Ultrasound (US) imaging is a critical diagnostic tool for assessing human kidneys. A US transducer works by transmitting radiofrequency sound waves into the body. These waves interact with tissues and tissue interfaces, changing them and returning them to the transducer as echoes. Its piezoelectric crystals vibrate in response, converting the echoes into electrical signals, which are then processed using complex algorithms to provide cross-sectional images of the body’s underlying tissue layers. US does not use ionizing radiation and is noninvasive, meaning that it does not require any penetration of the skin. In both acute care and ambulatory settings, US imaging can reveal information on kidney morphology, physical features, function, and probable anomalies. US is used as the first-line imaging modality for previously undiagnosed native and transplanted, abnormal kidney function. Several studies have argued for the formal incorporation of sonography into training and clinical practice, citing its increasing utility and accessibility in nephrology. Taken together, advances in beamforming, image acquisition, and image processing make portable US a reality while lowering costs by several orders of magnitude. One of these advances is point-of-care US. It is a US examination performed by nephrologists at the patient’s bedside, often treated as an extension of physical examination. Point-of-care US has become more accessible and widespread with increasingly portable, even handheld, US equipment. To successfully use US as an adjunct to clinical decision making, a thorough understanding of the technology and its variants is required, particularly in the context of chronic kidney disease (CKD) and kidney transplantation.

This review discusses US and its derivatives as well as their clinical applications. Brightness mode (B-mode), color Doppler, power Doppler, and spectral Doppler US are all types of US often used in disease evaluation. Additional types, including contrast-enhanced US and US-based elastography, have seen tremendous research efforts and may be worth considering for routine clinical use. This review focuses on the most common types for which published literature on CKD and kidney transplantation is accessible. This article summarizes the mechanism of action for each variation, reviews the type of data obtained, and synthesizes pertinent research demonstrating its therapeutic utility in CKD and transplantation.

**B-MODE IMAGING**

B-mode US is a 2-dimensional, cross-sectional depiction of anatomy in grayscale. A pixel’s depth in the image represents a tissue’s distance from the transducer, and its intensity represents echogenicity, which is the ability of the tissue to reflect the US signal. Tissue interfaces and microstructures influence echogenicity, capturing underlying tissue variations. Lower imaging frequencies allow the imaging of deeper tissues, such as native kidneys in the abdominal cavity’s back wall. The trade-off for penetration depth is that frequency is inversely linked to spatial resolution; lower frequencies have worse resolution (Fig 1). A transplanted kidney, located in the recipient’s iliac fossa, is closer to the abdominal skin surface, allowing higher frequencies (Fig 1).

The anthropomorphic measurements provided by B-mode US include the length and volume of kidneys. Kidney length is defined as the maximum distance from pole to pole, measured in a longitudinal view, with a normal range of 10-12 cm. The left kidney is longer than the right, with median lengths of 11.2 and 10.9 cm, respectively. Widjaja et al. used US imaging to quantify the native kidney lengths of 69 adults and compared them with single kidney function using radionuclide imaging. They found the length to have a moderate positive correlation ($r^2 = 0.48$) with the estimated glomerular filtration rate (eGFR) of the native single kidneys, although Zanoli et al. discovered that the correlation between length and eGFR varied based on the eGFR equation. Measured in a longitudinal view from the kidney’s midpole boundary to
the base of the medullary pyramids, cortical thickness is a common metric. The normal cortical thickness is 7-10 mm; reduced cortical thickness may indicate progressive kidney disease or decreased eGFR.\textsuperscript{11,15,16}

With respect to volume, the normal range in men is 110-190 mL and in women is 90-150 mL.\textsuperscript{17} It is possible to measure volume by simplifying the kidney’s shape as spherical or ellipsoid and measuring several distances. Better still is to contour the kidney in each US frame and sum the contoured area. Manual contouring is the gold standard for US-based volume estimation; however, it is very time consuming and labor intensive. Studies by Zanoli et al\textsuperscript{14} and Sanusi et al\textsuperscript{18} reported favorable relationships between kidney volume and 24-hour creatinine clearance as well as eGFR estimated using various equations. Volume interpretation requires caution as Kim et al\textsuperscript{19} found that 2-dimensional, US-based volumes underestimated computed tomography volumes by 15%.

Nephrologists can use these parameters to understand the state of kidney disease. A kidney length of ≤8 cm is related to kidney failure.\textsuperscript{20} If the kidney loses its length or volume, this is attributed to atrophy or fibrosis.\textsuperscript{8} A unilateral decrease may specifically indicate hypoperfusion, such as in renal artery stenosis,\textsuperscript{8} whereas bilateral hypotrophic kidneys with decreased volumes may indicate advanced disease, such as in kidney failure. Fluid retention, inflammation, protein deposition, and acute tubular necrosis or neoplasms are linked to increased kidney volume.\textsuperscript{8}

Renal echogenicity is frequently used as a kidney health biomarker. The echogenicity of renal parenchyma is assessed by comparing it with a reference tissue, such as the liver, which should be less echogenic.\textsuperscript{11,21} Moghazzi et al\textsuperscript{12} retrospectively evaluated the correlation between cortical echogenicity and histopathologic parameters, finding a strong correlation with severe disease and increased relative echogenicity. Similarly, Page et al\textsuperscript{23} found a link between glomerular sclerosis detected using biopsy and cortical echogenicity. Echogenicity must be carefully considered because it depends on the US machine setup, image acquisition factors, or hydration status. Additionally, occult liver disease may increase the liver’s echogenicity, causing a misleading negative comparison with the renal cortex. The echogenicity of the cortex and medulla are easily compared. The inability to distinguish between them is known as the loss of corticomedullary differentiation.\textsuperscript{24} This observation is nonspecific in both native and transplanted kidneys.\textsuperscript{24} Infection, autosomal recessive kidney disease, renal vein thrombosis, and rejection are all conditions that may present with the loss of corticomedullary differentiation.\textsuperscript{25,26}

B-mode imaging lies in point-of-care adoption. The feasibility and usability of these morphologic and echogenic properties are considerably boosted by accessible US imaging. Further research on understanding how easily nephrologists can acquire clinically meaningful images is required, as is research on existing technical challenges to further adoption.

**DOPPLER IMAGING**

Doppler imaging is used to assess renal vascular flow and patency. When a pulsed US wave encounters a moving medium, the resultant echo undergoes a frequency shift.\textsuperscript{10} In the human body, this moving medium is commonly blood inside vessels. The frequency decreases as the medium moves away from the transducer and increases as it moves toward it.\textsuperscript{16} Derived from these shifts is flow velocity.\textsuperscript{10} The types of Doppler US can be color Doppler, power Doppler, or spectral Doppler imaging. In Fig 2, color Doppler imaging overlays the color map of flow velocity onto a B-mode image also showing directionality. Power Doppler imaging employs a color map that sacrifices directionality for increased sensitivity to detect blood flow. Spectral Doppler imaging produces a “waveform” of velocities across time and can be employed in continuous or pulsed wave patterns. Continuous waves measure high velocities but cannot localize them because they employ different crystals to send and receive radiofrequency waves at the same time. Pulsed waves can localize velocities but are subject to aliasing.
Doppler US is widely used to assess transplanted kidneys, although it is difficult to be performed in native kidneys because of the depth of the organ. It can be used to detect renal vascular disorders such as stenosis or thrombosis. For example, increased peak systolic velocities surpassing 200 cm/sec, a 3.5:1 peak systolic velocity ratio between the renal artery and the vascular tributary proximal to it, and aliasing are all signs of the renin angiotensin system. The use of pulsed-wave spectral Doppler imaging is required. A systematic review found that peak systolic velocity had the highest sensitivity (85%) and specificity (92%) compared with other US parameters in the diagnosis of this devastating complication.28 With increasing kidney size and reversed parenchymal vascular flow, the absence of venous flow from renal vein thromboses is instructive. Doppler US can also be used after biopsy to evaluate postprocedure complications, such as intrarenal arteriovenous fistula, which occurs up to 18% of the time.29 Power Doppler imaging is useful in the diagnosis of kidney ischemia or infarction because its greater sensitivity helps in the detection of minor vascular alterations such as capillary bed changes.30

The renal resistive index (RRI) can be derived from Doppler US. This is a unitless, surrogate measure of intrarenal parenchymal pathology, defined as the ratio of the difference between peak systolic velocity and end-diastolic velocity to the peak systolic velocity. It is measured in arcuate or interlobar arteries. When RRI is ≤0.7, it reassures the nephrologist of the absence of severe kidney damage.31 In the native kidney setting, a controversy arises when elevated RRI and histopathologic markers are associated. Some studies have linked increased RRI with glomerulosclerosis progression, glomerular disease, arteriolosclerosis, and interstitial fibrosis, whereas others have found no correlation.32-36 Elevated RRI may have prognostic value because it has been associated with worsening kidney function,37,38 cardiovascular risk scores,39 and progressive diabetic nephropathy.40 In kidney transplantation, renal vein and renal artery thromboses have been associated with low RRI values in the immediate postoperative period.41 Wang et al reported that donor kidneys from deceased individuals have higher RRIs (0.73 ± 0.10) than control kidneys from living donors (0.66 ± 0.11). RRI is yet to be proven as a predictive factor for kidney transplant outcomes, including long-term allograft survival.41

Some researchers have contended that variation in RRI is related to extrarenal variables rather than inherent structural changes in the kidney, both in native and transplanted contexts. RRI is affected by age, heart rate, blood pressure, systemic vascular resistance, and hydration.42 O’Neill43 presented a mathematical approach to the interpretation of RRI, suggesting that it is more easily impacted by pulse pressure, renal capillary wedge pressure, and vascular compliance. Rather than intrarenal changes, the author argued that it reflects systemic hemodynamics.43 Others have suggested that increases in posttransplantation RRI are linked to the organ’s new vascular environment in the recipient.44 Seiler et al45 showed that RRI may not be specific to kidneys. They reported a correlation between RRI and increased common carotid thickness but not kidney-specific markers.45 However, as Grün et al46 reported in their investigation of variations in resistive indices between the spleen and the kidney, the use of 2 indices may reduce extrarenal influence and enhance kidney specificity. Overall, these studies suggest caution while interpreting RRI as a kidney-specific pathology indication.

Doppler US-acquired values are subject to external factors, such as the imaging plane, operator technique, and transducer location, making valid, accurate, and repeatable measurements difficult. Future research should consider extrarenal hemodynamic variables that may affect RRI values. Given the difficulty in conducting high-quality Doppler imaging studies without experienced personnel, the use of Doppler US at the bedside may be best suited for determining vascular patency or its absence.

**CONTRAST-ENHANCED US**

A technique known as contrast-enhanced US is used to investigate blood flow and perfusion in greater detail.47 A contrast medium—a nontoxic, biologically inert

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**Figure 2.** Sample images of color Doppler imaging used to assess a kidney’s vasculature. (B) A renal resistive index of 0.67 was calculated from the spectral information obtained.
microbubble with a diameter $<10\ \mu m$—is injected into the systemic circulation.\textsuperscript{47} The contrast medium dissolves on its own within minutes of being injected and has no effect on kidney function or the systemic circulation in any other manner. Although contrast-enhanced US is less expensive than color Doppler imaging, it provides a more accurate assessment of the microvasculature and perfusion in narrow blood arteries, where color Doppler imaging may require significant operator expertise or blood flow may be too slow.\textsuperscript{48}

Contrast-enhanced US enables improved visualization of perfusion and the provision of absolute, quantitative values through the observation of destruction and replenishment of the contrast medium, which is characterized using time-intensity curves.\textsuperscript{49} These curves can be used to compute perfusion characteristics, such as time to peak, rising time, area under the curve, peak intensity, and mean transit time. The contrast agents are typically injected intravenously as either a bolus or an infusion.\textsuperscript{47} With the use of bolus injections, it is possible to image the contrast agent as it enters and exits the image, with the imaging period ranging between 3 and 5 minutes per bolus injection.\textsuperscript{47} Infusion provides for extended imaging times (up to 15 minutes), but it does not allow the imaging of the agent leaving the image.\textsuperscript{47} Contrast-enhanced US can be used to assess ischemic diseases, including infarction and necrosis, as well as the states of relative hypervascularization, such as malignant kidney lesions.\textsuperscript{49,50}

Ma et al.\textsuperscript{41} investigated the role of contrast-enhanced US in 33 patients with CKD and diabetes. They discovered that the total area under the time-intensity curve was only moderately correlated with eGFR and that patients with early- and late-stage CKD had significantly different rising time and time-to-peak parameters.\textsuperscript{51} These parameters mirror the hemodynamic environment, showing slower kidney perfusion in advanced disease.\textsuperscript{52} Dong et al.\textsuperscript{12} demonstrated, using a bolus injection in 41 patients with suspected CKD stages 1-3, that the area under the curve and the derived peak intensity, but not the time to peak, were significantly different from those in healthy controls even though the set of parameters was different from that used by Ma et al.\textsuperscript{51} The use of a derived peak intensity of $<12\ dB$ was the best predictor of the onset of CKD, achieving an accuracy of 79%, a sensitivity of 76%, and a specificity of 81%.\textsuperscript{52} Girometti et al.\textsuperscript{43} used contrast-enhanced US to evaluate acute diseases such as kidney infarction. Using contrast-enhanced US, they found a significantly higher ($P = 0.0002$) detection rate of infarction than with the use of color Doppler imaging.\textsuperscript{51} Finally, Chang et al.\textsuperscript{10} used contrast-enhanced US to evaluate indeterminate kidney lesions in patients with and without CKD. Across all patients, contrast-enhanced US achieved high sensitivity (96%) and moderate specificity (50%) for malignancy detection, whereas the sensitivity dropped to 90% and specificity increased to 55% only in those with CKD.\textsuperscript{50} However, this was based on a radiologist’s interpretation of contrast-enhanced US images rather than any specific perfusion parameter. In contrast to these studies, Jeong et al.\textsuperscript{74} discovered no relationship between perfusion parameters and kidney function.

Several publications have shown that contrast-enhanced US parameters can be used to identify abnormal kidney function in patients who have undergone transplantation. Fischer et al.\textsuperscript{55} published 1 of the earliest studies that found that the arrival time of the contrast medium from the renal artery to the cortex was significantly delayed in patients with acute rejection compared with that in controls. Although Yang et al.\textsuperscript{56} successfully used contrast-enhanced US to differentiate between acute and chronic transplanted abnormal kidney function, the researchers were unable to differentiate between rejection subtypes. Contrast-enhanced US had a sensitivity of 86%, a specificity of 90%, and an area under the curve of 0.94 in a systematic review of posttransplantation complications, such as rejection or vascular pathologies, in 542 patients.\textsuperscript{57}

Currently, there is paucity of research on contrast-enhanced US in the kidney. Additional contrast agents, specialized US machines, and general lack of competence in using contrast-enhanced US are all factors. Furthermore, the requirement for contrast agent injections distinguishes this variant as the only invasive US variant, complicating its adoption even further. More research is needed to determine the efficacy of contrast-enhanced US in the detection of early intrinsic kidney disease pathologies and early kidney transplant abnormalities such as rejection.

**ELASTOGRAPHY**

Regardless of the primary diagnosis, kidney disease frequently follows a common histologic pathway that includes inflammation, sclerosis, atrophy, maladaptive hemodynamic and nonhemodynamic responses, and fibrosis. These various states might have a local or global effect on the kidney. Kidney biopsy is the gold standard for the assessment of its pathology; however, it carries with it the potential complications of an invasive procedure. Can US be used instead of biopsy for noninvasive evaluation of disease conditions because it is noninvasive? Elastography, a type of US imaging, is a possible alternative.

Elastography is used to measure tissue elasticity, allowing for subsurface “palpation.”\textsuperscript{58,59} This US variation’s mechanism of action involves the transmission of acoustic energy into the body to cause transient displacements.\textsuperscript{58,59} This can be generated by the transducer or an external source.\textsuperscript{58,59} This energy causes a transient displacement of the tissue.\textsuperscript{58,59} The US transducer can be used to detect deformations because the displacement is slower than the speed of the US pulse waves.\textsuperscript{58,59} These deformations determine the tissue’s elasticity. Elastography can be measured either in a relative (to other tissues in the same image) or absolute (in standardized units and compared with a reference) manner.\textsuperscript{58,59} The outputs of elastography include shear wave velocity (measured in m/s), Young modulus (measured in kPa), or elastograms (Fig 3).\textsuperscript{58,59}
The variants of elastography include strain elastography (also known as quasistatic or qualitative elastography), transient elastography, acoustic radiation force impulse imaging, shear wave elastography, and shear wave absolute vibroelastography. External compression is applied to the tissue in strain elastography, with pulse-echo data collected before and after compression. Only a qualitative elastogram is produced because the amount of compression is not measured. Transient elastography improves on this by providing 1-dimensional quantitative measurement (a point). The acoustic radiation force impulse imaging technology further advances this by applying small acoustic radiation forces to induce displacements at a focal point or at multiple points. With the use of multiple points, a 2-dimensional elastogram within a region of interest can be obtained. Shear wave elastography uses shear waves that propagate laterally relative to the transducer and concentrate within regions of interest, causing displacements. Shear wave absolute vibroelastography employs an external low-frequency excitation source, allowing for 3-dimensional quantitative mapping of stiffness at greater depths. The key differences between these variants include qualitative versus quantitative outputs, imaging depths at which measurements can be obtained, the dimensionality of the measures (a single point, a small region of interest, or an entire volume), and the source of the excitatory stress (internal vs external). Because image acquisition protocols and data analysis approaches differ, it is difficult to compare the results of these technologies.

Elastography in the kidney has several potential applications. Consider fibrosis, a hallmark of CKD and chronic transplant rejection. As fibrosis accrues, there is an increase in collagen deposition and extracellular matrix at the microscopic level, in turn potentially impacting the overall stiffness of the kidney. Measuring this stiffness may have diagnostic and prognostic potential in clinical decision making.

According to Menzilcioglu et al, the use of strain imaging with a cutoff value of 0.93 (88% sensitivity and 95% specificity) can help detect CKD. Bob et al used acoustic radiation force impulse imaging to discover that patients with advanced CKD had significantly lower elasticity values than those with early-stage disease. Some groups found no significant difference in stiffness measured using acoustic radiation force impulse imaging between CKD stages. Similarly, shear wave elastography has had mixed results. Unlike Bob et al, Hassan et al found greater stiffness in patients with CKD stage 3 and 4 than in healthy participants. Although Leong et al reported that shear wave elastography is superior to kidney length and cortical thickness as the US markers of CKD, their cutoff value for healthy versus diseased native kidneys was 4.31 kPa. As of now, no in situ reference values for native kidneys have been developed.

Because of its superficial placement, a transplanted kidney is ideal for elastography. Gao et al found that “normalized strain” (defined as the ratio of cortical strain to the strain in the surrounding structures) was substantially linked with the biopsy-proven degree of fibrosis.
Challenges and Opportunities in Kidney US

Kidney US has several limitations. In all derivatives, image acquisition and interpretation fall under operator dependencies and remain barriers to its use. Clinically acceptable images, which may be technically complex to achieve, require considerable expertise. Subjective interpretation of images persists, resulting in interrater variability. Manual measurements of the length and volume entail manual labor and may introduce intrarater and interrater variability. Artificial intelligence may mitigate these issues. It may enhance nephrologists’ ability to acquire and interpret images, regardless of their baseline skill. Additionally, thorough interpretation has not yet been fully integrated into medical education, necessitating additional training and effort. The modification of fellowships, residencies, and medical undergraduate programs to incorporate US training will require significant program support, the availability of machines and qualified instructors, and mechanisms for assessing competency. There is a clear interest in this training because several US curricula have been outlined across the stages of medical training.

New technologies may also offer unforeseen opportunities. Chen et al demonstrated the use of superresolution ultrasound imaging in the detection of alterations in the renal microvasculature in a murine model of acute kidney injury. They demonstrated the ability to achieve a resolution of 50 μm and observed changes in the microvascular density and tortuosity; these metrics would be difficult to obtain with conventional techniques. As another example, Hosain et al created a novel variant of acoustic radiation force impulse imaging and explored how the inherent anisotropic nature of kidneys is emphasized by employing this variant and how it serves as a biomarker, a promising avenue of research. In a seminal article, Hysi et al used photoacoustic imaging, an emerging variant of US that leverages laser pulses, to directly image fibrosis. They demonstrated this US variant’s ability to directly image collagen with phenomenal accuracy in rat, porcine, and ex vivo human kidneys. Although it requires in vivo validation and clinical translation, this study represents a noninvasive kidney fibrosis measurement milestone.

Conclusion

In conclusion, US and its derivatives have a broad range of potential for improving the management of kidney disease...
by nephrologists. US can and continues to deliver clinically useful information in a noninvasive, real-time manner, with applications ranging from simple size measurements using B-mode imaging to perfusion and vascular assessment in Doppler and contrast-enhanced US to the assessment of stiffness and elastic properties using US elastography. With the advancement of technology in the field, low-cost, high-quality, portable US scanning to provide multiparametric quantification may eliminate tests that are orders of magnitude more expensive and eliminate traditional, invasive biopsies. A nephrologist’s arsenal needs US now and in the future.

ARTICLE INFORMATION

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