

Is there a correlation between kidney shear wave velocity measured with VTQ and histological parameters in patients with chronic glomerulonephritis? A pilot study

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Abstract

Aim: To analyze the relationship between shear wave velocity in the kidney measured by point shear wave elastography using Virtual Touch Quantification (VTQ) (Siemens Acuson S2000) and histological parameters obtained from renal biopsies, in patients with chronic glomerulonephritis (CGN). **Material and methods:** The study group included 20 patients (mean age 47.95±13.59 years) with different types of CGN, that had undergone renal biopsy and 57 normal controls (mean age 38.07±17.32 years). In all patients, five valid stiffness measurements were obtained in each kidney, with the patient in lateral decubitus. Regarding the histological results, we assessed the presence or absence of glomerulosclerosis, interstitial fibrosis, and arteriolo-hyalinosis. **Results:** In patients with CGN we obtained the following mean values of VTQ values: right kidney: 2.12±0.81 m/s, left kidney 1.65±0.54 m/s, while in the normal controls significantly higher VTQ values were obtained: right kidney 2.69±0.72 m/s (p=0.004), left kidney 2.48±0.73 m/s (p<0.0001). In patients with CGN no statistically significant correlations between VTQ values and eGFR (r=0.37, p=0.12) or proteinuria (r=0.2, p=0.37) were found. We found significantly lower VTQ values in patients with interstitial fibrosis (1.46 vs. 1.99 m/s, p<0.05) and also in patients with arteriolo-hyalinosis (1.55 vs. 2.47 m/s, p<0.05). **Conclusion:** Our pilot study shows that shear wave velocity values in patients with CGN are significantly lower compared to normal controls, and there is a tendency to decrease with the decrease of eGFR, with the presence of interstitial fibrosis and of arteriolo-hyalinosis.

Keywords: Virtual Touch Quantification (VTQ); chronic glomerulonephritis; renal biopsies; ARFI

Introduction

The use of ultrasound based elastography is becoming important in the non-invasive assessment of different organs: liver fibrosis [1,2], spleen stiffness, for predicting portal hypertension [3,4], thyroid nodules [5,6], prostate [7], focal liver lesions [8], or chronic kidney disease [9].

Virtual Touch Quantification (VTQ) is a point-shear wave elastography method, also known as acoustic radia-

tion force impulse (ARFI) quantification, which relies on the tissue response to an ultrasound “push” beam applied in a region of interest (ROI). It induces tissue displacement that propagates away from the impulse, generating shear waves whose velocity (SWV) can be measured and quantified in m/s. The maximum theoretically obtainable velocity is approximately 6 m/s [10].

Ultrasound based elastography has not yet been introduced in clinical practice for kidney assessment due to difficulties related to the high anisotropy of the renal tissue [11]. Despite these difficulties there are data showing a strong interobserver reproducibility of the method [12,13], making this non-invasive approach attractive for the assessment of renal disease.

Regarding the approach of patients with renal disease, the results of published studies are surprising. Unlike the liver, which shows an increase in stiffness with the pro-

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gression of liver fibrosis, kidney SWV is decreasing with the progression of chronic kidney disease [12,14,15]. The question is how does the progression of renal fibrosis influence kidney SWV?

Despite the fact that elastography is an accurate approach to liver fibrosis grading, data published so far regarding the influence of specific histological changes on the renal stiffness is quite scarce [9]. The aim of the present study is to assess the relationship between kidney SWV and chronic histological changes (glomerulosclerosis, interstitial fibrosis, arteriolo-hyalinosis) in patients diagnosed with chronic glomerulonephritis (CGN).

Material and methods

Patients

Our prospective study included patients with chronic glomerulonephritis (CGN) diagnosed and treated in the Nephrology Department of the Emergency County Hospital Timisoara, Romania. Patients undergoing hemodialysis, peritoneal dialysis, renal transplant recipients, as well as patients with unilateral or bilateral hydronephrosis, kidney stones, and renal tumors were excluded. All the tests (laboratory tests, ultrasonography, and elastography) were performed in the same day, with the patients in fasting conditions.

The control group consists of normal subjects selected from patients hospitalized in various departments of our hospital, without history of chronic kidney disease, with normal serum biological tests (serum creatinine and blood urea nitrogen) and urinary tests (defined as absence of proteinuria and hematuria). The renal ultrasonography was normal in these subjects, the size of the kidneys was more than 10 cm in the long axis, and the difference in length between the right and left kidney was less than 1.5 cm.

All subjects signed an informed consent; the study was approved by the local Ethics Committee and was in accordance with the Helsinki Declaration of 1975.

In all subjects serum creatinine, blood urea nitrogen were determined and used to estimate the glomerular filtration rate (eGFR) using the CKD EPI formula [16]. In patients with CGN, urinary tests (24 hour-proteinuria and spot urinary albumin/creatinine ratio) were also performed.

B mode ultrasound examination

The kidney length and the renal parenchyma thickness were recorded.

Elastography assessment

The kidney SWV was assessed using a Siemens Acuson S2000™ ultrasound system (Siemens AG, Erlan-

gen, Germany), software version 2.0, by using Virtual Touch™ Tissue Quantification application, with a convex array probe of 1-6 MHz.

The subjects were positioned in right and left lateral decubitus. The ROI, a “box” with a predefined size (5 mm width/ 10 mm length), was positioned in the mid-portion of the kidney, in the renal parenchyma (containing cortex and medulla). The ROI’s main axis was set parallel to the renal pyramid axis (perpendicular to the surface of the kidney).

The kidney SWV measurement was performed using minimal scanning pressure, while the patients were asked to stop breathing, in order to minimize breathing motion. In each subject, 5 valid measurements in each kidney were obtained and a median value was calculated, the result being expressed in meters/second (m/s). The kidney SWV value and measurement depth are displayed on the screen. The maximum depth in which VTQ measurements can be performed is 8 cm. If the measurement was not valid, “X.XX” was displayed on the screen. If 5 valid measurements could not be obtained after 15 shots we considered that measurement as a “failure”.

Renal biopsy

In all patients with CGN renal biopsy was performed after the elastographic assessment. Renal biopsy was performed under local anesthesia by Xyline 1% and 16 or 18 G biopsy needles were used. Renal biopsy specimens were preserved in 10% formaldehyde, embedded in paraffin, sectioned at 6-8 micrometers and afterwards stained with hematoxylin-eosin, trichrome Gomori and PAS. The samples were assessed by a pathologist in light microscopy. In order to quantify histological changes we adapted a scoring system initially used for lupus nephritis and for vasculitis [17]. The extent of glomerulosclerosis was established by dividing each glomerulus into eight segments. Each segment was scored for the presence of sclerosis. The number of affected segments was used in order to calculate the percentage of affected glomeruli for glomerulosclerosis. Points were attributed as follows: 1 point for <20% involvement, 2 points for 21–40%, 3 points for 41–60%, 4 points for 61–80%, and 5 points for >80%. Interstitial fibrosis and arteriolar hyalinosis were assessed semi-quantitatively: <30% of tubules, interstitial area or arterioles affected was considered as mild (1 point), 31%- 60% involvement was considered moderate (2 points), while >61% involvement was considered severe (3 points).

Statistical analysis

The statistical analysis was performed using the MedCalc Software, version 12.4.0. (MedCalc program, Belgium). The distribution of the numerical variables was tested by the Kolmogorov-Smirnov test. According to the normal or non-normal distribution of numerical varia-

bles, mean value and standard deviation or median value and range intervals were presented. Student's t-test was used for group comparisons of continuous variables with normal distribution otherwise Mann-Whitney U test was applied. Qualitative variables were presented as numbers and percentages. A p-value < 0.05 was considered as significant for each statistic test.

Results

The study group included 20 patients with different types of CGN in whom a renal biopsy was performed and the control group included 57 patients without renal disease. The main patients' characteristics are presented in Table I.

Five valid VTQ measurements were obtained in 75/77 patients (97.4%) in the right kidney and in all patients in the left kidney. Since the mean kidney SWVs were similar in both kidneys in the study group, as well as in the control group, further analyses were performed considering kidney SWV obtained in the left kidney.

Comparing the two groups, we observed significantly higher mean left kidney SWVs in the control group compared to the study group (2.48±/−0.73 m/s vs. 1.65±/−0.65 m/s, p<0.0001).

In the control group, kidney SWV decreased with the increase in age and with the increase in measurement depth, but no significant correlation with BMI was found. Concerning the study group, we found no correlation of kidney SWV with age, measurement depth, BMI (Table II) or proteinuria. A weak correlation between kidney SWV and eGFR was established, but without statistical significance (r=0.37, p=0.12).

In the histological specimens the glomerulosclerosis was present in 8 patients, interstitial fibrosis in 12 patients, and arteriolo-hyalinosis in 6 patients. As expected, the presence of chronic renal lesions (glomerulosclerosis, interstitial fibrosis, arteriolo-hyalinosis) was associated with a decrease in kidney length, but the differences were not significant (mean kidney length in the study group 96.9 mm, while in the control group 113.5 mm, p>0.05). Concerning elastographic measurements, we found out that the presence of interstitial fibrosis and of arteriolo-hyalinosis, but not of glomerulosclerosis were associated with significantly lower kidney SWV (Table III).

The mean scores assessing the severity of chronic renal histological changes using the above-mentioned semi-quantitative scoring system were: 2.6±0.74 for glomerulosclerosis, 2.1±0.83 for interstitial fibrosis, and 2.3±0.51 for arteriolo-hyalinosis. When we correlated these scores with kidney SWVs, we found no significant correlations (all p>0.05).

Table I. Main patients' characteristics.

Parameter	Control group	Study group
Number of subjects	57	20
Age (years)	38.07±17.32	47.95±13.59
Number of male subjects	25 (43.85%)	12 (60%)
Body mass index (BMI)(kg/m ²)	23.3±4.8	28.3±5.6
Measurement depth (cm):		
– right kidney	4.35±1.47	5.5±1.42
– left kidney	4.42±1.42	5.5±1.04
eGFR (ml/min)	108.43±38.28	52.0±37.9
Proteinuria (g/24h)	NA	3.59±3.5
SWV left kidney (m/s)	2.48±0.73	1.65±0.54
SWV right kidney (m/s)	2.69±0.72	2.12±0.81

BMI – body mass index; eGFR – estimated glomerular filtration rate, SWV – shear wave velocity, NA – not applicable

Table II. Correlation coefficient (r), and significance (p) of the relationship between kidney SWV measured using VTQ and different parameters in the control and in the study group

Kidney SWV	Control group	Study group
Age (years)	r=-0.40, p=0.002	r=0.2, p=0.37
BMI (kg/m ²)	r=-0.19, p=0.14	r=0.15, p=0.49
Measurement depth (cm)	r=-0.63, p=0.008	r=0.09, p=0.66
Proteinuria (g/24h)	NA	r=0.2, p=0.37
eGFR	r=0.15, p=0.42	r=0.27, p=0.95

BMI – body mass index; eGFR – estimated glomerular filtration rate, SWV – shear wave velocity, NA – not applicable

Table III. Kidney SWV values in patients with or without histological changes (glomerulosclerosis, interstitial fibrosis, arteriolo-hyalinosis)

Chronic renal histological changes	N	Mean kidney size (mm)	Mean kidney SWV (m/s)
Glomerulosclerosis	+	8 93.7	2.19
	-	12 114.4	2.12
Interstitial fibrosis	+	12 99.16	1.46*
	-	8 117	1.99*
Arteriolo-hyalinosis	+	6 98	1.55*
	-	14 109.3	2.47*

N: number of patients; +: present; -: absent; * – statistically significant difference (p<0.05)

Discussions

As mentioned above, data available so far regarding the use of VTQ elastography in the kidneys showed that kidney SWV is decreasing with the progression of kidney disease, which is contradictory to the data available for the liver, where liver fibrosis is associated with an increase in liver SWV [12,14,15]. In our study group, we confirmed

previous observations regarding the fact that kidney SWV is significantly lower in patients with CGN as compared to normal controls. Therefore, it is important to find out what factors are primarily influencing kidney SWV.

The first studies regarding the correlation between kidney SWV and histological changes were performed on renal transplant recipients. Syversveen et al found no significant correlation between SWV and fibrosis in chronic allograft nephropathy [18]. However, other researchers showed a moderate positive correlation between VTQ (ARFI) values and fibrosis, kidney SWV values increasing in acute graft rejection [19, 20]. More recent studies showed that there are other factors besides fibrosis influencing the kidney SWV, such as time after transplantation or kidney weight to body weight ratio, the latter influencing renal hemodynamics [21].

The main goal of our study was to evaluate the extent of histological changes that influence the kidney SWV and if there is a possibility to use SWV in clinical practice for assessing patients with CGN. SWVs in the kidney correlated to certain histological lesions (interstitial fibrosis, arteriolo-hyalinosis) in CGN, while kidney size measured by gray scale ultrasonography was not influenced by the presence of any histological changes.

The presence of interstitial fibrosis and of arteriolo-hyalinosis was associated with lower values of kidney SWV. Our results are similar to those published by Hu et al; the authors showed that SWV decreased with the worsening of histological parameters [15].

Other studies published so far, comparing histological results with elastography in native kidneys, did not reach similar conclusions: Wang et al found no correlation of kidney SWV with: interstitial fibrosis, tubular atrophy, glomerulosclerosis index [9], while Cui et al found that renal fibrosis is associated with an increase of SWV [22].

These contradictory results make us raise the question whether elastography will be helpful in the assessment of renal fibrosis in clinical practice. The presence or absence of different histological parameters is not associated to specific elastographic patterns or cut off values. There is also no correlation between kidney SWV and the severity of histological changes. Other factors, such as impaired vascularization, might influence kidney SWV, the severity of fibrosis acting only indirectly, possibly through renal blood flow.

The decrease of renal blood flow due to interstitial fibrosis and arteriolo-hyalinosis could be the direct cause of decrease of kidney SWV in our patients. The presence of glomerulosclerosis showed no influence on kidney SWV, because probably it has no direct influence on renal blood flow. The direct proof of the fact that a decrease of renal blood flow is associated with a decrease of kidney

SWV, has been brought in different studies [23-25]. In an experimental animal model, Gennison et al [23] showed a decrease of renal stiffness after renal blood flow reduction due to renal artery ligation. Asano et al [25] showed an association between increased pulse wave velocity and decreased kidney SWV, highlighting arteriosclerosis as main mechanism that influences renal stiffness.

A number of factors not disease-related are emerging as being linked to kidney SWV in our study. In the control group we found an indirect correlation between age and kidney SWV similar to previously published studies [12,14]. The relationship between renal stiffness and age could also be related to the decreased renal blood flow in elderly.

Another factor that influenced kidney SWV in our subjects was the depth of measurement; the decrease of the measured SWV was previously related to an increase in depth in studies performed on phantoms [26,27] or liver [28,29]. A marker of disease activity, proteinuria, has been mentioned in the literature as an influencing factor for kidney SWV [27], but we found no significant correlation between proteinuria and kidney SWV in our patients.

An important limitation of renal elastography is the high anisotropy of the renal tissue. This might induce a bias regarding the way the ultrasound push pulse enters the kidney, either parallel or perpendicular to the renal pyramid axis [23]. Therefore, we standardized the measurements, performing all of them in the mid portion of the renal parenchyma, with the ROI's main axis parallel to the renal pyramid axis. Another important limitation of our study is the small number of patients with renal biopsy that were included and, also, the lack of renal blood flow quantification in the studied subjects.

Conclusions

Kidney SWV values using point shear wave elastography technology in patients with CGN are significantly lower compared to normal controls. Kidney SWV values decrease with the presence of interstitial fibrosis and of arteriolo-hyalinosis. Elastography is superior to B-mode ultrasound in the assessment of the severity of renal histological changes; however, it is a method that still requires extensive research.

Conflict of interest: none

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