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Novel Therapeutics: Can Hydrogels Work to Treat Kidney Disease?

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Abstract

Background: Hydrogels are water-swollen networks that can be made from a variety of natural and synthetic polymers. Numerous chemistries can be utilized to formulate hydrogels that are injectable, enabling facile *in situ* delivery of therapeutics such as cytokines or cells.

Summary: Cells delivered via injectable hydrogels survive injection better than cells injected in saline or media suspension. Several materials have been used to investigate the use of injectable hydrogels to treat animal models of kidney disease. Species studied to date include mice and rats. This review summarizes the various materials, encapsulated therapeutic payloads and preclinical models of kidney disease employed to investigate hydrogel injection. Transcutaneous measurements of glomerular filtration rate have demonstrated that delivery of hydrogels under the kidney capsule does not impair kidney function.

Key messages: Studies to date have shown the safety and efficacy of hydrogel therapies to treat kidney disease, and numerous studies have demonstrated that hydrogel therapy alone reduces inflammation and fibrosis.

Keywords

acute kidney injury; biomaterials; cell therapy; hydrogels; kidney disease

General Approach & Clinical Feasibility of Injectable Hydrogels to Treat Kidney Disease:

While an array of non-injectable biomaterials exist, we have limited this review to injectable hydrogels that have been studied to treat kidney disease. The anatomical location of

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both native and transplanted kidneys lend themselves to minimally-invasive local delivery approaches. In a fashion similar to performing an ultrasound-guided kidney biopsy, needles can be introduced under the kidney capsule for the injection of hydrogels that optionally contain therapeutic cargo (Figure 1). In pre-clinical models, the kidneys are approached surgically via a dorsal approach. The animal models summarized herein utilize unilateral therapy, even in the setting of bilateral disease, and have been limited to mice and rats. To date, preclinical rodent models of kidney disease that have utilized injectable hydrogels include: Adriamycin nephrotoxic acute kidney injury (AKI), unilateral and bilateral ischemia-reperfusion AKI, lipopolysaccharide (LPS) and cecal ligation puncture (CLP) models of sepsis-AKI, glycerol model of rhabdomyolysis AKI, and unilateral ureteral obstruction (UUO) of chronic kidney disease (CKD). The materials and therapeutics used in these animal models are discussed below and summarized in Table 1.

Materials and Properties of Injectable Hydrogels studied in Preclinical Kidney Disease Models:

Various materials can be used to create an injectable hydrogel. Recent reviews have summarized the various aspects of polymer selection and hydrogel formulation that investigators must consider in the selection of the material.[1, 2] Here, we summarize the materials that have been used to-date in the formulation of injectable hydrogels for the treatment of kidney disease.

Chitosan:

Chitosan is a natural polysaccharide derived from shells of crustaceans that can be formulated into injectable hydrogels for therapeutic delivery. Gao *et al.* performed bilateral ischemia-reperfusion AKI in rats and cohorts received adipose derived mesenchymal stem cells (ADMSCs) either via phosphate buffered saline or a thermosensitive chitosan hydrogel 10 minutes into the injury.[3] Hydrogel delivery improved initial ADMSC retention within the kidney local persistence for 21 days; groups treated with ADMSCs via hydrogel showed an improvement in functional and histological kidney outcomes. Feng *et al.* created a chitosan hydrogel with insulin-like growth factor-1 (IGF-1) binding sites as a pro-survival factor to deliver ADMSCs in a unilateral ischemia-reperfusion AKI model 15 minutes after injury.[4] Treated kidneys demonstrated improved angiogenesis and a reduction in fibrosis.

Collagen:

Huang *et al.* developed a co-gel consisting of collagen and decellularized vascular matrix. They then delivered MSCs in a rat model of unilateral ischemia-reperfusion AKI.[5] Groups treated with MSCs via the hydrogel demonstrated reduced apoptosis and an improvement in vascularization and kidney function. Lee *et al.* investigated whether a collagen hydrogel injected into the kidney cortex after ischemia-reperfusion AKI could elicit a favorable host immune response.[6] At 4 weeks post-injury, engogenous cells with stem cell and progenitor cell markers had engrafted within the hydrogel; these regions had a significantly higher number of glomeruli than untreated regions.

Hyaluronic Acid (HA):

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan. HA is endogenous to the human body, making it biocompatible, with numerous clinical applications in the field of biomaterials. In 2010, Ratliff *et al.* published the first study describing HA as a biomaterial to treat kidney disease. They used a hydrogel composed of thiolated HA and collagen coated with pronectin to deliver epithelial progenitor cells under the kidney capsule in murine models of nephrotoxic AKI and ischemia-reperfusion AKI.[7] In a separate set of experiments, they delivered the hydrogel and EPCs to the ear to enable intravital imaging of the EPCs before and after hydrogel degradation by hyaluronidase. This study demonstrated the feasibility of hydrogels as a niche for cell therapy, that hydrogels improved cell viability, protected cells from nephrotoxic insults, and improved sequestration in ischemic kidneys. Subsequent studies from this group demonstrated similar improvements in murine models of sepsis AKI.[8] Soranno and Rodell have utilized a shear-thinning HA hydrogel formed via guest-host chemistry to delivery interleukin-10 (IL-10) and anti-tranforming growth factor-β (anti-TGFβ) in a unilateral ureteral obstruction (UUO) model of CKD, and IL-10 in a model of bilateral ischemia-reperfusion AKI.[9, 10] In both models, the guest-host hydrogel alone improved histological outcomes, even in the absence of encapsulated biotherapeutics. Others have demonstrated that HA has an immunomodulatory effect, including via molecular-weight dependent alteration of macrophage phenotype.[11] In the context of ischemia-reperfusion AKI, hydrogel therapy alone also reduced serum interleukin-6 (IL-6) 1 month after treatment. IL-6 has been implicated in a host of systemic sequelea resulting from AKI, implying that hydrogel therapy to the kidneys may also improve systemic outcomes of AKI.

Poly(ethylene) glycol (PEG):

In 2012, Dankers *et al.* investigated the local inflammatory response to various PEG-based hydrogels injected subcapsularly in healthy rats. Histology revealed minimal macrophage infiltration, α-SMA or collagen III activity up to 15 days after injection and serum creatinine was not impacted.[12] Tsurkan *et al.* used microaggregates of mult-armed PEG coated in heparin to deliver basic fibroblast growth factor (bFGF) and murine epidermal growth factor (EGF) in a murine model of rhabdomyolysis. Treated kidneys demonstrated improvement in cell proliferation after injury.[13] Lu *et al.* developed a self-assembling Dock-and-Lock PEG-based hydrogel which was used to deliver IL-10 in a murine UUO model of CKD. While the hydrogel alone reduced long-term fibrosis, IL-10 encapsulation further reduced macrophage infiltration and local apoptisis.[14, 15]

Therapeutics Delivered via Injectable Hydrogels:

Injectable hydrogels can be used to deliver a variety of therapeutics locally to the kidney, or elsewhere. Therapeutics have included growth factors, cytokines, epithelial progenitor cells, and mesenchymal stem cells. Hydrogels can be tuned to degrade quickley or slowly *in vivo*, and the therapeutic cargo stays *in situ* during that time. For cell therapy - in which the paracrine effects of the cells are the desired therapeutic - hydrogels improve cell survival during injection and also sequester the cells locally at the desired location, thereby improving therapeutic efficacy. Various imaging techniques can be used to quantify the localization of either the hydrogel depot and/or the delivered therapeutic over time. For example, Gao and Feng both used luciferase labeled ADMSCs to serially track cell location *in vivo* after injection via their thermosensitive chitosan hydrogels under the kidney capsule in murine model of AKI.[3, 4] Soranno, Lu and Rodell have used a near-infrared fluorescence (Cy5.5 or Cy7.5), covalently bound to their PEG and HA hydrogels or model biomolecules (mouse serum albumin) to longitudinally assess hydrogel degradation and therapeutic release *in vivo*.[15, 9, 10]

Assessing Kidney Function after Hydrogel Therapy

Until recently, the biocompatibility of hydrogels delivered subcapsularly, or intrarenally, to treat kidney disease has been limited to standard histological and biomarker evaluation. Soranno *et al.* developed a solitary kidney model and used transcutaneous glomerular filtration rate (tGFR) devices (MediBeacon) to measure kidney function pre- and post-injection.[16] First, a unilateral nephrectomy was performed and the contralateral kidney was allowed to compensate for one month. TGFR was measured pre-nephrectomy, a month later (pre-injection) and then serially after injection of 15 μL of HA hydrogel under the kidney capsule. Using this model, the investigators demonstrated that delivery of HA under the kidney capsule had no effect on measured tGFR when compared to unmanipulated controls and groups injected with saline under the kidney capsule. This approach adds a functional assessment to determining the biocompatibility and safety of hydrogels to treat kidney disease.

Translational Considerations

Numerous injectable hydrogels are currently used clinically, particularly in the field of dermatology, however none have been tested clinically for nephrological indications.[17] Further studies are needed to translate these novel therapeutics into clinical care. A potential next step would be to perform safety and biocompatibility studies *ex vivo* on discarded donor kidneys on pump. The selection of hydrogel tested would depend on the overall goal of therapy and duration of treatment.

Conclusions:

Numerous preclinical studies have demonstrated the feasibility and utility of using injectable hydrogels to treat various types of kidney diseases. Injectable hydrogels uniquely enable the local delivery of therapeutic cell and drug cargo, thus overcoming clinical obstacles that have included systemic biodistribution, cell viability, and persistent sequestration. In many cases, hydrogel delivery alone has proven to be beneficial. Translational studies are warranted to further investigate these novel therapeutics to treat kidney disease.

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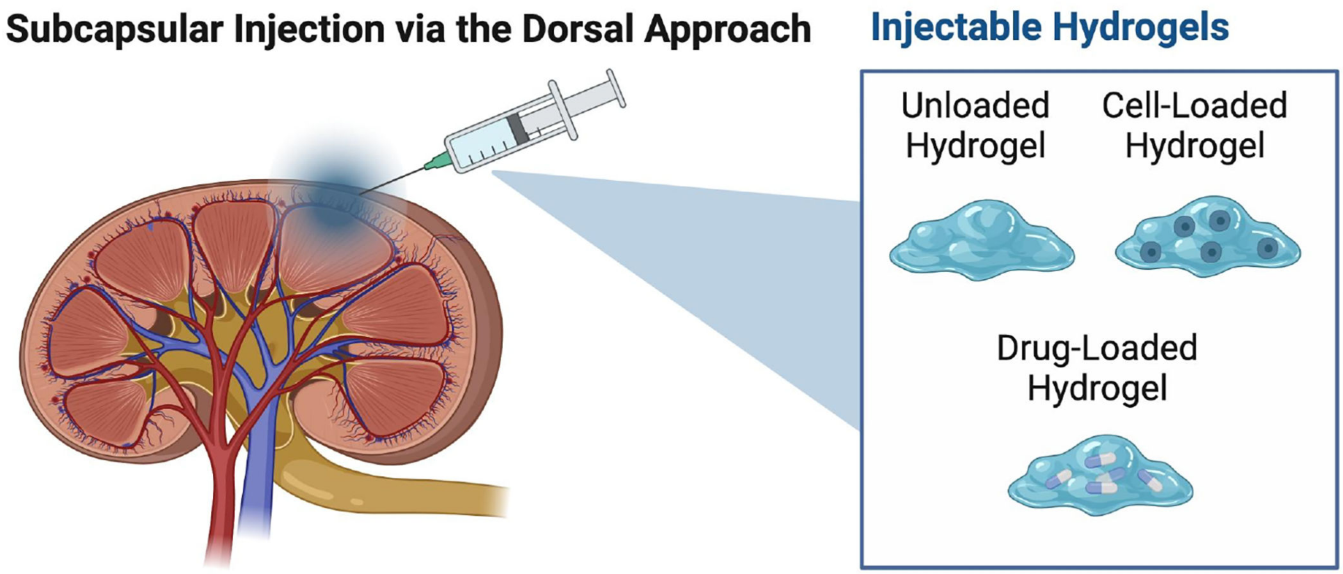

Figure 1.

Schematic diagram of subcapsular renal delivery of injectable hydrogels. Hydrogels can be made of natural or synthetic materials, and are chemically modified to attain specific properties. They can then be loaded with various therapeutics, including cells, biotherapeutics (e.g., growth factors, cytokines), or small-molecule drugs for local, sustained delivery. Made with BioRender.

Table 1:

Summary of preclinical studies using injectable hydrogels to treat kidney disease

Citation	Hydrogel Material	Therapeutics	Species	Experimental Model	Findings
Ratliff, et al. 2010	Hyaluronic Acid (HA) and collagen	Endothelial Progenitor Cells (EPCs)	Mice	EPCs embedded in HA delivered to the ear after ischemia-reperfusion injury or Adriamycin injury.	Improvement in serum creatinine in mice treated with EPCs/HA. HA protected the encapsulated EPCs from Adriamycin toxicity.
Ghaly, et al. 2011	HA and collagen	EPCs	Mice	EPCs embedded in HA delivered to the kidney of lipopolysaccharide (LPS) and cecal ligation and puncture (CLP) models of sepsis AKI.	Improvement in in blood pressure and kidney function in mice treated with EPCs embedded in HA.
Dankers, et al. 2012	Poly(ethylene glycols) (PEG)	N/A	Rats	Hydrogels injected into the renal cortex.	Minimal inflammatory response in the renal cortex after injection of the hydrogels, suggesting supramolecular hydrogels may be useful for intrarenal drug delivery
Gao, et al. 2012	Chitosan	Adipose-derived mesenchymal stem cells (ADMSCs)	Rats	ADMSCs delivered via chitosan hydrogel after 40 minutes of bilateral ischemia- reperfusion injury.	ADMSC retention was improved via hydrogel delivery. Hydrogel therapy alone also reduced apoptosis.
Tsurkan, et al. 2013	PEG	Basic fibroblast growth factor (bFGF) Epidermal growth factor (EGF)	Mice	Growth factor loaded hydrogel injected subcapsularly to the left kidney in a glycerol model of rhabdomyolysis AKI. The contralateral kidney served as the control.	Kidneys treated with growth factors demonstrated an increase in cell proliferation (treated more so than untreated control). Hydrogel alone did not increase cell proliferation.
Soranno, et al. 2014	PEG	Interleukin-10 (IL-10)	Mice	Hydrogels with or without IL-10, or saline with or without IL-10 delivered subcapsularly to the left kidney 3 days after left unilateral ureteral obstruction (UUO).	Both hydrogel with IL-10, and hydrogel alone reduced macrophage infiltration and apoptosis 3 and 5 weeks after injury. Fibrosis was reduced in all treatment groups 5 weeks after injury.
Rodell, et al. 2015	HA	IL-10 anti-transforming growth factor-β (anti-TGFβ)	Mice	Hydrogels or saline with IL-10, anti-TGFβ, both or none delivered subcapsularly to the left kidney 3 days after left UUO.	Macrophage infiltration and apoptosis were decreased at 3 weeks. Fibrosis was reduced at 5 weeks in groups treated with either IL-10 or anti-TGFβ via HA, but was paradoxically increased in groups treated with both IL- 10 and anti-TGFβ.
Soranno, et al. 2016	HA	IL-10	Mice	Hydrogel or saline with or without IL-10 delivered subcapsularly to the left kidney 3 days after bilateral ischemia-reperfusion AKI. An additional treatment group received IL-10 via hydrogel subcutaneously.	Hydrogel therapy alone decreased serum interleukin-6 and kidney fibrosis 1 month after injury. All treatment groups displayed an improvement in systemic inflammation and kidney fibrosis.
Feng, et al. 2016	Chitosan	Adipose-derived mesenchymal stem cells (ADMSCs)	Mice	ADMSCs encapsulated within hydrogel delivered intrarenally to the left kidney at the time of bilateral ischemia-reperfusion AKI.	ADMSCs delivered via hydrogel had improved survival than without hydrogel, and resulted in decreased fibrosis and improvement in kidney function 2 weeks after injury.
Huang, et al. 2017	Collagen and decellularized vascular matrix	Mesenchymal stem cells (MSCs)	Rat	MSCs co-transplanted with the co-gel into the injured kidney following unilateral ischemia-reperfusion AKI.	Delivery of MSCs via hydrogels increased the therapeutic effects of MSC therapy, determined by a reduction in apoptosis, and tissue damage, and improvement in kidney function.
Lee, et al. 2018	Collagen	N/A	Mice Rats	Collagen hydrogel was delivered to healthy renal cortex, and 2	Four weeks after hydrogel injections, endogenous MSCs had engrafted within the collagen

Citation	Hydrogel Material	Therapeutics	Species	Experimental Model	Findings
				weeks after bilateral ischemia-reperfusion AKI.	hydrogel and there was evidence of glomerular and tubular regeneration; kidney function was improved in the ischemia-reperfusion rat model.
Soranno, et al. 2022	HA	N/A	Mice	Hydrogel or saline injected subcapsularly in a model of a solitary healthy kidney with transcutaneous glomerular filtration measurements (tGFR) pre- and posttreatment.	Injection of hydrogel subcapsularly did not impact measured kidney function. TGFR measurements can be employed to assess the functional biocompatibility of hydrogels used to treat kidney disease.