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Hydrogel and Polymeric Scaffolds in Renal Tissue Engineering: A Review of Innovations in Regenerative Therapy

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ABSTRACT

Chronic kidney disease (CKD) affects approximately 10% of the global population and often progresses to end-stage renal disease (ESRD), for which dialysis and transplantation remain the primary treatments despite significant limitations. This review presents a comparative analysis of hydrogel-based and polymeric scaffold biomaterials used in renal tissue engineering. Materials are evaluated based on fabrication strategies, mechanical properties, degradation behaviour, biocompatibility, and reported in vitro and in vivo functional outcomes. Comparative assessment emphasizes quantitative indicators including renal cell viability, nephron-like organization, vascularization efficiency, fibrosis reduction, and functional markers such as erythropoietin secretion and creatinine clearance. Hydrogels such as gelatin methacrylate (GelMA), alginate, polyethylene glycol (PEG), and extracellular matrix (ECM)-derived materials demonstrate enhanced cell survival and tissue-specific differentiation, while polymeric scaffolds including polycaprolactone (PCL) and poly(lactic-co-glycolic acid) (PLGA) offer superior mechanical stability and vascular integration, with reported vascular density increases of up to ~50% and significant reductions in fibrotic markers in preclinical models. However, quantitative benchmarking across studies remains limited by non-uniform protocols, short implantation durations, and inconsistent outcome metrics. Ethical considerations, immunological responses, and patient-specific risks associated with stem cell–scaffold integration are also insufficiently addressed. The absence of standardized evaluation frameworks limits definitive conclusions regarding therapeutic readiness, underscoring the need for unified performance metrics and long-term in vivo validation to advance clinical translation.
Keywords: Kidney Regeneration, Hydrogels, Polymeric Scaffolds, Tissue Engineering, Regenerative Medicine

1 INTRODUCTION

Chronic kidney disease (CKD) is a progressive and irreversible condition affecting approximately 10% of the global population, with major causes including diabetes, hypertension, autoimmune diseases, and congenital conditions such as polycystic kidney disease (Mohamed et al., 2023). The disease is characterized by damage to the glomerular and tubular structures, resulting in tubulointerstitial inflammation, fibrosis, glomerulosclerosis, and the eventual loss of renal function (Mohamed et al., 2023). As CKD advances, it can lead to end-stage renal disease (ESRD), a state where the kidneys lose nearly all their filtration capacity and patients must rely on renal replacement therapies to survive (Jansen et al., 2017). Currently, the main treatments are hemodialysis and kidney transplantation. While dialysis provides short to medium-term support by filtering metabolic waste, it fails to replicate the kidney's endocrine, regulatory, and homeostatic functions and is associated with a significantly reduced quality of life (Jansen et al., 2017). Transplantation offers a more comprehensive restoration of renal function, but its effectiveness is constrained by a global shortage of donor organs and the long-term risks of immunosuppressive therapy. Alarmingly, around 40% of patients are expected to lose their transplant function or die within ten years post-transplantation (Huling et al., 2019; Lee et al., 2024). Furthermore, the 5-year survival rate for dialysis patients is only 36%, in stark contrast to 86% for transplant recipients (Jansen et al., 2017). These statistics underscore the pressing need for alternative therapeutic strategies that can provide long-term, functional restoration of renal tissue. In response, researchers have turned to regenerative medicine, a multidisciplinary field that integrates stem cell biology, tissue engineering, and advanced biomaterial technologies to develop innovative solutions for kidney repair and replacement (Jansen et al., 2017; Mohamed et al., 2023).

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The extracellular matrix (ECM) plays a vital role in kidney development and function by providing a structural and biochemical scaffold that regulates cellular behaviour. In the native kidney, the ECM is composed of proteins such as collagen, elastin, laminin, and glycoproteins, which maintain nephron architecture and mediate critical signaling pathways (Jansen et al., 2017). During nephrogenesis, the ECM not only provides physical support but also acts as a reservoir for growth factors and morphogens that guide renal progenitor cell differentiation (Fransen et al., 2021). In tissue engineering, replicating these complex microenvironments is essential for the functional maturation of engineered kidney constructs. Both ECM-based hydrogels and broader scaffold systems, including synthetic and decellularized materials, have been developed to mimic these native cues (Bolinas et al., 2025; Sarker et al., 2018). For example, incorporating kidney-derived ECM into bioprinted constructs has been shown to improve tissue integrity, enhance epithelial polarization, and support long-term cell viability in renal models (Askari et al., 2021; Fransen et al., 2021). These results highlight the critical role of ECM-inspired hydrogels and scaffolds in designing functional platforms for kidney tissue engineering.

Mechanical signals are increasingly recognized as key regulators of cell behaviour, particularly in bioengineered systems that aim to replicate tissue-specific microenvironments. In the kidney, properties such as elasticity, stiffness, and porosity influence cell proliferation, polarity, and nephron organization through mechanotransduction (Ahmed, 2015; Mohamed et al., 2023). Hydrogels have been widely used for renal models due to their customizable mechanical properties and resemblance to the native ECM. For instance, GelMA and PEG-based hydrogels have been engineered to match the stiffness of renal tissues, improving differentiation and epithelial maturation (Askari et al., 2021; Bolinas et al., 2025). Beyond hydrogels, more structurally robust polymeric scaffolds such as polycaprolactone (PCL) and poly(lactic-co-glycolic acid) (PLGA) are being used in in vivo models for their tunable degradation rates and vascular integration potential (Huling et al., 2019; Miao et al., 2024). These materials are often fabricated with defined pore sizes and fiber alignment to support nutrient transport, angiogenesis, and immune compatibility, which are essential for translating tissue constructs into therapeutic systems (Fujimori et al., 2024; Serbo & Gerecht, 2013). Collectively, these biomechanical features not only support tissue architecture but also actively direct cellular behaviour, enabling more physiologically relevant kidney tissue engineering platforms.

Stem cell-based therapies have become a cornerstone of regenerative strategies for kidney repair due to their potential to replace lost or damaged cells and restore tissue function (Jansen et al., 2017; Lee et al., 2024). Among these, human induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) have been widely studied for their ability to differentiate into renal cell lineages under defined conditions (Fransen et al., 2021; Sarker et al., 2018). In vitro protocols now allow for the generation of 3D kidney organoids, self-organizing cell clusters that partially recapitulate nephron structures and developmental processes (Askari et al., 2021; Fransen et al., 2021). These organoids serve not only as disease models but also as sources of renal progenitor cells for tissue engineering applications (Fransen et al., 2021). However, efficient stem cell differentiation requires carefully controlled environments, often provided by biomaterials that offer both biochemical cues and structural support (Bolinas et al., 2025; Huling et al., 2019; Mohamed et al., 2023). Extracellular vesicles (EVs), derived from stem or progenitor cells, are also being incorporated into scaffolds to deliver regenerative signals without the risks associated with direct cell transplantation (Lee et al., 2024). This convergence of stem cell biology and material science opens new avenues for personalized therapies and bioartificial kidney development (Huling et al., 2019; Mohamed et al., 2023).

This paper will examine the potential of hydrogel-based biomaterials in kidney tissue engineering, emphasizing their functional capabilities, physical characteristics, and design considerations. Several hydrogel types, including GelMA, alginate, PEG, and ECM-derived materials, are compared in the debate, with an emphasis on their benefits and drawbacks in promoting kidney regeneration. Applications of these hydrogels in 3D bioprinting and organoid systems are also investigated, along with their effects on functional performance, cell viability, and spatial patterning. In the paper's conclusion, the present difficulties, worldwide viewpoints, and potential paths forward in converting these biomaterials into therapeutically useful treatments are critically examined.

2 HYDROGEL-BASED BIOMATERIALS FOR KIDNEY TISSUE ENGINEERING

Compared to metallic and inorganic materials, polymers are generally more favourable for tissue regeneration due to their low density, tunable degradability, chemical versatility, and reduced environmental impact (Ahmed, 2015). Among polymer-based biomaterials, hydrogels have emerged as particularly promising candidates in tissue engineering because of their three-dimensional hydrophilic nature, which provides high water absorption and effective mass transfer (Yang, 2022). These properties, combined with their ability to conform to various shapes and mimic the physical characteristics of living tissues, make hydrogels uniquely suited for supporting cellular processes in regenerative applications (Vedadghavami et al., 2017). Figure 1 visualizes the swelling behaviour of hydrogel polymers in response to various external stimuli.

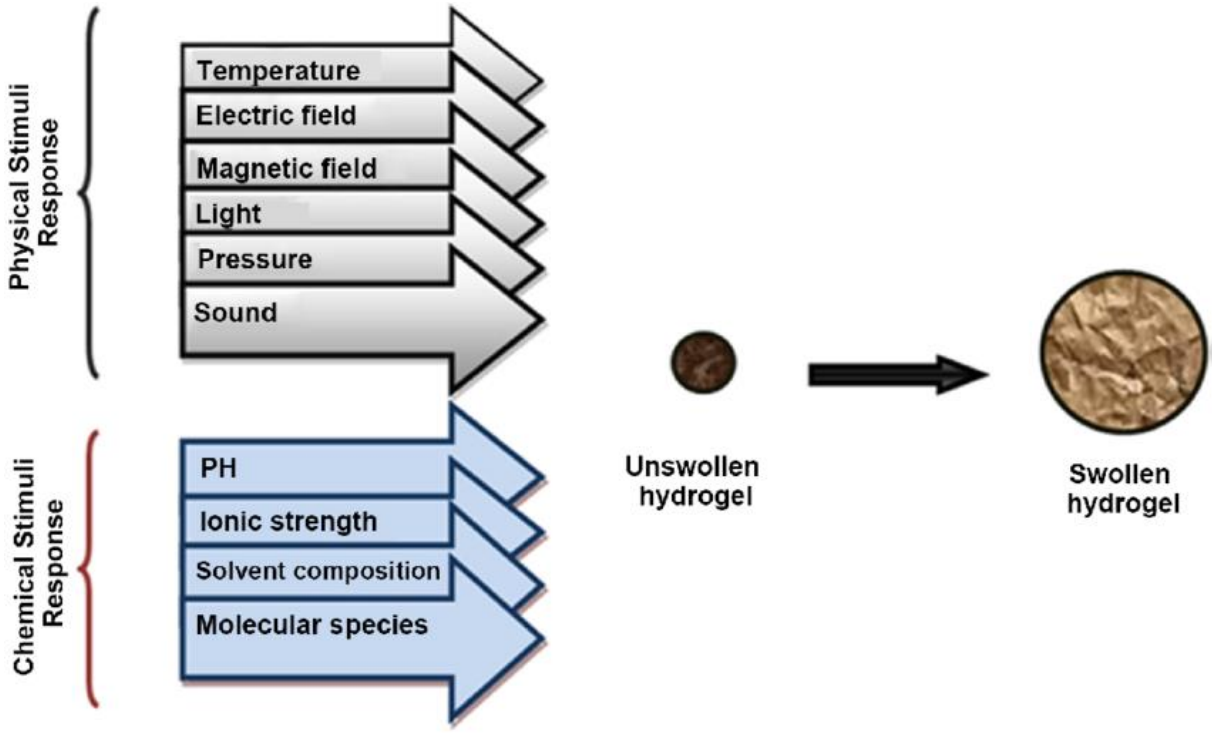

Figure 1: Stimuli response of swelling hydrogel (Ahmed, 2015)

2.1 Functional Roles of Biomaterials

Hydrogels have important functions in tissue engineering, notably kidney regeneration, by providing structural support, enhancing cell communication, and allowing for regulated drug administration. One of the primary roles of hydrogels is to provide structural support and biomimicry. Their high water content and porous nature allow efficient nutrient and waste exchange, supporting cell survival and proliferation. By tuning their mechanical properties such as stiffness, elasticity, and porosity, hydrogels can simulate the mechanical environment of renal tissues and influence cellular organization and function. This structural mimicry has been shown to enhance epithelial polarization and tubule formation in kidney models (Askari et al., 2021; Weaver, 2017).

Hydrogels not only provide physical support, but they also participate in cell signaling and microenvironmental regulation (Eltom et al., 2019). They can be tailored to include bioactive chemicals like adhesion peptides, growth factors, and extracellular vesicles, allowing for precise control of cellular behaviour. In kidney regeneration, this is crucial for directing stem cell differentiation into renal-specific lineages and ensuring adequate cell-cell communication within designed tissues (Ahmed, 2015; Eltom et al., 2019).

Hydrogels also serve as regulated delivery methods for medications and growth hormones. Their polymeric nature enables the encapsulation and slow release of therapeutic chemicals, resulting in localized, sustained delivery to the injury or regeneration site (Askari et al., 2021). In renal applications, this property is especially advantageous for delivering anti-inflammatory chemicals or nephroprotective medicines in a tailored manner, decreasing systemic adverse effects and encouraging regeneration (Vedadghavami et al., 2017).

2.2 Material Properties

The physical and chemical properties of hydrogels are fundamental to kidney tissue engineering The ability of hydrogels to replicate the ECM and provide an environment that supports cell survival, differentiation, and tissue regeneration is fundamental to kidney tissue engineering. The successful use of hydrogels depends on three fundamental material characteristics: mechanical strength, swelling behaviour, and biocompatibility.

For hydrogels to sustain the cellular environment and endure physiological demands, they need to be mechanically stable. A hydrogel scaffold's composition, crosslinking density, and polymer chain length all affect how stiff and elastic it is. These characteristics affect tissue development, adhesion, and cell fate. For example, by altering the molecular weight and crosslinking conditions, hydrogels based on PEG exhibit mechanical characteristics that may be adjusted. Sequential interpenetrating network (seqIPN) PEG hydrogels, which closely resemble soft tissues like the kidney, have been created using UV-initiated thiol-ene chemistry and exhibit tensile moduli ranging from 175 to 555 kPa (Yang, 2022). Rheological testing as visually shown in Figure 2 helps determine whether these materials are suitable for implantation under stress by highlighting how they react to deformation.

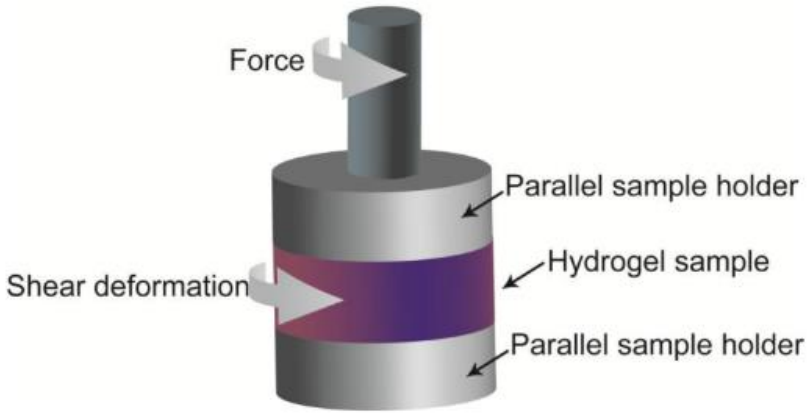

Figure 2: Rheology measurements on a hydrogel sample (Yang, 2022)

2.3 Design Considerations

Hydrogels must also be compatible with biological systems and ideally support cellular communication and integration. Materials derived from natural ECM (such as kidney decellularized matrices) inherently contain biochemical cues that promote adhesion and differentiation. Synthetic polymers like PEG offer the advantage of design flexibility and reduced immunogenicity but often require biofunctionalization. For example, incorporating cell-adhesive peptides or ECM proteins can enhance their bioactivity (Mohamed et al., 2023; Yang, 2022). PEG has been widely accepted for biomedical use by the FDA due to its safety and versatility. Biodegradable PEG hydrogels have also been successfully employed in drug delivery systems due to their tunable properties and ability to encapsulate diverse therapeutic agents (Dankers et al., 2012). This is depicted in Figure 3, showing how drugs are released in a localized manner as the material degrades (Yang, 2022).

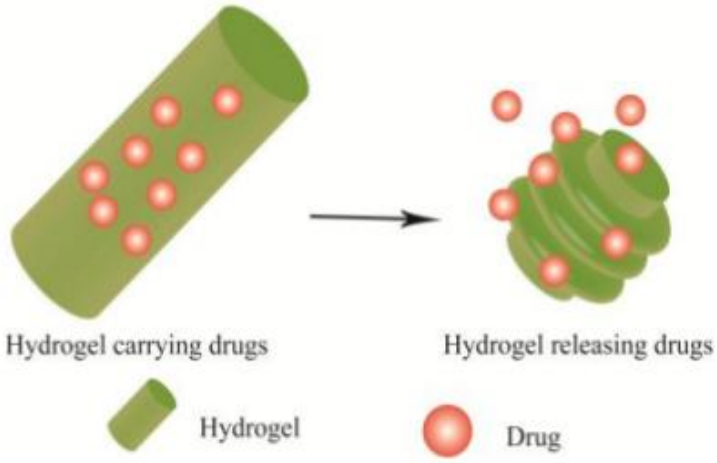

Figure 3: Illustration of a drug-delivery system that uses a biodegradable PEG hydrogel carrying drugs and releasing them at a certain location (Yang, 2022)

A number of design considerations need to be handled when creating hydrogels for use in kidneys. The choice of material is crucial; natural polymers offer better biological compatibility, while synthetic polymers, such as PEG, offer exact control over mechanical and chemical properties. Rapid gelation and reliable network creation are made possible by crosslinking approaches such UV-initiated thiol-ene chemistry (Halperin-Sternfeld et al., 2017; Yang, 2022). In order to prevent early scaffold collapse or long-term obstruction, the pace of degradation must also coincide with the tissue formation timetable. The constructed construct is guaranteed to support kidney-specific functions over time by the strategic integration of variables such as mesh size, porosity, and mechanical flexibility (Yang, 2022).

3 BIOMATERIALS IN 3D KIDNEY MODELS AND ORGANOID SYSTEMS

Recent advances in three-dimensional (3D) bioprinting have positioned biomaterials as essential components in the fabrication of complex tissue-engineered constructs, including renal models and organoid systems. Hydrogel-based extrusion bioprinting, in particular, has gained attention for its ability to integrate living cells, growth factors, and bioactive materials into spatially organized structures. This technique has been widely applied to various tissue types such as skin, bone, cartilage, and muscle, and is increasingly being adapted for kidney tissue engineering due to its capacity to replicate both the architectural and functional aspects of renal tissue (Askari et al., 2021). Among all biomaterials, hydrogels are consistently highlighted for their capacity to mimic the ECM, maintain high cell viability, and form hydrated, porous networks that support nutrient diffusion, cellular organization, and waste exchange (Askari et al., 2021; Murphy & Atala, 2014). These features are especially critical in the context of kidney regeneration, where functional nephrons require a finely regulated microenvironment that promotes epithelial polarization, tubule formation, and filtration capacity.

3.1 Hydrogel Variants and Their Functional Suitability for Renal Applications

A variety of hydrogel formulations have demonstrated potential for kidney tissue engineering, particularly due to their compatibility with the renal microenvironment and ability to support cellular behaviour. GelMA is one of the most promising options, offering structural similarities to the native ECM and excellent biocompatibility. Its photocrosslinkable properties allow for precise spatial control, making it well-suited for encapsulating renal cells and supporting rapid cellular proliferation (Askari et al., 2021). Another widely used hydrogel, alginate, forms gels under mild physiological conditions and enables the deposition of living cells without cytotoxic effects. This characteristic is particularly valuable for constructing delicate nephron-like structures (Askari et al., 2021; Nezhad-Mokhtari et al., 2019). Collagen type I, a naturally occurring ECM protein, contributes to both scaffold integrity and bioactivity. Its presence supports epithelial cell polarization and stromal cell interaction, which are essential for mimicking functional kidney architecture (Askari et al., 2021). Additionally, PEG-based hydrogels are frequently explored for their tunable mechanical properties and chemical modifiability. By adjusting crosslinking density and molecular weight, PEG hydrogels can be engineered to replicate the stiffness gradients found in complex organs like the kidney, opening new avenues for structurally adaptive scaffold design (Askari et al., 2021).

In recent studies, three-dimensional renal organoid models were successfully generated from adult human kidney cells without the use of genetic modification or pluripotent stem cells (Ding et al., 2020). By incorporating solubilized, decellularized kidney ECM into the culture medium, the researchers enhanced renal cell viability and guided functional differentiation. This underscores the broader value of ECM-based hydrogels, which have been widely recognized for their ability to mimic native tissue environments and support tissue-specific maturation (Askari et al., 2021). Importantly, ECM derived from decellularized kidney tissue retained biomechanical and biochemical cues essential for organoid performance. One key functional improvement observed in this model was the induction of erythropoietin (EPO) expression under hypoxic conditions, an important physiological marker typically absent in conventional two-dimensional cultures (Ding et al., 2020). These results validate the relevance of hydrogel composition, particularly when aiming to replicate native kidney function in engineered systems.

3.2 Optimizing Cell Density for Renal Organoid Formation and Hydrogel Integration

A multicellular renal organoid model has been developed using native ECM without pluripotent stem cells, where various initial cell seeding densities were tested to evaluate their impact on renal organoid formation and viability (Ding et al., 2020). Cell concentrations ranged from 250 to 10,000 cells per 40 L drop, and all conditions produced spherical 3D organoid structures after seven days (Ding et al., 2020). However, both organoid size and structural cohesion were strongly dependent on the initial cell number. As illustrated in Figure 4, cell viability peaked at 8000 cells per well, indicating this density as the optimal threshold for forming compact, metabolically active, multicellular aggregates (Ding et al., 2020). At this concentration, cells exhibited robust self-organization without triggering central necrosis within the first 14 days of culture. Necrosis was only observed after day 21, suggesting that early-stage organoids at this density may be suitable for pre-vascularization or transplantation studies (Ding et al., 2020). These findings highlight the importance of optimizing cell-hydrogel interactions and implantation timing to enhance the clinical relevance of in vitro organoid models.

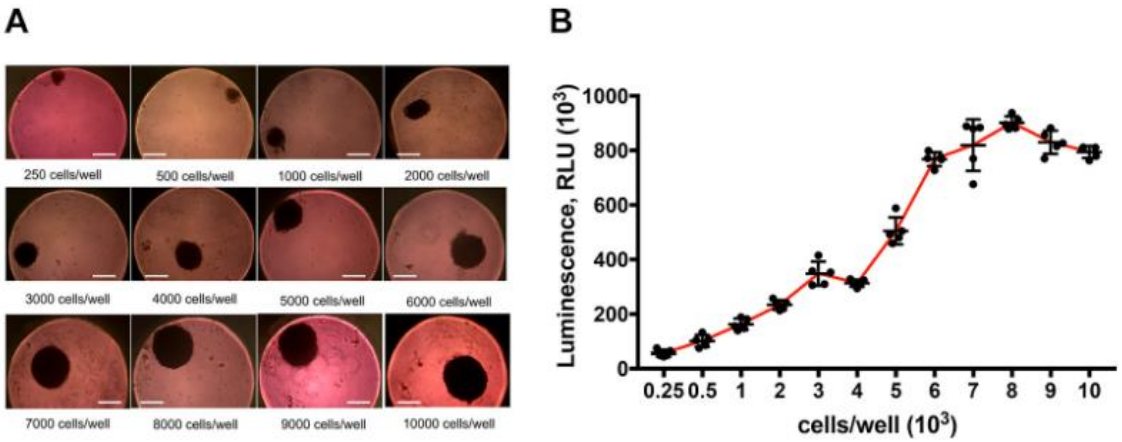

Figure 4: optimization of the manufacturing of organoids. (A) Size and shape of renal organoids made from varying cell counts. The ideal starting cell quantity for organoid cultivation was determined to be 8000 cells/well (scale bar: 200 µm). (B) Measurement of ATP for proliferation in renal organoids with varying cell counts (Ding et al., 2020).

3.3 Wear and Coefficient of Friction

The functional maturity of renal organoids can be assessed by their ability to perform key physiological functions, one of which is the secretion of EPO under hypoxic conditions. Ding et al. demonstrated that renal organoids derived from primary adult kidney cells, when cultured in ECM-supported environments, successfully produced measurable levels of EPO protein, which is a hormone essential for red blood cell synthesis and a hallmark of mature renal function (Ding et al., 2020). As illustrated in Figure 5, organoids exposed to low-oxygen environments (1% O) 2 secreted significantly higher levels of EPO, with peak expression occurring at 24 hours (Ding et al., 2020). This oxygen-dependent response closely mimics the behaviour of native kidney tissue and affirms the role of ECM-derived hydrogels in supporting organoid viability and functionality.

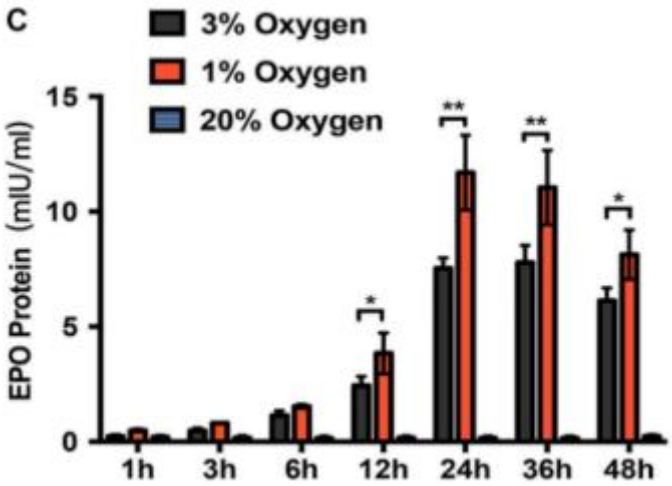

Figure 5: EPO Secretion Levels, Demonstrating Organoid Functionality Over Time (Ding et al., 2020).

These findings align with earlier discussions in 3.2, where it was emphasized that biologically active hydrogels, particularly those derived from ECM, not only provide structural support but also deliver essential biochemical cues that enable tissue-specific signaling and maturation (Askari et al., 2021). Similarly, ECM-based hydrogels allow the retention of native biomechanical properties, which play a role in maintaining gene expression patterns relevant to renal identity and hormonal responsiveness (Eltom et al., 2019).

Together, the bioprinting strategies and the functional validation offer a compelling biomaterials-based framework for advancing 3D kidney model development (Askari et al., 2021; Ding et al., 2020). Hydrogels such as GelMA, alginate, and ECM derivatives serve as both physical scaffolds and dynamic biochemical environments, facilitating cellular organization and function. When combined with extrusion-based bioprinting techniques that allow for precise spatial deposition, these systems create promising platforms for building functional, transplantable renal tissues in the future.

4 SCAFFOLD-ENHANCED REGENERATIVE STRATEGIES FOR IN VIVO KIDNEY REPAIR

A crucial stage in renal tissue engineering is the transfer from in vitro models to in vivo implantation, where scaffold-enhanced methods are used to address structural and functional deficiencies in damaged kidneys. Interventions other than dialysis or transplantation are being explored for chronic kidney disease (CKD), which leads to permanent nephron loss, fibrosis, and inflammation (Jansen et al., 2017; Mohamed et al., 2023). While hydrogels have been the primary focus of this study due to their favorable properties, they are in fact a subset of a broader category of scaffold materials, which are three-dimensional structures that support cell adhesion, signaling, and tissue development. The ECM-mimicking polymeric scaffolds and hydrogels have become attractive tools for in vivo repair because they offer bioactive cues, mechanical support, and a temporary framework for regeneration and cell infiltration (Lee et al., 2024). With an emphasis on material design, cell-scaffold interactions, vascular integration, and preclinical outcomes, this section examines the most recent scaffold-based strategies for in vivo kidney repair.

4.1 Cell-Scaffold Integration Strategies

Among these strategies, alginate-MSC scaffolds are of particular interest due to their dual role as structural carriers and therapeutic agents. Alginate, a natural polysaccharide, offers excellent biocompatibility and gentle gelation properties that protect encapsulated cells. When loaded with mesenchymal stem cells (MSCs), these scaffolds demonstrate strong paracrine effects, secreting anti-inflammatory cytokines that reduce renal fibrosis and promote tissue remodeling (Bolinas et al., 2025). In one study, alginate-MSC constructs led to decreased expression of fibrosis-associated markers such as TGF-β1 and α-SMA, while upregulating genes involved in tissue regeneration (Bolinas et al., 2025). The regenerative benefits go beyond gene expression. In vivo testing in rat models has shown that alginate-based scaffolds containing MSCs significantly improve kidney function, restore normal histological features, and preserve renal architecture even in fibrotic conditions (Sahoo & Biswal, 2021). Histological staining and biochemical analysis revealed reduced collagen deposition, minimized tubular injury, and improved creatinine clearance (Aya Imafuku et al., 2019; Miao et al., 2024). Figure 6 provides histological evidence of these therapeutic effects, illustrating reduced fibrosis in treated kidneys compared to untreated controls.

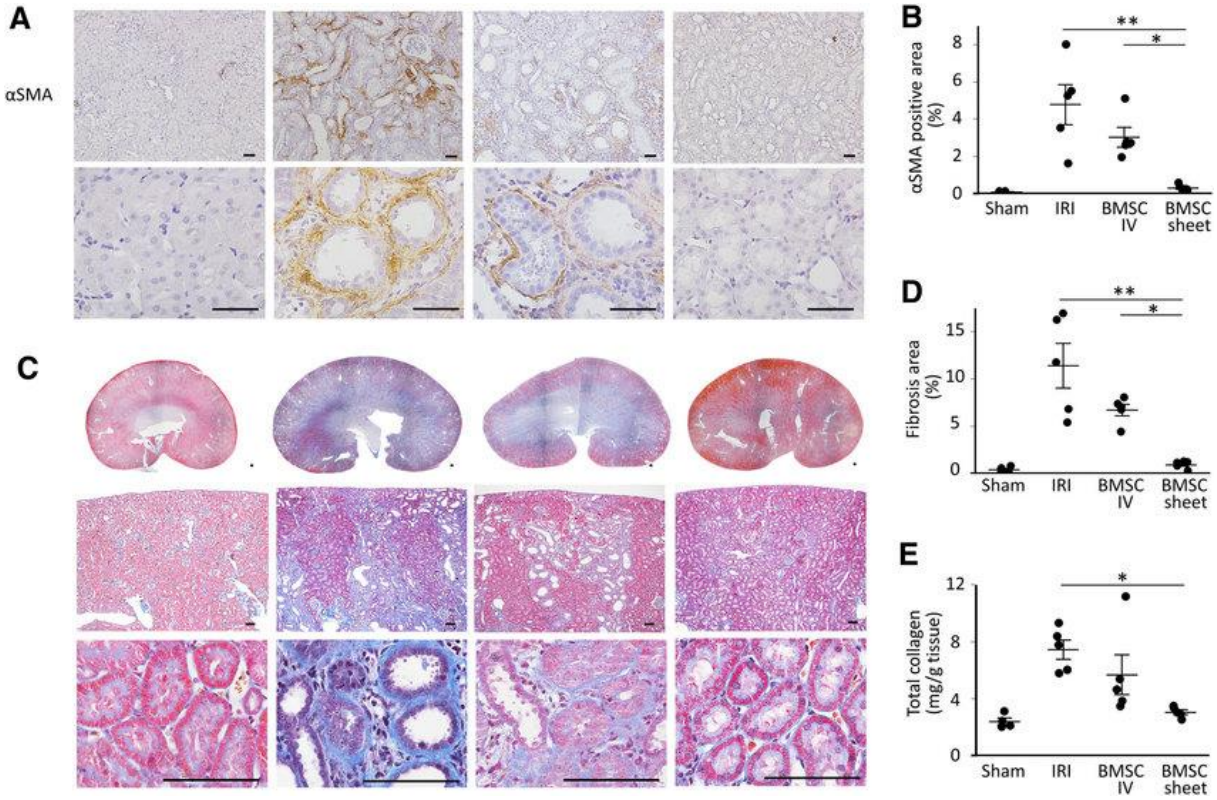

Figure 6: Histological evaluation of renal fibrosis in rats treated with MSC-based scaffolds. (A, B) show a reduced number of α-SMA-positive myofibroblasts in the scaffold-treated group compared to controls. (C, D) display Masson's trichrome staining, highlighting a smaller fibrotic area in the treated kidneys. (E) shows a significant decrease in total kidney collagen levels in the scaffold group, confirming antifibrotic effects (Aya Imafuku et al., 2019).

To improve scaffold stability and cell retention, alginate scaffolds have also been functionalized with cross-linking agents like CaCl2 and coated with polycations such as poly-L-lysine. These modifications enhance mechanical durability and regulate the release of bioactive signals (Miao et al., 2024). Additionally, some studies have introduced growth factor delivery into the scaffold design, such as vascular endothelial growth factor (VEGF), to enhance vascularization in ischemic tissues. Controlled release of VEGF from the scaffold can support endothelial cell proliferation and angiogenesis, which is crucial for tissue survival and integration (Miao et al., 2024).

4.2 Vascularization and Host Integration

A major challenge in renal tissue engineering is replicating the kidney's dense vascular network, which is essential for oxygen, nutrient transport, and waste removal. Without rapid and efficient vascular integration, implanted scaffolds often fail due to hypoxia-induced cell death and necrosis. Recent approaches have focused on modifying scaffold properties such as pore size, architecture, and surface biochemistry to enhance vascular ingrowth. For instance, PCL scaffolds with aligned fibers have been shown to increase vascular density by 50% compared to random fiber arrangements, promoting endothelial cell migration and organized vessel formation (Serbo & Gerecht, 2013). Similarly, sacrificial bioprinting has been applied to create perfusable vascular channels in preclinical kidney models, allowing for controlled nutrient perfusion and mimicking capillary exchange dynamics (Sarker et al., 2018).

Growth factor delivery remains another key strategy to encourage angiogenesis within scaffold materials. GelMA scaffolds conjugated with vascular endothelial growth factor (VEGF) have been shown to significantly reduce fibrosis and enhance microvascular density in injured kidneys (Aya Imafuku et al., 2019). Other scaffolds incorporate chemoattractants such as SDF-1 α, which stimulate the recruitment of host progenitor cells and support neovascularization (Fujimori et al., 2024). Beyond molecular strategies, studies have also explored scaffold materials seeded with endothelial progenitor cells (EPCs) or co-cultured with pericytes to support lumen formation and vessel stabilization (Masson-Meyers & Tayebi, 2021). The integration of these cells within degradable hydrogel or nanofiber scaffolds enables rapid remodeling and vascular penetration, especially when the matrix includes biomimetic cues like fibronectin or heparan sulfate (Nanning Lv et al., 2024).

Scaffold microstructure is just as critical. To enable efficient host integration and long-term function, studies suggest that pores larger than 200 μm are required to allow for effective nutrient diffusion and immune cell entry (Ghosh, 2024; Wang et al., 2024). Fabrication methods such as electrospinning have gained popularity for generating nanofibrous scaffolds with aligned fiber orientation, tunable porosity, and surface area conducive to endothelial attachment and migration. As illustrated in Figure 7, electrospinning setups use a high-voltage electric field to draw polymer fibers from a syringe toward a grounded collector, forming tightly aligned nanofibers (Ahmed, 2015). These fiber networks can be functionalized to release angiogenic factors or to guide vascular sprouting along their aligned structures. Though translating this into clinically sized renal constructs remains a challenge, electrospun scaffolds show strong promise for supporting vascularized tissue units in both preclinical and organoid models.

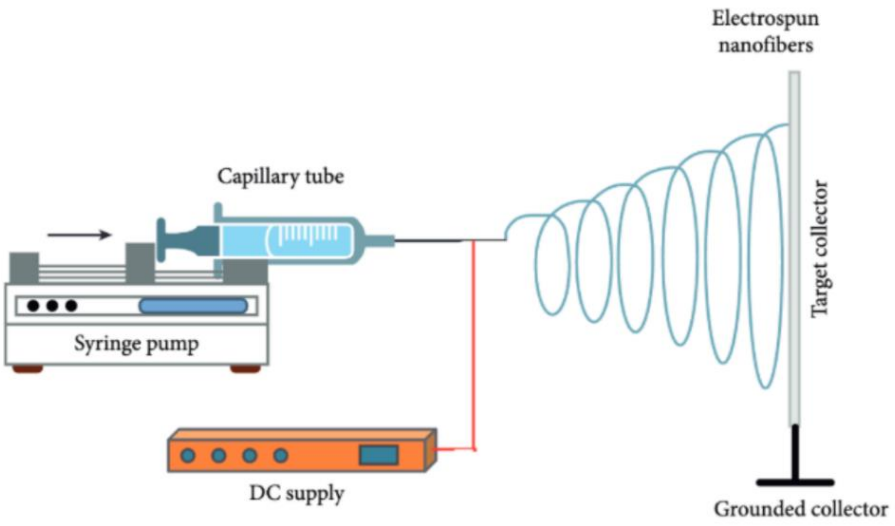

Figure 7: Electrospinning setup used for fabricating nanofibrous scaffolds. The diagram illustrates a syringe pump, high-voltage DC power supply, capillary tube, and grounded collector, which together generate aligned fibers suitable for vascular scaffold applications (Eltom et al., 2019).

4.3 Design, Technologies and Future Directions

Biocompatibility remains one of the most critical factors in scaffold design for renal repair. For instance, PLGA scaffolds with pore diameters ranging from 150–200 μm and porosity around 60% have demonstrated improved

vascular infiltration in cortical renal implants, offering an effective balance between mechanical support and nutrient permeability (Serbo & Gerecht, 2013). GelMA hydrogels with lower stiffness values (2-8 kPa) have been shown to reduce stress shielding while promoting epithelial polarization and proper cellular orientation (Eltom et al., 2019; Sarker et al., 2018). Synthetic scaffolds made from polymers like PLGA and PCL also allow fine-tuning of degradation rates and stiffness, making them versatile for patient-specific applications. In one in vivo study, PCL scaffolds functionalized with RGD peptides degraded over a 12-week period and encouraged fresh ECM formation while reducing fibrotic capsule formation, highlighting their potential for integration without chronic immune responses (Masson-Meyers & Tayebi, 2021). However, scaffolds that break down too rapidly run the danger of collapsing during tissue regeneration, and non-biodegradable implants may cause fibrosis or chronic inflammation (Wang et al., 2024).

More flexible and precisely guided scaffold technologies are currently becoming the norm in the sector. For instance, multi-material bioprinting techniques have surfaced that combine poly(ethylene glycol) diacrylate (PEGDA) networks to model vascular architecture with GelMA-based bioinks for nephron tubule creation. Functional filtration at the glomerular level remains a significant obstacle, despite the fact that this strategy seeks to mimic the kidney's intricate zonation (Pangjantuk et al., 2024). Another exciting avenue is the development of smart scaffolds that react to physiological inputs. Hydrogels designed to release antifibrotic medications in response to local pH variations, especially in fibrotic, acidic environments, provide CKD patients with focused treatment alternatives (Nanning Lv et al., 2024). Unfortunately, due to translational barriers, often caused by concerns regarding bioresorption rates, immunogenicity, or consistency, only a limited number of scaffold-based drug delivery systems have progressed to Phase I clinical trials (Pangjantuk et al., 2024).

Addressing current research gaps and enhancing scaffold safety and effectiveness will be essential to future advancements. Decellularized ECM kidney scaffolds, for instance, have shown partial transplant integration in animal models; nonetheless, after implantation, up to 20% of individuals experienced inflammation or allergic responses (Fujimori et al., 2024). Furthermore, methods to stop fibrotic encapsulation, including altering scaffold surfaces with anti-fibrotic peptides, are still in the early phases of development, and the majority of degradation studies are restricted to brief timeframes (usually six months or less) (Biswal & Sahoo, 2021; Nanning Lv et al., 2024). Future scaffold design success will rely on biomaterials engineers, renal biologists, and physicians working together in an interdisciplinary manner to develop systems that strike a balance between innovation and long-term translational viability.

5 DISCUSSIONS

The development of biologically active materials that can control cell behaviour has significantly advanced kidney tissue engineering, moving away from passive scaffolds that offered only mechanical support. Hydrogels have evolved from inert matrices into ECM-mimetic systems incorporating adhesion peptides and growth factors to support tissue architecture and cell differentiation (Askari et al., 2021; Mohamed et al., 2023). Similarly, the transition from 2D cultures to 3D kidney organoid systems represents a major shift in functional modeling, allowing better replication of native kidney microenvironments and improved cell-cell interactions (Fransen et al., 2021; Jansen et al., 2017). One key functional milestone is EPO secretion under hypoxic conditions, observed in ECM-derived hydrogel-supported organoids, a function absent in traditional 2D systems (Ding et al., 2020). These advancements underscore the increasing sophistication of biomaterials in replicating both kidney structure and physiological behaviour.

Current hydrogel and scaffold designs offer several advantages for renal tissue engineering. Materials such as GelMA, alginate, and PEG provide tunable stiffness, porosity, and degradation rates, which can be optimized for renal cell viability, nutrient transport, and mechanical compatibility (Askari et al., 2021; Eltom et al., 2019; Mohamed et al., 2023). These hydrogels have enabled 3D bioprinting platforms to achieve organized constructs with high cell survival, while ECM-derived formulations enhance biochemical signaling (Eltom et al., 2019). Despite this progress, key limitations persist. Most engineered constructs lack adequate vascularization, leading to hypoxia and tissue necrosis beyond 2-3 weeks of culture (Huling et al., 2019; Lee et al., 2024). In vivo translation poses additional challenges, including immune responses, variable scaffold degradation, and limited scalability. Furthermore, combining synthetic scaffolds with iPSC-derived organoids raises ethical and regulatory concerns, especially regarding long-term safety and standardization (Halperin-Sternfeld et al., 2017; Weaver, 2017).

Countries have taken distinct approaches to the clinical translation of kidney tissue engineering. The United States emphasizes translational research supported by structured FDA pathways, enabling materials like PEGDA to progress into early-stage trials (Aston et al., 2013; Aya Imafuku et al., 2019; Sarker et al., 2018). However, stringent regulatory oversight can slow innovation. Japan, in contrast, has fostered faster clinical integration by supporting iPSC-based renal organoids within scaffold systems and maintaining more permissive regulatory policies (Yang, 2022). This has allowed for early clinical exploration of scaffold-enhanced kidney therapies and human-xenogeneic organoid applications (Fransen et al., 2021; Serbo & Gerecht, 2013). These differences reflect how national policy and regulation shape the development and deployment of biomaterials. The necessity to strike a balance between innovation and compliance is highlighted by these discrepancies for this study. While safety is guaranteed by U.S. frameworks, Japan's adaptability shows how preclinical testing of hydrogel-scaffold hybrids like GelMA-ECM composites can be accelerated under flexible regulations.

While bioprinting technologies have advanced rapidly, the fabrication of a fully functional kidney remains a long-term goal. The kidney's highly complex structures including glomerular networks, filtration barriers, tubular segments, and hormonal signaling mechanisms are difficult to replicate in vitro (Ahmed, 2015; Bolinas et al., 2025). Although nephron-like units and renal patches have been engineered, full-scale functional filtration and long-term survival remain elusive (Fransen et al., 2021; Jansen et al., 2017; Lee et al., 2024). Nevertheless, recent improvements in organoid maturation, vascular integration, and smart biomaterials lay a strong foundation for progress. In the short term, bioprinted renal tissues are expected to support drug testing and partial regenerative functions while full-organ construction remains in development (Eltom et al., 2019; Huling et al., 2019).

Although individual studies report quantitative outcomes such as vascular density, stiffness ranges, and fibrotic marker reduction, direct benchmarking across scaffold systems remains challenging due to inconsistent evaluation metrics, variable animal models, and short study durations. Parameters such as vascular density, functional protein secretion, and renal clearance are often measured using non-uniform protocols, limiting cross-study comparability(Mirmoghtadaei et al., 2022).The absence of standardized performance benchmarks restricts objective assessment of therapeutic readiness and highlights the need for consensus metrics in renal tissue engineering.

The clinical translation of stem cell-scaffold systems raises ethical and immunological challenges that remain insufficiently addressed in current renal tissue engineering literature. Stem cell sourcing, particularly involving iPSCs and ESCs, introduces ethical and regulatory concerns related to consent, genetic manipulation, and long-term safety. Immunological risks include inflammatory responses, fibrotic encapsulation, and scaffold rejection, especially in allogeneic or xenogeneic constructs. Additionally, patient-specific factors such as immune status, disease progression, comorbidities, and variability in extracellular matrix remodeling may significantly influence scaffold integration and therapeutic outcomes (Mollaki, 2021). Addressing these risks through patient-specific design strategies and long-term immunological studies is essential for safe clinical translation.

Despite these advancements, challenges such as poor vascular integration, material degradation inconsistencies, and ethical considerations continue to limit clinical translation. Standardizing scaffold design and refining in vivo testing protocols will be critical steps in overcoming these barriers.

CONCLUSIONS

1. Hydrogels are now recognized as key biomaterials in renal tissue regeneration. Their ECM-like structure, tunable stiffness, and biochemical signaling capabilities enable them to actively support cell behaviour and spatial organization.
2. The biological relevance of kidney models has been greatly increased by the switch from 2D cultures to 3D organoid systems. These systems exhibit physiological features such as erythropoietin production under hypoxia, which was uncommon in previous models, in addition to enabling the spatial organization of several renal cell types. This emphasizes how crucial dynamic 3D environments that are supported by hydrogels that imitate extracellular matrices are.
3. Despite progress, clinical translation is hindered by vascularization challenges, limited long-term integration, immune compatibility, and the absence of standardized evaluation metrics, which weakens objective assessment of therapeutic readiness.Addressing these gaps is essential to advancing from engineered tissue patches to fully functional, implantable kidneys.
4. The pace and course of kidney research using biomaterials are impacted by variations in regulatory policies across the globe. While Japan's more lenient laws on the use of stem cells and regenerative medicine have facilitated the quicker translation of iPSC-based organoids, the United States places more emphasis on early-phase testing through FDA-regulated routes. Future development can be influenced by acknowledging and learning from these global patterns.
5. Despite tremendous advancements in hydrogel chemistry, organoid maturation, and bioprinting accuracy, the ultimate goal of creating a fully functional, transplantable kidney is still far from reach. In addition to material innovation, a deeper comprehension of immunological responses, renal physiology, and long-term integration mechanisms will be necessary to close this gap. Future research should focus on the following key areas to accelerate clinical translation and maximize therapeutic potential:
    - Development of vascularized scaffolds that promote endothelial cell integration, lower hypoxia, and ease perfusion through coaxial or multi-material bioprinting techniques with GelMA-PEG hybrids in rat models.
    - Long-term in vivo studies to assess tissue remodeling, immunological tolerance, scaffold breakdown rates, and functional retention.
    - Engineering hybrid hydrogels with enough mechanical strength, adjustable degradation, and ECM-mimetic bioactivity to sustain intricate renal architecture.
    - Creation of clinical-grade cell sourcing procedures and ethical frameworks to guarantee safety, scalability, and repeatability in stem cell–scaffold integration
    - Standardization of data sharing systems and bioprinting procedures to facilitate cross-national and cross-institutional cooperation in development and regulatory approval.

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