Review

Value of ultrasound elastography in the diagnosis of native kidney fibrosis

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Abstract

In the last decade ultrasound elastography, an already widely used technique in the diagnosis of hepatic fibrosis, has raised the attention of nephrologists as a potential valuable noninvasive tool for the diagnosis of renal fibrosis. Due to renal deep location and anatomic complexity, the shear wave techniques are the most appropriate elastography methods for exploring native kidneys. Recent research offers promising results, but further larger studies are required for a better standardization of this method and also for establishing reference values of normal kidney elasticity. This article reviews the studies conducted for exploring the native kidney, highlighting the advantages and limitations of ultrasound elastography for assessing fibrosis development in chronic kidney diseases.

Keywords: renal elasticity, ultrasound elastography, kidney fibrosis, chronic kidney disease.

Introduction

For many years, ultrasonography has become the most valuable imagistic investigation in renal diseases. It can be used regardless of serum creatinine, it is noninvasive and it is also applicable in pregnancy. Renal biopsies under ultrasonography guidance are already performed as routine in clinical practice. Thus, since the incidence of chronic kidney disease (CKD) is constantly increasing [1], new methods are required for a non-invasive early detection of renal fibrosis and for assessing the degree of fibrosis in different stages of CKD. In the last decades, promising results in this respect have emerged not just from various biological markers [2], but also from a new field of ultrasound examination, i.e. elastography. Elastography – a method which provides information about tissue stiffness [3] – has already proved valuable for the diagnosis and assessment of the severity of liver fibrosis. However, regarding renal diseases, ultrasound (US) elastography is still in the pioneering stage due to anatomical characteristics of the kidney and the complexity of the pathological processes incriminated by renal dysfunction.

The present article reviews the existing ultrasound elastography techniques and their applicability in renal pathology, focusing on renal fibrosis and CKD.

Ultrasound elastography techniques

Elastography uses ultrasound to assess and quantify the stiffness or the elasticity of a tissue. The method permits an accurate quantitative diagnosis of the differences in tissues stiffness in contrast with the classic palpation which is subjective. Additionally, it is superior to conven-
tional ultrasonography which does not provide accurate information on elastic properties of an organ, because the propagation of ultrasound is relative homogeneous in different biological tissues [4].

The basic principle of elastography is to generate a stress in a tissue and then to measure the strain induced by this stress [5]. The tissue stiffness is quantified with Young modulus, defined by the ratio between the applied stress and the induced strain and expressed in pressure units – Pascals or kilo Pascals [6,7]. Depending on the external force applied on a tissue, several types of elastography can be performed.

In static or quasi-static US elastography, an external compression is applied on the interest organ and a qualitative map with the tissue strains before and after compression is provided. Young module cannot be calculated in this method, because the magnitude of the stress applied is unknown; an image with the strain, frequently called elastogram, is displayed and compared with healthy tissue [7,8].

Transient elastography provides a one-dimensional quantitative image of examined tissue stiffness. The underlying principle is to produce a transient skin vibration with a device and then to record, with a 1D transducer, the shear waves that propagate within the examined tissue. A quantitative line of tissue stiffness is obtained [7]. This method, also developed in 2D with the result of obtaining a map of Young’s modulus in the examined tissue [7], is already approved in clinical guidelines for the quantification of hepatic fibrosis [9].

Acoustic Radiation Force Impulse Imaging (ARFI) or Acoustic Radiation Force Imaging is another elastography method which allows construction of a qualitative stiffness map of the examined tissue. It uses a focused beam of ultrasound to apply a localized radiation force in small volumes of the tissue to be tested and for short durations [10]; this force induces variable tissue displacement varying upon the stiffness of the tissue at the focal spot [7,10]. Making measurements in different places, finally it can be obtained a 2D map stiffness [7].

Shear Wave Elasticity Imaging (SWEI) is a method similar to ARFI – a radiation force is sent into the tissue, but, in contrast with ARFI, the shear waves created by this push and propagated laterally from the beam axis are measured [11]. A limitation of US generated shear waves is the weakness of these waves, with little displacement of the tissue and rapid dissipation of the propagation; therefore, for larger displacements, increased power of the focused beam is required with the risk of overheating [10,12].

The shear wave velocity measurement is also the principle of the most advanced type of US elastography – Supersonic Shear Imaging (SSI) [13,14]. In SSI technology, a supersonic shear wave source is generated within the tissue, the amplitude of shear waves being increased while limiting the acoustic power; multiple radiation beam pushes can be successively focused at different points in the examined tissue and they generate a shear wave with a supersonic speed [13,15]. The pushes are sent from the source at different depths at a higher speed than the speed of the generated shear waves; in the end, all shear waves concentrate in a small area, a “Mach cone” shape, which increases their amplitude and the distance of their propagation [13]. The generated shear waves are then mapped quantitatively by using ultrafast imaging technique [13].

Ultrasound elastography in renal diseases

Static elastography methods, with extensive usage in the pathology of superficial organs [16] such as thyroid or breast, have no utility in renal exploration because of the deeply profound location of the native kidney, a situation in which a compression directly on the organ cannot be applied [17]; furthermore, because of the non-uniform pattern of fibrosis in CKD or other diffuse pathologies (such as glomerulonephritis or renal allograft fibrosis), there is no healthy tissue to compare with the elastography results [18].

In addition, in renal diseases, 1D transient elastography has an applicability only in the transplanted kidney [19,20], because this is positioned superficially, under the skin. In transient elastography, the sample volume is placed 4 cm long in a window with little variations below the skin surface (25-65 mm) and there is no ultrasound guidance to position the sample on the native kidney which is located at variable depths [18]. Therefore, errors of interpretations of the results may arise when exploring native kidneys. Additionally, the sample must be positioned behind a solid structure, which may further complicate the kidney exploration because several organs are present in the way to the kidney [18].

Shear wave-based techniques seem to be more appropriate for native kidney stiffness assessment because they allow exploring selectively the different compartments in the kidney; several animal or human studies have been performed with varying results (Tables I). The results are encouraging but, at the same time, numerous uncertainties arise from this research as a result of the modalities to perform the technique, the complexity of the kidney architecture or the heterogeneous and dynamic processes possible at this site without a pathognomonic marker to compare with.
Table I. Shear wave-based US elastography studies performed in the native kidney

<table>
<thead>
<tr>
<th>Study number of patients or animal models</th>
<th>Technique</th>
<th>Type of research</th>
<th>Conclusions with statistic relevance</th>
<th>Mean value of YM (kPa) or SWV (m/s)</th>
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<tbody>
<tr>
<td>Arda et al (2011) 127 patients [21]</td>
<td>SWEI</td>
<td>healthy kidneys</td>
<td>elasticity varies with tissue anisotropy and, with vascular and urinary pressure levels; inner cortex higher elasticity values than outer cortex, attributable to perfusion differences</td>
<td>cortex: 5.2±2.9 kPa (men); 4.9±2.9 kPa (women) renal pelvis: 24.7±4.9 kPa (men); 23.1±5.5 kPa (women)</td>
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<tr>
<td>Gennisson et al (2012) 3 pigs [22]</td>
<td>SSI</td>
<td>healthy kidneys (pig kidney)</td>
<td>– elasticity varies with tissue anisotropy and, with vascular and urinary pressure levels; inner cortex higher elasticity values than outer cortex, attributable to perfusion differences</td>
<td>inner cortex: 8.1±1.9 kPa outer cortex: 6.9±1.4 kPa</td>
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<tr>
<td>Grenier et al (2013) [18]</td>
<td>SSI</td>
<td>healthy kidney</td>
<td>cortical elasticity values were higher than medullary values</td>
<td>medullary stiffness: 10.8±2.7 kPa cortical stiffness: 15.4±2.5 kPa</td>
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<td>Guo et al (2013) 327 healthy patients, 64 CKD [23]</td>
<td>ARFI</td>
<td>healthy versus CKD</td>
<td>– comparing with each CKD stage, SWV was clearly increased in healthy individuals – ARFI predicts only CKD stage 5 – SWV linked only to e-GFR, urea nitrogen, and creatinine</td>
<td>healthy controls: 2.15±0.51 m/s CKD stage 1, 2, 3, 4 and 5: 1.81±0.43 m/s, 1.79±0.29 m/s, 1.81±0.44 m/s, 1.64±0.55 m/s, respectively 1.36±0.17 m/s Cut-off value for predicting CKD = 1.88 m/s</td>
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<td>Bruno et al (2013) 28 with VUR, 16 healthy pts [24]</td>
<td>ARFI</td>
<td>healthy versus primary or secondary VUR</td>
<td>– SWVs in the “affected” kidneys significantly higher than SWVs in both “contralateral” and “healthy” kidneys – significant difference between SWVs in the “contralateral” and “healthy” kidneys – significant higher SWV in secondary VUR comparing with primary VUR</td>
<td>SWV in the “affected” kidneys: 5.70±1.71 m/s; in contralateral: 4.09±0.97 m/s; in healthy kidneys: 3.13±0.09 m/s SWV in secondary VUR: 6.59±1.45 m/s; in primary VUR: 5.35±1.72 m/s</td>
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<td>Cui et al (2014) 76 patients [25]</td>
<td>ARFI</td>
<td>healthy versus CKD – renal biopsy outer cortex</td>
<td>– SWV values were significantly increased in the mild and moderate fibrosis groups when comparing with non-fibrosis – no significant difference between the mild and moderate fibrosis groups</td>
<td>non-fibrosis: 1.59±0.14 mild fibrosis: 2.15±0.38 moderate fibrosis: 2.29±0.53 severe fibrosis: 2.24 m/s Cut off for predicting renal fibrosis &gt; 1.67 m/s</td>
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<tr>
<td>Sohn et al (2014) 19 healthy subjects, 30 hydronephrosis patients [26]</td>
<td>ARFI</td>
<td>healthy versus hydronephrosis</td>
<td>median SWV in kidneys with high-grade hydronephrosis were higher than those in normal kidneys but were not different between hydronephrotic kidneys with and without uretero-pelvic junction obstruction</td>
<td>high-grade hydronephrosis: 2.02 m/s normal kidneys: 1.75 m/s</td>
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<td>Bob et al (2014) 68 healthy subjects, 20 kidney pathology [27]</td>
<td>ARFI</td>
<td>healthy versus different kidney diseases</td>
<td>mean kidney SWVs were higher, but not statistically significant, in subjects without known kidney pathology as compared with those with kidney diseases</td>
<td>without kidney pathology: 2.42±0.70 m/s (operator 1); 2.54±0.83 m/s (operator 2) with kidney diseases: 2.11±0.79 m/s (operator 1); 2.14±0.84 m/s (operator 2)</td>
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<tr>
<td>Study (Year)</td>
<td>Subjects/Groups</td>
<td>Method</td>
<td>Findings</td>
<td>Cut-off values</td>
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<td>Asano et al (2014)</td>
<td>ARFI healthy versus CKD</td>
<td>SWV</td>
<td>SWV is more influenced by the decrease of renal blood flow than the progression of tissue fibrosis; significant positive correlation between the SWV and eGFR in both cortex and medulla</td>
<td>SWV in healthy: 2.20 m/s in the cortex and 2.75 m/s in the medulla</td>
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<tr>
<td>Hu et al (2014)</td>
<td>ARFI healthy versus CKD</td>
<td>SWV</td>
<td>Mean SWV in kidneys severely impaired was significantly lower than that mildly impaired, moderately impaired, and control groups. SWV correlated significantly with pathological parameters, serum creatinine, and eGFR in both cortex and medulla</td>
<td>Cut-off values: 2.65 m/s for mildly impaired kidneys; 2.50 m/s for moderately impaired kidneys; 2.33 m/s for severely impaired kidneys</td>
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<td>Yu et al (2014)</td>
<td>ARFI diabetes mellitus versus healthy</td>
<td>SWV</td>
<td>No significant difference between the normoalbuminuria and control. Significant difference between the microalbuminuria and macroalbuminuria and control. Significant difference between each pair of type 2 diabetes groups.</td>
<td>Control: 2.22±0.47 m/s Normo-albuminuria: 2.29±0.20 m/s Microalbuminuria: 2.53±0.16 m/s Macroalbuminuria: 2.98±0.32 m/s Cut-off value for predicting DN = 2.43 m/s</td>
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<td>Tian et al (2014)</td>
<td>ARFI gouty kidney versus healthy</td>
<td>SWV</td>
<td>Parenchymal and sinus SWV significant higher in gouty kidney than in control. Urinary β2-microglobulin positively correlated with the SWV of renal parenchyma in gouty kidney.</td>
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<td>Samir et al (2015)</td>
<td>SWEI healthy versus CKD</td>
<td>YM</td>
<td>CKD was associated with increased median YM and higher median intra-subject inter-measurement estimated YM's variability.</td>
<td>Healthy controls: 4.40 kPa (3.68, 5.70) CKD: 9.40 kPa (5.55 – 22.35) Cut-off value for predicting CKD = 5.3 kPa</td>
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<td>Göya et al (2015)</td>
<td>ARFI healthy versus DN</td>
<td>SWV</td>
<td>In healthy volunteers, there was a statistically significant correlation between SWV and age and sex. ARFI was able to distinguish between the different DN, except for stage 5.</td>
<td>Healthy controls: 2.35 m/s DN stage 1, 2, 3, 4 and 5: 2.87; 3.14; 2.95; 2.68; 2.55 m/s Cut-off value for predicting DN = 2.43 m/s</td>
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<tr>
<td>Bota et al (2015)</td>
<td>ARFI healthy kidneys</td>
<td>SWV</td>
<td>SWVs are influenced mainly by age and gender and less by measurement depth.</td>
<td>Right kidney – 2.49±0.81 m/s Left kidney – 2.36±0.75 m/s</td>
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</table>

*SWEI = Shear Wave Elasticity Imaging; SSI = Supersonic Shear Imaging; ARFI = Acoustic Radiation Force Impulse Imaging or Acoustic Radiation Force Imaging; CKD = chronic kidney disease; DN = diabetic nephropathy; VUR = vesicoureteral reflux; SWV = shear wave velocity; DMSA = dimercaptosuccinic acid
The most important problem is the lack of defining the normal limits of stiffness in the native, healthy kidney, as it is already defined for other organs as liver [36-38], breast [39], or thyroid [40]. Measurements taken so far have significant variations between studies, highlighting the necessity for extensive trials on healthy kidneys. For example, the elasticity values of renal cortex varies, upon different assessments, between 15.4±2.5 kPa [18] to 5.0±29.5 kPa [21] or even 4.40 (3.68, 5.70) kPa [32] for Young’s modulus in SSI or SWEl, and between 1.75 m/s [25] to 2.54±0.83 m/s [27] for shear wave velocity in ARFI. The kidney region examined is important, as significant differences in elasticity have been reported between the outer and inner cortex [22], between the medullary and cortical portion of the kidney [18], and between the cortex and renal pelvis [21]. Several factors may influence the variability of the results.

In ARFI, the power of the force applied on the transducer by the operator [18,41,42], the distance from source to target [21,27,34,42] – in current imaging methods is important as is the maximal depth is 8 cm [8], and also the frequency of the probe [42,43], all of these being potential modifiers of measured shear wave velocity. Furthermore, placement of the probe on the cortex may be difficult in advanced CKD because of a small cortical parenchyma thickness.

Anisotropy is present in all renal compartments, especially in the medullary region [22,44,45], and this is important when interpreting the results; sending the ultrasound beam in a perpendicular axis on these structures will lead to higher elasticity values because the shear waves propagate more rapid; when the ultrasound beam is sent parallel to a highly anisotropic structure, the elasticity values will be lower because the shear waves will propagate slower and will dissipate as a result of multiple interfaces created by the blood vessels, renal tubuli and stromal compartments [18,22]. Therefore, measurements of the stiffness in the same part of the kidney (subcapsular, cortex and medulla) are advisable to obtain valid and uniform results [20,27] and also establish universal technique standards in the future for reliable and comparable results.

Vascularization is another factor influencing the measured elasticity values of the kidney. Reduced kidney elasticity after ligation renal artery and, conversely increased elasticity after ligation in the renal vein were reported in an animal study by Genisson et al [22]. Moreover, Asano et al raised the possibility that, in CKD, increased stiffness kidney measured in ARFI may be induced more by vascular abnormalities in this disease than by renal parenchymal fibrosis [28].

Urinary obstruction must be ruled out before performing US elastography, as several studies have reported the linear increase of renal tissue elasticity associated with elevated urinary pressure [22,26].

Gender [21,34], race [27], weight or body mass index (BMI) [20], and also age [23,34,46] can modify the results in US elastography and several studies have found significant variations of renal parenchymal elasticity in these parameters [20,21,23,27,34,46].

The examinations must be performed while the subjects hold their breath, which can be difficult especially in pediatric patients [26].

Inter-observer agreement is reported in various studies at different ICC (intra-class coefficients correlation), from 0.71 [27] to 0.47 [47] or even 0.31 [48], being smaller than those for the assessment of liver fibrosis [49,50]. These variations are explained by the deeper location of the native kidney compared to the liver, by the different experience of the operators in the field of renal US elastography, or may be due to the type of kidney examined, native or transplanted [27]. Intra-observer variation coefficients are also reported between 20% [51] and 24% [48].

Evaluating fibrosis in native kidney with US elastography

CKD is characterized by progressive scarring of the renal parenchyma with loss of intrinsic renal cells and increased production of extracellular matrix, ultimately leading to fibrosis that affects all components of the kidney – glomeruli, tubules, interstitium and vessels, irrespective of the primary renal insult [52]. Several mediators that induce fibrosis in the common pathway of CKD progression have been identified (transforming growth factor β1 (TGF-β1), connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF) etc) [52] and experimental studies performed until the present offer hope for reversal or stopping the fibrogenic process in CKD using various interventions (anti-TGF-β1 or anti-EGF antibodies, inhibitors of TGF-β1 or EGF receptors, administration of hepatocyte growth factor or bone morphogenetic protein 7 (BMP-7), synthetic inhibitors of tissue transglutaminase etc) [52]. Unfortunately, ideal markers for assessing the degree of fibrosis are lacking, except for the kidney biopsy which is not only an invasive procedure, but has several limitations and contraindications [53]. Therefore, kidney US elastography opens new perspectives as it would permit the decrease of biopsy and also can be used to track fibrosis progression in repeatable examinations.

Several US elastography studies have been performed until the present for assessing fibrosis in the native kidney. In an experimental study performed by Derieppe et
al [54], glomerulosclerosis and increased urinary protein / creatinine ratio were associated with an increased elasticity of renal parenchyma. In the native kidney, human studies have reported various markers associated with increased kidney stiffness: estimated glomerular filtrate rate (eGFR) [23,28,29], urinary albumin / creatinine or protein / creatinine ratio [30,33], serum creatinine [23,29], urea nitrogen [23], elasticity values in healthy native kidneys [23-33,35], kidney biopsies [25], other imaging tests etc [24,26,35]. Thus, there are studies finding no significant correlation between markers of chronic kidney injury and elasticity of renal parenchyma in native [27] or transplanted kidney [48,51], and also studies which could not prove a significant difference of elasticity between various renal regions in healthy kidneys: outer and inner cortex, medullary and cortical portion of the kidney, cortex and renal pelvis. Furthermore, the impact of various pathological processes (e.g. diabetic nephropathy, hydronephrosis, glomerulopathies etc) on the stiffness of the kidney presents large variations in different studies.

In conclusion, elastography is a promising tool for assessing kidney fibrosis; further studies are required in order to establish a standardized technique method and also normal and pathological reference values.

Conflict of interests: none

References

Ileana Peride et al Value of ultrasound elastography in the diagnosis of native kidney fibrosis


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