Emerging and Advanced Treatment Therapies in Kidney Disease: A Comprehensive Review

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Abstract

The kidney is an intricate and essential organ responsible for regulating bodily fluids through urine production, extracting waste products from the blood, and performing multiple vital functions.

The prevalence of renal diseases is increasing globally, underscoring the necessity for appropriate treatment strategies. When a healthy kidney sustains injury, the affected renal tissue undergoes a series of pathological and physiological changes, resulting in various kidney disorders. Changes may involve abnormal glomerular filtration, filtration barrier alteration, tubular blockage, vasoconstriction, interstitial swelling and proteolytic enzyme activation. At present, therapeutic options for this kidney disease are restricted to dialysis and transplantation. Limitations associated with kidney dialysis, insufficient organ donations for transplantation, high costs of the procedure, advanced age, and comorbid conditions contribute to reduced life quality, increased illness, and long-term survival difficulties.

Tissue engineering, a fast-growing area within biomedical engineering, aims to develop biological alternatives that can support, enhance, or replace tissue functions and help repair tissue damage. Overall, kidney tissue engineering represents a progressive and potentially effective strategy for addressing kidney disease. Kidney tissue engineering presents a viable approach for the restoration of impaired renal function, diminishing dependence on transplantation, addressing congenital renal disorders, and facilitating research into kidney disease mechanisms. It is an innovative approach to improving kidney health and treatment outcomes.

This review highlights advances in kidney tissue engineering, with emphasis on cell-based and non-cell-based therapies as well as different methods of tissue fabrication. These approaches mimics the kidney's current environment, facilitate cell growth, promote blood vessel formation, and address related challenges. The advancement in this field now provides engineered renal structures and cell-based therapies as alternatives for treating renal failure, including regeneration of diseased kidneys.

1. Introduction

The kidney is an essential organ that consists of more than 20 distinct cell types and compartments, all of which are connected to both parasympathetic and sympathetic nerves [54]. The kidneys filter waste from the blood; approximately one-third of all blood pumped by the heart goes to the kidneys for this purpose. As blood passes through, the kidneys remove wastes produced by protein metabolism and muscle activity—such as creatinine ,ammonia, uric acid and urea helping to keep the body's internal balance [1]. The kidneys have a bean-like shape and are positioned along the back wall of the abdomen. Their outer, rounded side faces away from the body, while the inner, indented side faces inward [6]. Protected by ribs, back muscles, and surrounding perirenal fat, each kidney has a renal capsule for structural support.

The kidneys are responsible for three principal functions: tubular secretion, tubular reabsorption and tubular secretion. In the process of

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glomerular filtration, blood enters the glomerulus through the afferent arteriole, where the liquid portion (filtrate) is transferred into Bowman's capsule. Tubular reabsorption is the process by which vital substances like water, glucose, amino acids, and ions are transferred from the nephron tubes back into the bloodstream. On the other hand, tubular secretion is the mechanism that moves waste products such as certain drugs, urea, and creatinine from the blood into the nephron tubes to be excreted [53]. Acute kidney injury (AKI) and chronic kidney disease (CKD) are increasingly prevalent global health concerns, with both incidence and death rates rising over recent decades [8]. Chronic kidney disease is characterized by a decreased glomerular filtration rate and elevated urinary albumin excretion [8]. Acute kidney injury (AKI) is characterized by a rapid increase in serum creatinine levels and decreased urine output, which frequently progresses to chronic kidney disease (CKD) [57].

Tissue engineering constitutes a specialized area within regenerative medicine that is dedicated to the restoration or replacement of impaired tissues by replicating natural biological processes. This technique involves constructing tissues or organs to replace diseased or injured organs [49].

Despite rapid progress in the field, the ongoing shortage of organ donors and limited alternatives continue to cause thousands of deaths annually. Tissue engineering may present a solution by developing tissues that are intended to repair damage and support healing within the human body. This review evaluates the contribution of tissue engineering to the advancement of kidney tissue regeneration.

2.0 Emerging Tissue Engineering Strategies For Kidney Regeneration

2.1. Cell Based Therapy

Tissue engineering facilitates cell-based therapies, offering a potential approach for replacing damaged or injured renal cells with healthy counterparts, which may contribute to the restoration of normal kidney function. Research into cell-based treatments for kidney disease began by examining how kidneys naturally repair themselves after being damaged. Therapies involving primary kidney cells , stem cells and other types of cell have shown encouraging results in improving renal function for chronic kidney disease [9]. The following are some of the cell types used for kidney regeneration.

2.1.1 Primary Kidney Cells

Primary cells were collected from both healthy and diseased kidney tissues and then cultivated in culture [9]. Proximal tubular cells (PTCs) constitute the most abundant type of renal cell in healthy kidneys, making up about 60% of total kidney cells. PTCs are essential for protein and electrolyte reabsorption, hydrolase activity, and EPO production [59,60]. Other types of kidney cells include podocytes, collecting duct cells, distal tubular cells, and cells from the Loop of Henle.

While many studies emphasize the culture and physiology of proximal tubule cells (PTCs), there are also established protocols for other types of kidney cells.

Baer et al. [19] used magnetic beads coated with Tamm-Horsfall glycoprotein to isolate human renal epithelial cells from the thick ascending limb and early distal tubule. Their research showed that these cultivated cells are valuable for in vitro experiments involving nephron segments and may be viable cell sources for renal failure treatment.

Presnell et al. [58] introduced a method for culturing primary cells isolated from each major kidney compartment. Both tubular cell-enriched and erythropoietin-producing subpopulations were reliably generated from healthy and diseased renal tissues.

Chung et al. [8] created a method for expanding primary kidney cells from human tissue. Most cultured cells were of proximal tubular origin, with fewer distal tubular cells and podocytes. When grown in a 3D culture, the cells developed tubule-like formations that demonstrated functional capabilities. This method of harvesting and culturing cells appears promising as a cell-based therapy option for treating renal failure.

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2.1.2. Embryonic Stem Cells

Embryonic stem cells originate from the inner cell mass of the embryo. These cells can renew themselves and have pluripotency, enabling differentiation into nearly all cell types within the body [9].

Steenhard et al. [61] demonstrated that embryonic stem cells can efficiently integrate into embryonic kidney tissue in vitro, forming kidney-like organs and supporting their therapeutic potential. However, issues such as uncontrolled growth, teratoma formation in vivo, and legal and ethical concerns limit further development.

Vigneau et al. [21] found that embryonic stem cells expressing brachyury, which marks mesoderm specification, became renal progenitors after treatment with activin A. This discovery indicates that embryonic stem cells may help regenerate kidneys and assist in organ failure recovery.

2.1.3. Amniotic Fluid-Derived Stem Cells

Amniotic fluid-derived stem cells are also recognized as a valuable resource for renal tissue regeneration. Stem or progenitor cells with the ability to renew itself and multi differentiation abilities are found across fetal, neonatal, and adult tissues. Stem cells derived from amniotic fluid (AFSCs) obtained from fetuses present a valuable option for regenerative medicine, as they are simple to obtain and exhibit strong abilities for self-renewal and differentiation [63]. Human amniotic fluid stem cells constitute a viable and ethically acceptable source of unaltered pluripotent cells that may be utilized for kidney regeneration.

Perin et al. [22] injected male donors human amniotic fluid-derived stem cells into murine embryonic kidneys using an in vitro culture system, demonstrating that these stem cells can proliferate, survive, and integrate during organ development.

Siegel et al. [62] discovered that the mammalian target of rapamycin is crucial for the renal separation of stem cells derived from human amniotic fluid.

2.1.4. Mesenchymal Stem Cells (Msc)

Mesenchymal stem cells are frequently utilized because of their minimal immunomodulatory properties and substantial regenerative potential.

Mesenchymal stem cells (MSCs) can be sourced from bone marrow (BM-MSCs), which have shown positive effects in acute renal injury models through paracrine actions such as reducing inflammation and promoting repair [68]. However, some studies report that BM-MSC infusion may also lead to interstitial fibrosis and Angio myeloproliferative changes in renal disease models [72,73].

Reinders et al. [45] conducted a safety and feasibility study involving kidney allograft patients. They administered autologous Bone Marrow-Mesenchymal Stem Cells (BM-MSCs) to these patients and monitored their clinical and immune responses for up to 24 weeks following the injections. The study found that autologous BM-MSC injection helped resolve interstitial fibrosis/tubular atrophy (IF/TA), a major cause of long-term renal allograft loss. Based on these results, the authors concluded that using autologous BM-MSCs in kidney transplant recipients with subclinical rejection and IF/TA is safe and clinically feasible [45].

Adipose-derived mesenchymal stem cells (ADMSCs) are another type of MSC. Research by De Almeida et al. [76] found that introducing ADMSCs into an acute renal injury model led to reduced kidney fibrosis after six weeks. Similarly, Chen et al. [70] reported that when ADMSCs were injected directly into the kidney, they promoted angiogenesis and maintained the integrity of kidney structures, ultimately restoring kidney function within 14 days. Additional studies using mouse models have also shown that ADSCs can improve renal function [71].

A study conducted by Tan et al. [31] investigated the effects of mesenchymal stem cell (MSC) infusion in kidney transplant recipients, specifically in the context of acute rejection related to graft-versus-host disease, compared to groups that did not receive cellular therapy. The results indicated that autologous MSC administration, as opposed to no treatment,

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was associated with a reduced incidence of acute rejection, a lower risk of infection, and improved estimated renal function one-year post-transplantation [31].

In a clinical trial conducted by Perico et al. [32], the feasibility and therapeutic potential of autologous MSC injection were assessed. Following kidney transplantation, the study reported that infusion of autologous MSCs resulted in favorable immunomodulatory effects, as evidenced by an increase in regulatory T cell populations in peripheral blood and improved control over CD8+ T cell activity, contributing to reduced immune rejection.

2.2. Non-Cell Based Therapy

Biomaterials employed in kidney tissue engineering are classified into three primary groups: synthetic polymers, natural polymers and composite biomaterials.

2.2.1 Synthetic Polymers

2.2.1.1. Polyglycolic Scaffold

Pariente et al. [20] performed research using a polyglycolic scaffold to transplant separated kidney segments onto three-dimensional biodegradable PGA polymer scaffolds. The developed tissue showed both tubules and glomeruli, demonstrating that kidney structures can be regenerated by transplanting renal segments. Furthermore, nuclear transfer methods have been used to create other renal structures from different cell sources.

2.2.2 Natural Polymers

Natural polymers such as chitosan, hyaluronic acid, collagen, alginate, fibrin, agarose, and gelatin offer alternatives to decellularized tissues. Below are studies that several studies that have been carried out using hyaluronic acid, collagen vitrigel,collagen Matrigel and acellular tissue matrices.

2.2.2.1. Hyaluronic Acid

Hyaluronic acid has been identified as a potentially optimal scaffold for kidney tissue engineering. Turney et al. [47] investigated the application of hyaluronic acid in patients with end-stage renal failure undergoing hemodialysis and concluded that hyaluronic acid may also serve as a biochemical marker for individuals whose condition worsens despite receiving renal replacement therapy.

Rosines et al. [25] created a three-dimensional cell culture technique using hyaluronic scaffolds to form kidney-like tissues using fetal kidney cells. Collagen-based hydrogels have also been shown to regenerate structures that look like kidney when cultured in vitro, suggesting potential for renal failure treatment.

2.2.2.2 Collagen Vitrigel

Wang and colleagues [33] obtained glomerular epithelial cells and mesangial cells by isolating them from kidney tissue. These cells were then cultured on a collagen vitrigel, which is a thin, durable, and transparent membrane composed of collagen gel. This vitrigel mimics the natural glomerular basement membrane, providing a suitable environment. When kidney cells are grown together on it, the membrane supports the reconstruction of renal glomerular tissue.

2.2.2.3 Collagen Matrigel

Lu et al. [48] reconstructed kidney-like tissue in vitro by utilizing a 3D scaffold made of collagen matrigel combined with neonatal rat renal cells and subsequently applied this system in vivo. The cells cultured in three dimensions retained their characteristics, ability to migrate, and capacity for albumin uptake [48].

2.2.2.4 Hydrogels

Hydrogels serve multiple roles in medical research, such as acting as cell carriers, providing scaffolds that enhance cell adhesion and proliferation, functioning as fillers to repair tissue defects and support healing, and serving as drug delivery systems [75]. Hydrogels exhibit distinctive characteristics, including biomechanical properties analogous to natural soft issue, tunable pore structures, biocompatibility, reduced inflammatory responses, and ease of chemical modification. By replicating the extracellular matrix of biological tissues, hydrogels offer an optimal setting for cell growth and proliferation [74].

Hydrogel architectures offer dynamic properties that enable controlled, biomimetic environments

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for organoid encapsulation. Differentiation processes within hydrogels can be precisely regulated and are physiologically pertinent, thereby improving the consistency and development of organoids [76]. Hydrogels' unique properties allow for their production in various shapes, including bulk gels, microgels, nanogels, fibers, films, and patches to suit different uses. Injectable hydrogels are especially popular in treatments since they can be administered without surgery and may contain drugs, cell or growth factors[53].

Numerous studies aim to better replicate the 3D structure of native body tissue to maximize hydrogel scaffold efficiency. For example, anti-fibrosis hydrogels have been developed using extracellular matrix-mimicking scaffolds with natural collagen from swim bladders and chondroitin sulfate derivatives [77].

Selecting the appropriate hydrogel shape is crucial in smart polymer development. Various factors influence hydrogel properties and applications, but challenges remain for kidney tissue engineering, including mechanical control, vascularization, and longevity of structures. Continued developments in materials science and cell biology are anticipated to further improve the efficacy of hydrogels in the treatment of kidney diseases [53].

2.2.2.5. Acellular Tissue Matrices

Acellular tissue matrices (also referred to as decellularized scaffolds) are biological frameworks derived from natural tissues, in which all cellular components are removed while conserving the architecture of the extracellular matrix (ECM) and bioactive cues essential for tissue regeneration [26,29] These matrices have been successfully applied in kidney tissue engineering, where decellularized renal scaffolds support recellularization and partial functional recovery [44].

Ross E.A. et al.[7] created 3D kidney scaffolds from rat kidneys that have been decellularized using detergent perfusion and subsequently reseeded them with renal cells. The scaffolds preserved ECM structure and some kidney functions, like glomerular filtration, showing that nephron architecture can be maintained and repopulated.

Nakayama et al. [67] decellularized a porcine kidney, preserving key ECM components like collagen IV, fibronectin and laminin. The resulting scaffold supported endothelial and epithelial cell growth in vitro, suggesting large-animal kidney matrices could be viable for human-scale regeneration.

2.3. Composite Biomaterials

Composite biomaterials combine natural and synthetic components, or different types of biomaterials. For example, polyglycolic acid (PGA), a synthetic polymer, can be combined with collagen, a natural material [13] Hydroxyapatite–polymer composites mix hydroxyapatite (HA), a mineral, with a synthetic polymer [44].

Toosi and colleagues [13] created a composite scaffold made of collagen and PGA for use in bone tissue engineering. By combining collagen's biocompatibility with PGA's mechanical strength, the scaffold showed improved structural properties and supported cell adhesion, proliferation, and differentiation, making it a good biodegradable scaffold for bone regeneration.

Gaharwar et al. [44] reviewed the evolution of biomimetic composite scaffolds combining bio ceramics using collagen or gelatin for bone tissue engineering. The study highlighted that such composites mimic the natural bone extracellular matrix, providing enhanced mechanical strength and bioactivity. These scaffolds facilitate cell proliferation, adhesion, and differentiation, positioning them as promising candidates for efficient bone regeneration.

3.0 Tissue Engineering Fabrication Method

3.1. 3d Printing

3D printing, or additive manufacturing, refers to the technique of constructing three-dimensional objects by sequentially adding material in layers. This technology enables the fabrication of complex and bespoke components derived from digital 3D models. Notably, its applications extend to fields such as tissue engineering and organ repair, including potential relevance for kidney regeneration.

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Over the past few years, three dimensional bioprinting has established itself as a cutting-edge technique in the fields of organ restoration and tissue engineering. This advanced technology facilitates the fabrication of viable, functional tissues by utilizing biomaterials, patient-derived cells and sophisticated three-dimensional printing systems. The process involves incorporating cells into bio-ink with suitable biomaterials, which are subsequently deposited by each layer onto a scaffold through a controlled extrusion system such as a syringe or nozzle [78].

Extrusion printers, commonly used in bioprinting, deposit layers of bioink—containing cells, biomaterials, and growth factors—through a nozzle onto a scaffold or substrate.

Jo H et al. [79] created an autologous patch with a bioprinter to test its effect on End Kidney State Disease (ESKD) treatment. They used fibrinogen and thrombin from omentum tissue, printed the patch, and transplanted it into rats. Two weeks later, the mesh patch group showed less renal tubule damage and improved fibrosis markers compared to the fibrin patch group.

Designing and bioprinting a viable, functional kidney is challenging due to the organ's delicate cells, specialized requirements, and complex vascular network. Achieving high-resolution replication of kidney architecture and ensuring sufficient nutrient and oxygen delivery are significant obstacles. Current 3D bioprinting faces issues like integration with host tissue, angiogenesis, scaffold complexity, high costs, reproducibility, and creating functional nephrons [53].

3.2. Other Emerging Technology

Additional technologies under development for kidney regeneration include electrospinning, a technique that facilitates the production of continuous nano- and microscale fibers from diverse materials through multiple methodologies [80]. This approach remains underexplored within the field of kidney tissue engineering [81]. Another innovative technology is the organ-on-a-chip, which enables the simulation and creation of miniature models of various human organs, including the kidney, for diverse laboratory applications [53]. These chips are composed of living cells within an environment that closely replicates the targeted organ tissues. Kidney-on-a-chip platforms offer significant potential in advancing kidney models that capture essential physiological characteristics of the tissue microenvironment in vitro, supporting research into the mechanisms of kidney function and disease. Additionally, these technologies are widely utilized as platforms for nephrotoxicity screening [82].

4.0 Limitations of Tissue Engineering Strategies

Current strategies in kidney tissue engineering encounter several significant limitations that require careful consideration. Key challenges include the need for the development of robust preclinical models capable of accurately replicating clinical scenarios, the implementation of advanced methodologies to address immunological concerns, and the formulation of comprehensive approaches to elucidate the intricate mechanisms underlying improved renal function including physiological parameters and incorporation with host vascular and nervous systems. Moreover, more clinical trials are essential to rigorously assess the safeness and effectiveness of therapeutic cells intended for kidney disease treatment.

Further research is necessary to identify growth factors that reliably stimulate tissue proliferation and to establish effective methods for their delivery, whether ex vivo or directly into transplanted cells. The integration of host vasculature with grafts remains a substantial technical hurdle, particularly in creating seamless connections with existing ureters. Additional complexities arise in sourcing suitable organs, standardizing scaffold fabrication and cell seeding protocols, achieving consistent organ revascularization, and enhancing organ preservation techniques. Advancing the field also demands a deeper understanding of organogenesis, elucidation of organ-specific disease mechanisms, and the pursuit of innovative therapeutic interventions.

Ongoing research efforts are crucial to consistently identify and deliver growth factors that support tissue proliferation, both ex vivo and within transplanted cells. Enduring

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obstacles exist regarding the successful integration of host blood supply with grafted tissues particularly with respect to establishing functional vascular-ureteral connections as well as the identification of viable organ sources, harmonization of scaffold construction and cell seeding methodologies, promotion of reliable organ revascularization, and optimization of storage protocols [28,30]. Furthermore, it is imperative to expand foundational knowledge of organ development, explore disease pathogenesis, and develop novel treatment modalities for continued advancement in kidney tissue engineering.

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