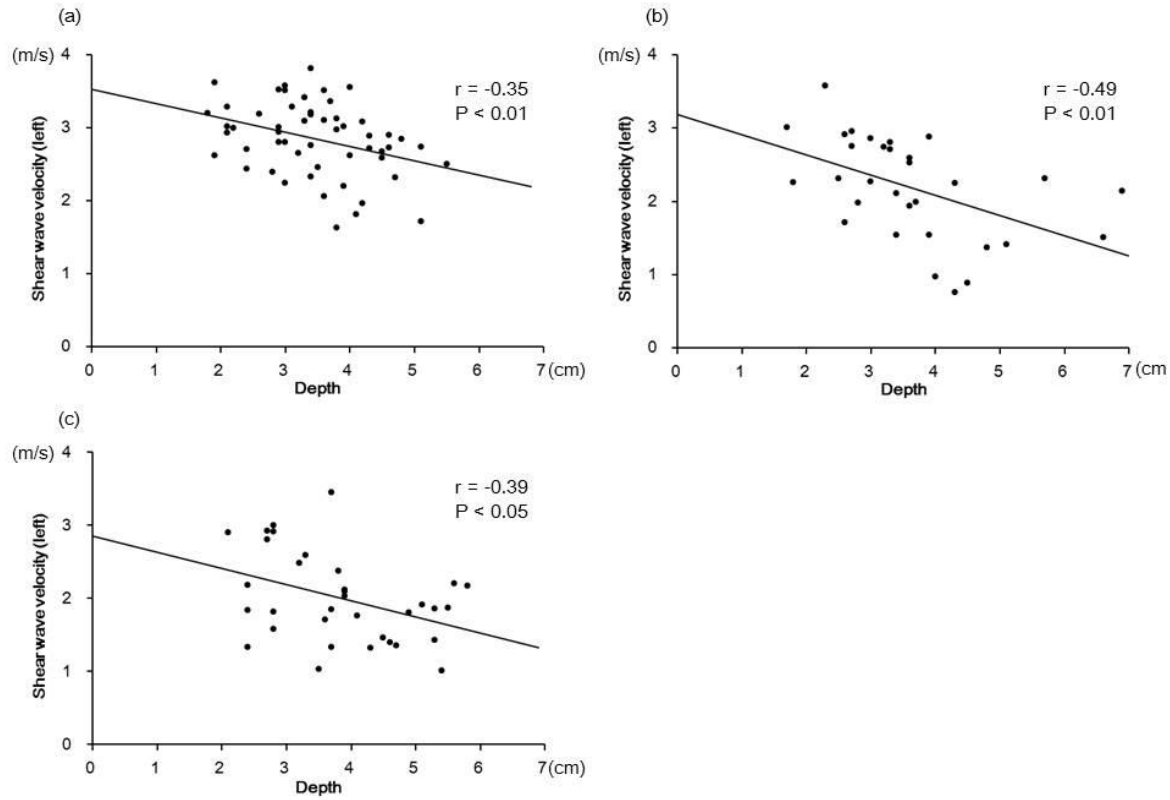

Figure 4. Correlation between depth of ROI for measurement and the SWV among each group at the left kidney. Correlation among the control group (a), non-CKD group (b), and ESRD group (c). Among each group, depth of ROI is negatively correlated to the SWV (control group, $r = -0.35$, $p < 0.01$; non-CKD group, $r = -0.49$, $p < 0.01$; ESRD group, $r = -0.39$, $p < 0.05$).

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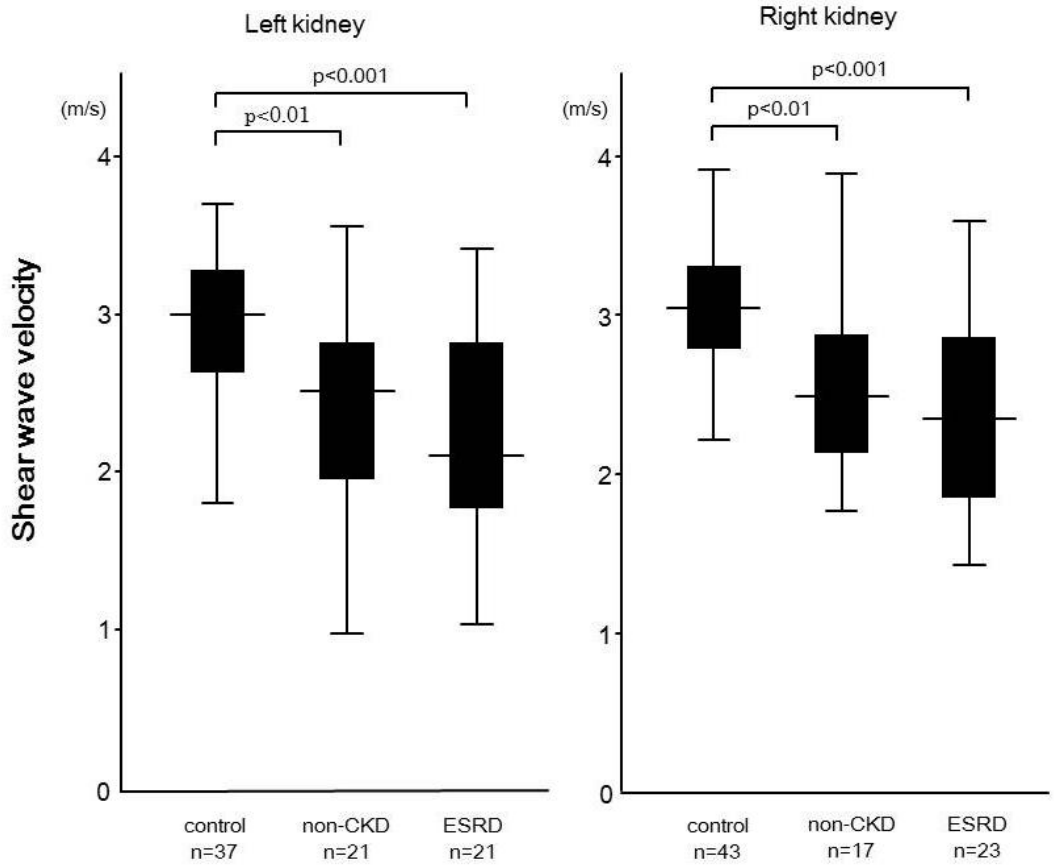

Figure 5. SWVs at the left kidney measured at a depth between 2 to 4 cm. The SWV in the control group was significantly higher than in the non-CKD group and in the ESRD group ($p < 0.01$, $p < 0.001$ respectively); however, there was no significant difference between the non-CKD group and the ESRD group.

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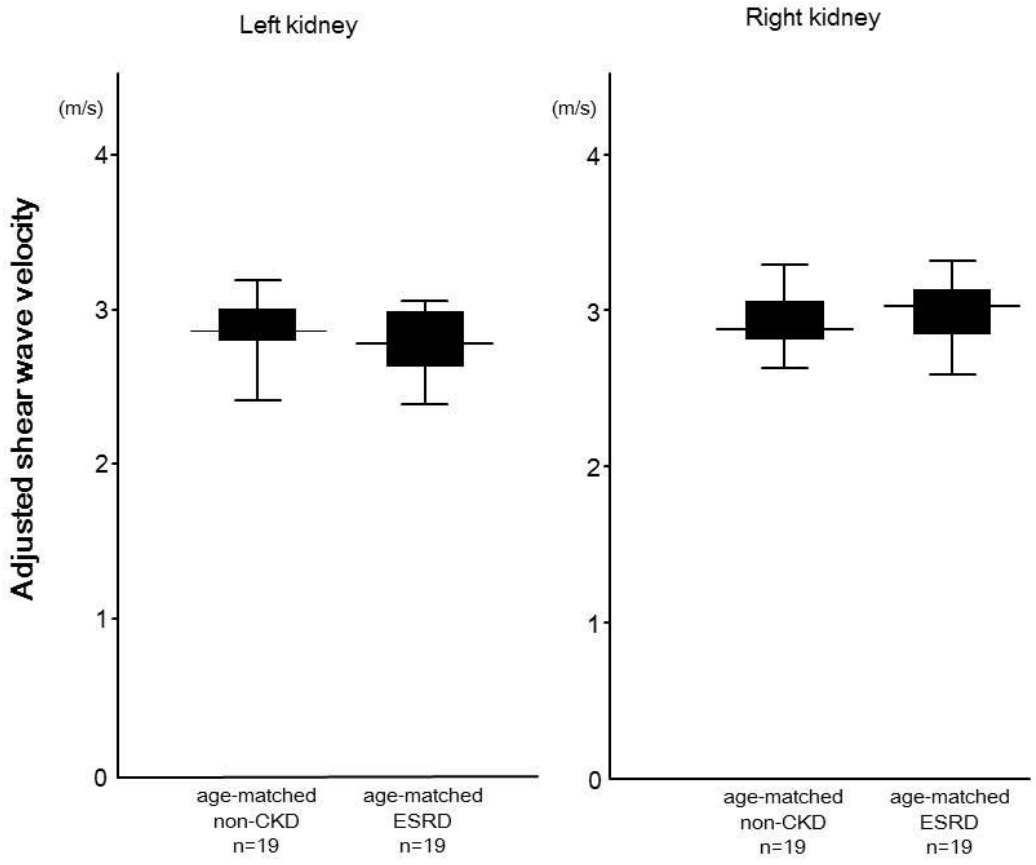

Figure 6. Comparison of renal SWV between age-matched non-CKD group and ESRD group.

There was no significant difference in renal SWVs between the non-CKD group and the ESRD group. The SWV was adjusted for the depth as follows; adjusted SWV (left) = 3.52857 - 0.197 × depth, adjusted SWV (right) = 3.64024 - 0.1925 × depth.

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Table 1. Patient's characteristics

	Control	Non-CKD	ESRD
Number	59	31	39
Male/Female	59/0	24/7	25/14
Age, median (range)	23.0 (20-35)	59.0 (17-94)	72.0 (38-86)
Kidney length (cm)			
Right	10.2 (9.3-11.5)	10.3 (8.5-11.9)	8.3 (7.0-9.0)
Left	10.3 (9.1-11.4)	10.2 (8.3-12.2)	8.0 (6.3-9.3)
Cause of ESRD			
Diabetic nephropathy			16
Nephrosclerosis			8
Chronic glomerular nephritis			2
Other			3
Unknown			10

CKD, chronic kidney disease; ESRD, end-stage renal disease

Table 2. Age-matched patients over 40 years of age

	Age-matched non-CKD group	Age-matched ESRD group	P-value
Number	19	19	
Male/Female	15/4	12/7	0.28
Age, median (range)	70.0 (40-88)	70.0 (41-86)	0.90
SWV parameters			
Right kidney			
Measured SWV (m/s)	2.28 (1.48-3.31)	2.22 (1.57-3.49)	0.98
Depth (cm)	4.0 (1.8-5.3)	3.2 (1.7-5.5)	0.20
Adjusted SWV (m/s)	2.87 (2.62-3.29)	3.02 (2.58-3.31)	0.20
Left kidney			
Measured SWV (m/s)	2.26 (0.89-3.01)	1.85 (1.03-3.00)	0.13
Depth (cm)	3.4 (1.7-5.7)	3.8 (2.4-5.8)	0.20
Adjusted SWV (m/s)	2.86 (2.41-3.19)	2.78 (2.39-3.06)	0.20

CKD, chronic kidney disease; ESRD, end-stage renal disease; SWV, shear wave velocity

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