New Ultrasound Techniques Promise Further Advances in AKI and CKD

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ABSTRACT

AKI and CKD are important clinical problems because they affect many patients and the associated diagnostic and treatment paradigms are imperfect. Ultrasound is a cost-effective, noninvasive, and simple imaging modality that offers a multitude of means to improve the diagnosis, monitoring, and treatment of both AKI and CKD, especially considering recent advances in this technique. Ultrasound alone can attenuate AKI and prevent CKD by stimulating the splenic cholinergic anti-inflammatory pathway. Additionally, microbubble contrast agents are improving the sensitivity and specificity of ultrasound for diagnosing kidney disease, especially when these agents are conjugated to ligand-specific mAbs or peptides, which make the dynamic assessment of disease progression and response to treatment possible. More recently, drug-loaded microbubbles have been developed and the load release by ultrasound exposure has been shown to be a highly specific treatment modality, making the potential applications of ultrasound even more promising. This review focuses on the multiple strategies for using ultrasound with and without microbubble technology for enhancing our understanding of the pathophysiology of AKI and CKD.


AKI is a common and costly disease process caused by a multitude of insults to the kidney vasculature, tubules, and interstitium.1 AKI is common, especially in the intensive care unit setting, where it develops in 15%–25% of critically ill patients.2–4 In addition to causing significant morbidity and mortality, the economic burden of AKI is greater than both myocardial infarction and gastrointestinal bleeding, with an adjusted increase in both cost of hospitalization and length of stay.5 Furthermore, recent studies in patients with AKI have demonstrated an increased risk for the subsequent development of CKD, which further exacerbates the patient-specific and societal effect of AKI.6–10 Therefore, targeted means for early diagnosis, progression monitoring, and treatment of AKI are important areas of focus to both decrease healthcare utilization and improve patient outcomes, but are currently lacking.11 The purpose of this review is to highlight recent advances in ultrasound (US) imaging of the kidney, with an emphasis on contrast-enhanced US (CEUS), to meet the need for improved diagnosis, monitoring, and treatment of patients with AKI.

IMAGING STRATEGIES IN KIDNEY DISEASE

Given the incidence of AKI, especially in hospitalized and critically ill patients, as well as the prevalence of CKD in the United States population, imaging in these patients is extremely important to diagnose and monitor disease progression. Several different imaging modalities have been used to gather information on kidney anatomy (to rule out obstruction), differentiate AKI from CKD, and to obtain information on renal blood flow and GFRs.12 However, traditional imaging modalities come with specific limitations and contraindications in patients with kidney disease. Contrast-enhanced computed tomography and magnetic resonance imaging are extremely limited because of the inherent patient risk associated with contrast-induced toxicity.13–15 In addition to being nonportable, these modalities are costly, and, therefore, not as amenable to serial imaging to monitor disease progression. US is the most popular imaging modality when it comes to diagnosing kidney disease. Doppler US is routinely used during a clinical examination to assess renal blood flow and diagnose vascular abnormalities because a resistance to blood flow can occur in both CKD and AKI.16,17 A more recent advance in US imaging was the introduction of contrast agents, which are non-toxic gas-filled microbubbles (MBs) that
oscillate when exposed to an acoustic field and thus are able to enhance the signal intensity from the vasculature by up to 25 dB when visualized using nonlinear US imaging modes. These agents have long been used in cardiac imaging but are also superior for imaging the intrarenal vasculature because they are non-nephrotoxic and do not diffuse out of the vascular space. Given the potential for this imaging modality to address the lack of current diagnostic and therapeutic modalities for patients with AKI, these techniques and their applications, limitations, and areas for advancement will be discussed further below (summarized in Table 1). In addition, newer techniques that utilize US with and without MB are currently in development as a therapeutic strategy for drug delivery and/or modulation of the post-AKI immune response and will also be discussed.

**US AND THE CHOLINERGIC ANTI-INFLAMMATORY PATHWAY IN AKI**

The therapeutic benefits of low-intensity US have been known for decades and used by physical therapists to reduce local swelling and chronic tissue inflammation. Recent findings from the Okusa laboratory have highlighted the potential for US to dampen disease progression after AKI. To study the utility of CEUS imaging after AKI, their laboratory serendipitously discovered that US alone prevents renal inflammation and dysfunction as well as the development of CKD by stimulating the splenic cholinergic anti-inflammatory pathway. In these studies, mice were subjected to US 24 hours before ischemia-reperfusion injury (IRI), which was shown to prevent not only acute deterioration of kidney function and accumulation of neutrophils and mononuclear phagocytes in the kidney but also chronic intrarenal collagen deposition secondary to fibrosis as seen in CKD. Because left-, but not right-sided, US treatment before IRI attenuated renal dysfunction, the US-mediated protection was localized to the spleen and subsequently shown to be dependent upon cholinergic stimulation of CD4+ T cells. These findings were further confirmed using splenectomized mice and bone marrow chimeras transplanted with hematopoietic cells from α-7 nicotinic acetylcholine receptor (α-7nAChR)-deficient mice, which demonstrated that the protection provided by US before IRI is dependent upon acetylcholine-dependent signaling in splenocytes. Because splenic sympathetomy with 6-hydroxydopamine negated the protective effects of US, vagal cholinergic stimulation of splenocytes was shown to be the mechanism underlying the protective effects of US in AKI mediated by IRI. Collectively, these findings suggest that US is of significant therapeutic potential in AKI by modulating the splenic cholinergic anti-inflammatory pathway. Testing the effects of US intervention in AKI using large animal models is an important next step. To successfully translate to humans, carefully detailed preclinical studies in these larger animal models are needed. These studies should investigate the effect of kidney depth and size differences while defining optimal US treatment parameters. Given the safety, relatively low cost, availability, and portability of US, these findings could have immediate ramifications for patients with AKI if they can then be validated in humans.

In the kidney, the positive consequences of US therapy appear to be mediated not by a direct effect on the kidney tissue itself, but instead because of post-injury immunomodulation that is dependent upon the spleen. The specific cellular subsets that are modulated by US therapy remain to be determined, which is important because a wide array of inflammatory cells present in the spleen and have been demonstrated to play an important yet dynamic role in modulating AKI. Although the first step is to validate these findings in patients with AKI, an important extension of this work will be to determine if US exposure demonstrates utility in preventing AKI in critically ill patients who are not only most at risk for this disease state to develop, but also most at risk to suffer major morbidity and mortality. These studies would be relatively facile, as US is readily available for most hospitalized intensive care unit patients and because the use of US in these patients would confer the additional benefit of monitoring the progression of renal disease and its treatment. Furthermore, the application of these findings to the field of renal transplantation is particularly promising as an avenue to dampen the alloimmune response without the deleterious side-effects of pharmacologic immunosuppression. As discussed below, coemploying MB contrast agents with or without molecular targeting and/or a therapeutic payload would only strengthen these assertions. Thus, the potential benefits of US are multifold and only beginning to be understood.

**CEUS IN THE DIAGNOSIS OF KIDNEY DISEASE**

In 2016, the US Food and Drug Administration approved the first commercial MB contrast agent (Lumason; Bracco Diagnostics) for US imaging of the liver and characterization of focal liver lesions in adult and pediatric patients. The expanded indication of this contrast agent will likely serve as a catalyst for increased clinical and off-label use of these MBs such as in the diagnosis of kidney diseases. Additionally, MB technology continues to evolve rapidly, with more powerful contrast agents capable of guided drug delivery currently under investigation. Under appropriate conditions, CEUS can be used as a non-invasive imaging tool for collecting quantitative measurements of regional renal perfusion and microvascular function. By analyzing the temporal characteristics of MB flow and clearance (on the order of minutes) from circulation, surrogate parameters related to tissue perfusion and blood velocity can be obtained. To that end, CEUS was recently shown feasible for the early detection and monitoring of AKI. In these studies, rats that had previously undergone right nephrectomy were subjected to 30 minutes of IRI, followed by US imaging at specific postinjury time points. Early after injury (5 hours), CEUS measurements from injured rats indicated that perfusion was considerably lower, whereas perfusion returned to similar levels as in control animals 48 hours after injury. Although these studies
### Table 1. Summary of studies utilizing US in kidney diseases

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<tr>
<th>Stage</th>
<th>Model (Species)</th>
<th>MB Target</th>
<th>Summary</th>
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<tr>
<td>Diagnosis and monitoring</td>
<td>IRI (mouse)</td>
<td>ICAM-1</td>
<td>US imaging of ICAM-1-targeted MBs can effectively evaluate IRI progression</td>
<td>70</td>
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<td>IRI (rat)</td>
<td>Oxidative stress</td>
<td>NA</td>
<td>Catalase-loaded nanospheres to detect oxidative stress after IRI</td>
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<td>Crush injury (rabbit)</td>
<td>NA</td>
<td>CD3, CD4, and CD8</td>
<td>Enhanced detection of early acute rejection and differentiation from IRI and calcineurin inhibitor toxicity</td>
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<td>Allograft rejection (rat)</td>
<td>NA</td>
<td>Thrombomodulin</td>
<td>US imaging of thrombomodulin-targeted MBs can detect early changes in renal perfusion in diabetic rats</td>
<td>73</td>
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<tr>
<td>DN (humans)</td>
<td>NA</td>
<td></td>
<td></td>
<td>74</td>
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<tr>
<td>DN (rats)</td>
<td>NA</td>
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<td>75</td>
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<tr>
<td>Allograft rejection (rat)</td>
<td>CD3</td>
<td>CD3-targeted MBs are a highly specific means to assess allograft rejection</td>
<td>76</td>
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<td>Allograft rejection (human)</td>
<td>NA</td>
<td>CEUS</td>
<td>Progressive delayed renal enhancement and perfusion in ischemic CKD</td>
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<tr>
<td>IRI (rat)</td>
<td>NA</td>
<td></td>
<td>Post-IRI CEUS imaging shows an initial reduction in renal perfusion followed by progressive recovery compared with controls</td>
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<td>IRI bypass (human)</td>
<td>NA</td>
<td>CEUS</td>
<td>Alterations in renal microcirculation during cardiopulmonary bypass are detectable with CEUS</td>
<td>79</td>
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<td>Ischemic CKD (dog)</td>
<td>NA</td>
<td></td>
<td></td>
<td>80</td>
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<td>IRI (mouse)</td>
<td>P-selectin</td>
<td></td>
<td>Post-IRI, P-selectin expression (an index of ischemic injury): CMJ region (432.1) &gt; cortex (369.4) &gt; medulla (86.5).</td>
<td>81</td>
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<td>IRI (rabbit)</td>
<td>Neutrophils</td>
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<td>US imaging of neutrophil-targeted MBs can be used to evaluate the severity of IRI-induced AKI</td>
<td>82</td>
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<td>Renal infarct (human)</td>
<td>NA</td>
<td>CEUS</td>
<td>US is a reproducible tool to detect acute renal infarcts in men with a diagnostic performance approaching that of CT</td>
<td>83</td>
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<td>Chronic allograft nephropathy</td>
<td>NA</td>
<td>CEUS</td>
<td>CEUS reached a higher sensitivity, specificity, and accuracy than color Doppler US</td>
<td>84</td>
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<td>IRI (rat)</td>
<td>VCAM-1 and P-selectin</td>
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<td>US imaging of MBs targeted to vascular inflammatory markers correlates with injury progression in IRI</td>
<td>85, 86</td>
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<td>Allograft rejection (human)</td>
<td>NA</td>
<td>CEUS</td>
<td>CEUS provides prognostic information by distinguishing between acute rejection and ATN in transplant recipients</td>
<td>87</td>
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<td>Allograft function (human)</td>
<td>NA</td>
<td>Tissue elasticity imaging is a sensitive method for diagnosing renal allograft function</td>
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<td>Renal tissue fibrosis (human)</td>
<td>NA</td>
<td>Tissue elasticity imaging can detect renal fibrosis associated with CKD</td>
<td>89</td>
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<table>
<thead>
<tr>
<th>Stage</th>
<th>Model (Species)</th>
<th>Disease Target</th>
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<td>Treatment</td>
<td>UUO (mouse)</td>
<td>Connective tissue GF</td>
<td>US-stimulated delivery of shRNA targeting CTGF reduces renal fibrosis after UUO</td>
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<td>BMSC homing (mouse)</td>
<td>NA</td>
<td>TNF-α</td>
<td>US therapy alone causes vascular endothelial changes that enhances renal homing of BMSC</td>
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<td>IRI (mouse)</td>
<td>Intermedin</td>
<td>SDF-1</td>
<td>US-stimulated delivery of anti-TNF-α siRNA reduces AKI</td>
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<tr>
<td>UUO (mouse)</td>
<td>NA</td>
<td>Intermedin</td>
<td>US-stimulated delivery of intermedin prevents renal fibrosis after UUO</td>
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<td>DN (rat)</td>
<td>MSC and SDF-1</td>
<td></td>
<td>US-stimulated MBs loaded with SDF-1 promote MSC homing to the kidney in DN and promote renal repair</td>
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<td>DN (rat)</td>
<td>Capillary permeability</td>
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<td>US-stimulated MBs increase renal interstitial capillary permeability and may enhance drug and gene delivery in DN</td>
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<td>MSCs</td>
<td></td>
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<td>92, 93</td>
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<td>GN</td>
<td>Smad7</td>
<td></td>
<td>Renal overexpression of Smad7 via US-stimulated gene transfection blocks renal fibrosis, inflammation, and injury</td>
<td>94</td>
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<td>Hypertension</td>
<td>GRK4</td>
<td></td>
<td>US-stimulated delivery of GRK4 siRNA to the kidney lowers BP</td>
<td>95</td>
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Summary of peer-reviewed studies describing the use of US and MB contrast agents for the diagnosis and monitoring (top of table) or treatment (bottom of table) of kidney diseases including AKI, CKD, and allograft rejection. Where applicable, the mAb target or disease mediator is indicated in columns headed MB Target and Disease Target, or NA is listed if no specific target was used in the study. ICAM-1, intracellular adhesion molecule 1; NA, not applicable; DN, diabetic nephropathy; CMJ, corticomedullary junction; CT, computed tomography; VCAM-1, vascular cell adhesion molecule 1; ATN, acute tubular necrosis; UUO, unilateral ureteral obstruction; GF, growth factor; shRNA, short hairpin RNA; CTGF, connective tissue growth factor; BMSC, bone marrow stromal cell; siRNA, short interfering RNA; MSC, mesenchymal stem cell; HgCl2, mercury chloride.
Implicate CEUS as useful in the monitoring of AKI progression, future studies are needed to determine if CEUS can stratify the extent of AKI, which could help to guide therapy. This could be accomplished experimentally by comparing groups with increasing duration of ischemic injury and correlating this time with serum creatinine values and CEUS findings. Importantly, determining how the dynamic nature of postinjury CEUS findings in rodents will correlate with AKI progression in humans with numerous comorbidities and/or critical illness as well as disparate mechanisms of injury is an important consideration if these findings are to be translated to the bedside. In addition, the predictive value of CEUS in determining the likelihood that a patient or experimental animal will recover from AKI, progress to CKD, or succumb to their disease is an important area of future study.

CEUS also holds promise in the field of renal transplantation, where a noninvasive and low-cost means to assess graft function and monitor or predict rejection would revolutionize the care of patients in the post-transplant setting. Recently, CEUS was used to assess the perfusion status of transplanted kidneys and compared with the gold standard of graft tissue biopsy.29,30 In this study, there were significant changes in renal perfusion that were detectable by CEUS in patients experiencing acute rejection compared with stable transplant patients. These findings allowed the authors to develop a new and highly accurate index to predict acute rejection.29 This imaging modality offers clear advantages when compared with similar techniques utilizing X-ray computed tomography.31 As discussed below, the potential to use US in combination with MB may also offer a novel, highly graft-specific means to deliver immunosuppressive drugs to the graft.

Despite the clinical momentum associated with CEUS, a more direct method for assessing the microvascular inflammatory response might prove useful for not only

![Figure 1](image_url)

**Figure 1.** Targeted MBs for the diagnosis and monitoring of AKI and its progression. (A) Schematic representation of MB contrast agent and a targeting strategy using an mAb. MBs comprise a gas core surrounded by a lipid shell, which can be targeted to specific anatomic compartments or disease-specific antigens by conjugation to an mAb, such as anti–P-selectin, which is upregulated in the vasculature after injury. (B) Grayscale renal US image overlaid with molecular US signal color-coded image of P-selectin–targeted MBs injected before or after 4 or 24 hours of IRI in rats. Note significant signal enhancement at 4 hours, concomitant with renal tissue inflammation, followed by subsequent signal reduction at 24 hours secondary to recovery from the short ischemic conditions. Anti–P-selectin antibody is targeted to areas of vascular activation, such as those which occur after AKI. Modified from reference 37, with permission.
quantifying the degree of tissue injury but also for determining the effect of intervention and treatment. Molecular US imaging has the potential to detect molecular changes before phenotypic changes become apparent and holds promise for the highly sensitive detection of disease biomarkers.32,33 Similar to most other forms of molecular imaging, molecular US imaging relies on the detection of a reporter capable of providing signal enhancement reflecting a molecular process of interest. Of importance, identification of inflammation-related receptors overexpressed in injured renal tissue can be exploited as targets for next-generation ligand-labeled MB contrast agents.34–38 One general conjugation strategy has been to attach disease-specific mAb to the contrast agent shell surface via a high-affinity molecular bridge39 (Figure 1). After injection, these mAb-labeled MB contrast agents circulate systemically, bind at the target tissue,40 and are readily imaged by CEUS methods. Signal intensity can then be correlated with extent of injury, and monitored over time to assess disease progression or resolution.37

There is clear evidence that coupling US imaging with MB targeted to inflammatory markers is a promising means to detect changes in the renal vasculature that are indicative of AKI.37,41 In a study by our laboratory, rats subjected to 30 minutes of bilateral IRI or sham controls were assessed by US coupled with mAb-labeled MBs targeted to P-selectin or VCAM-1 4 and 24 hours after injury. Relative to control animals, there was significant signal enhancement at 4 hours in injured animals, with subsequent signal diminution at 24 hours. In addition, there were several interesting findings that point to noteworthy considerations for this imaging modality in the future, specifically as it relates to diagnosing and monitoring AKI. First, signal enhancement at 4 hours was two times more intense for P-selectin versus VCAM-1, suggesting that the selection of molecular targets for MB labeling significantly affects the sensitivity of this technique. Whether this is due to inherent properties of the mAb clones used in this study or the actual levels of the mAb ligands expressed on the vascular endothelium was not determined. Future experiments should be conducted to determine the optimal antigenic targets for MBs as it relates to time after injury as well as the injury mechanism. These considerations are important because the expression of injury markers changes significantly during injury progression and resolution, and this could be taken advantage of to temporally characterize the course of disease progression and resolution, monitor the effects of treatment, and predict eventual functional outcomes.42–45 Furthermore, it will be important going forward to identify additional MB ligand targets to more completely monitor the pathophysiology of injury in real-time. Whether target selection strictly depends upon ligand expression in the vasculature (such as P-selectin and VCAM-1), or could be expanded to soluble mediators that are released secondary to injury or during recovery, remains to be determined. For example, utilizing MB targeted to damage-associated molecular patterns that are released after injury may allow clinicians to identify patients in whom the injurious process is ongoing, and thus therapeutic strategies are failing.46,47 Alternatively, utilizing MB targeted to endogenous cytoprotective responses such as the enzyme heme oxygenase-1 (HO-1) may allow for not only the diagnosis of AKI but also a quantitative assessment of the patient response to injury.48 Or, in patients in whom the diagnosis of AKI versus CKD is unclear, MB targets that are specific to acute injury, such as neutrophils that home to and bind the

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<th>Table 2. US-based imaging modalities and their uses in kidney diseases</th>
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<td><strong>US Modality</strong></td>
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<td>US</td>
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<tr>
<td>Doppler US</td>
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<tr>
<td>CEUS</td>
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<tr>
<td>Molecular US</td>
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<td>US-stimulated MB destruction</td>
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<td>US-stimulated drug delivery</td>
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Summary of the multitude of uses for US in AKI and CKD and differentiates between the modalities that rely on MBs versus those that don’t. References are provided to highlight specific works that use a particular modality to test its efficacy in an experimental model of kidney disease or in patients.
vascular endothelium in the injured kidney, could be of significant diagnostic use.49,50 The applicability of such approaches is likely soon to become reality, because new contrast agents such as nanobubbles are currently in development and are capable of extravasating into the tissue.33

Available as a clinical option for nearly a decade now, US-based tissue elasticity imaging (in its many forms) allows a sensitive assessment of tissue stiffness. Several clinical studies have demonstrated the utility of US elasticity measurements for assessing tissue fibrosis in a safe and noninvasive manner.51–53 These US tissue elasticity measurement methods have several advantages over biopsies, which are invasive, painful, and associated with serious complications such as hemorrhage and nephrectomy. Notwithstanding, a limitation with these methods is that they are difficult to use on deep organs that cannot be mechanically stimulated easily or are readily imaged. Although still emerging as a diagnostic imaging modality, several promising clinical applications exist ranging from the detection of renal fibrosis in patients with CKD54,55 to the assessment of renal allograft function.56

US TREATMENT OF KIDNEY DISEASE

Although already known to be an excellent US contrast agent, MBs also have tremendous potential as an innovative method for the noninvasive delivery of therapeutic agents to diseased or injured renal tissue57 (Tables 1 and 2). There are three main strategies that have been explored. The first relies on the use of US to locally destroy (via inertial cavitation) circulating MBs preloaded with a therapeutic payload58 (Table 2). The second involves the direct delivery of therapeutic agents that have been bound to the MBs with or without the presence of US.59,60 The third known therapeutic use, termed US-stimulated drug delivery, relies on US exposure of circulating MBs leading them to resonate (via stable cavitation) and physically interact with blood vessels to induce a transient enhancement in renal vascular permeability61 (Table 2). Thereafter, any systemic therapeutic agent can more readily extravasate until this temporary window of increased permeabilization has been safely and physiologically reversed.62

These therapeutic approaches integrating US and MB are not mutually exclusive and several research groups are exploring a combination of different strategies to maximize treatment efficacy.

Using US to achieve renal specificity for drug delivery will expedite the translatability of years of promising basic science research. For example, our laboratory studies the role of the cytoprotective enzyme HO-1 in the prevention of various forms of pre-, post-, and intrinsic-renal AKI. The induction of HO-1 expression provides well documented protection against cisplatin-mediated AKI,63 but systemic induction of this enzyme is of limited utility in patients with cancer because, despite mixed evidence,64,65 there is fear that systemic pharmacologic induction of HO-1 will promote cancer cell survival and growth.66–68 However, employing US in patients with cancer receiving cisplatin-based chemotherapy to prevent intrinsic renal injury could be achieved by loading MBs with any one of a number of well described HO-1 inducers69 and achieving renal-specific delivery with US. Additionally, these uses of US-mediated drug delivery are of obvious utility in renal transplantation, where immunosuppression in the kidney is necessary but the undesired systemic toxicities of common drugs such as steroids, calcineurin inhibitors, and mycophenolate mofetil cause significant morbidity in transplant recipients. US coupled with MB contrast likely represents a unique and promising tool for the nephrologist to employ in patients with AKI because this imaging modality is a highly specific means to quickly and cost effectively diagnose kidney diseases at the bedside while potentially affecting disease progression at the same time. MB targeted to inflamed tissue using mAb only increases the sensitivity and specificity of this approach in the diagnosis of AKI. Furthermore, although findings from the Okusa laboratory convincingly demonstrate that US alone attenuates AKI and the subsequent development of CKD, the ability to add MB loaded with a therapeutic payload increases not only the diagnostic but also the therapeutic potential of this imaging strategy. Future studies must focus on translating the discoveries made in small animal models to the bedside in patients who are at risk for developing AKI, particularly in hospitalized and critically ill patients.

ACKNOWLEDGMENTS

This work was supported in part by funds provided by the Department of Bioengineering at the University of Texas at Dallas, National Institutes of Health grants K25EB017222 and R21CA212851, Texas CPRIT award RR150010 (to K.H.), and National Institutes of Health grants P30 DK079337 and R01 DK059600 (to A.A.).

DISCLOSURES

None.

REFERENCES


