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Harnessing Stem Cells for Kidney Regeneration : Progresses and Challenges in Clinical Translation

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Abstract. *The prevalence of chronic kidney disease is increasing worldwide and is considered a burden for health care systems and patients. However, there are only a few treatment options, and in most cases, the end-stage of the disease requires renal replacement. Stem cell-based therapy has gained popularity as a cutting-edge strategy in the field of regenerative nephrology. Numerous clinical studies on evaluating stem cells safety and tolerability have been carried out, leading to clinical translation of stem cells for kidney regeneration. This study will focues on progresses of recent clinical trials on stem cell therapy for various kidney diseases, while also highlighting key challenges in clinical translation and future directions in the field of regenerative nephrology.*

Keywords*: stem cells, mesenchymal stem cells, kidney regeneration, clinical application*

1. INTRODUCTION

Kidney disease is a major global health concern with chronic kidney disease (CKD) and Acute Kidney Injury (AKI) are two most common conditions that occur frequently. CKD is a progressive disorder that causes a gradual decline in kidney function, whereas AKI involves abrupt decrease in glomerular filtration and is often associated with acute events like sepsis or ischemic injury. The Global Burden Disease (GBD) reports that CKD is the 12th leading cause of death in 2017 with more than 850 million people, affecting over 10% of the general population worldwide with the distribution varying according (Jager et al., 2019; Kovesdy, 2022). Additionally, a meta-analysis of 100 studies with over 6.9 million patients revealed that the global prevalence of CKD stages 1 - 5 is estimated to be 13.4%, while advanced CKD (stage 3 - 5) is 10.6% (Hill et al., 2016). They also found that CKD is more common in elderly individuals, with the increased incidence from 13.7% in the 30 – 40 age group to 27.9% in the 70 – 80 age group (Hill et al., 2016). It is also known that the major risk factors contributing to increasing cases of CKD include diabetes mellitus and hypertension, implying by the the prevalence of CKD stages 3 – 4 reached 24.5% in diabetic patients compared to 4.9% in non-diabetic individuals in the US (*Centers for Disease Control and Prevention Chronic Kidney Disease (CKD) Surveillance System: 2021*, n.d.).

Although AKI contributes to relatively lower incidence than CKD, the incidence rate of newly diagnosed AKI has risen from 80 per 1,000 patient-years in 2007 to 242 per 1,000 patient-years in 2022. COVID-19 infections during the pandemic may have

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contributed to the increase in AKI incidence after 2019 (*Trends in Incidence Rate of Acute Kidney Injury by Diagnosis Code*, n.d.). While an episode of AKI can lead to the development of end-stage renal disease (ESRD) (Hoste et al., 2018), CKD increases both risks of cardiovascular disease and ESRD which demands replacement therapy such as dialysis or kidney transplantation (Irazabal et al., 2019). Therefore, both CKD and AKI contribute greatly to the economic burden of the health system, with high treatment cost due to the need for long-term follow-up and kidney transplantation as the main therapy for patients with ESRD (Malekshahabi et al., 2019).

Current CKD treatment still relies on conventional therapies such as dialysis and kidney transplantation. Unfortunately, dialysis only partially restores kidney function and does not halt the disease progression. Furthermore, problems like infection, malnutrition, and cardiovascular disease are linked to dialysis (Casiraghi et al., 2016). Kidney transplantation is a more effective therapeutic alternative, but some major challenges in applying it such as kidney donor shortage, the risk of immunological rejection, and the requirement for long-term immunosuppressive treatment (Peired et al., 2016). Therefore, innovative therapeutic approaches are needed to repair kidney function regeneratively in order to reduce risk problems from conventional renal replacement therapy.

In recent years, stem cell-based therapy has gained popularity as a cutting-edge strategy in the field of regenerative nephrology. Different types of stem cells have been explored in research of kidney regeneration including Mesenchymal Stem Cells (MSCs), renal progenitor cells, and induced pluripotent stem cells (iPSCs). MSCs which usually derived from bone marrow and adipose tissue have demonstrated the capacity to regenerate injured kidney tissues and immunomodulatory properties, improving tissue regeneration, reduce kidney inflammation, and slow the progression of CKD and AKI (Casiraghi et al., 2018; Li et al., 2022). Renal progenitor cells play a role in nephron-specific regeneration and differentiation into more mature renal cells (Rota et al., 2019). In addition, iPSCs also offer great regenerative potential despite the risk of abnormal differentiation leading to tumour-induced cells which is still a major concern in clinical applications (Casiraghi et al., 2016). A systematic review and meta-analysis study on 71 animal studies confirmed that cell-based therapies, especially MSCs, improve the impaired renal function and morphology in preclinical models of CKD (Papazova et al., 2015). Furthermore, recent studies have also investigated the use of combination therapies such as combining MSCs with melatonin, anti-fibrotic drugs, and other conventional medical treatments (Li et al., 2022; Zahran et al., 2020).

Building on the promising therapeutic effects observed in animal studies, research has advanced to multiple clinical trials investigating the efficacy of stem cell therapy for various kidney diseases including diabetic kidney disease (DKD), CKD, AKI, atherosclerotic renovascular disease (ARVD), autosomal dominant polycystic kidney disease (ADPKD), and lupus nephritis (LN). Thus, this review will provide an updated overview of recent clinical trials on stem cell therapy for several kidney diseases, while also highlighting key challenges in clinical translation and future directions in the field of regenerative nephrology.

2. METHODOLOGY

The keyword of ("stem cells"[MeSH] OR "stem cell therapy"[MeSH] OR "mesenchymal stem cells"[MeSH] OR "renal progenitor cells" OR "induced pluripotent stem cells") AND ("kidney disease"[MeSH] OR "chronic kidney disease" OR "renal failure" OR "acute kidney injury") AND ("clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "case series") were used in literature searches on PubMed by January 31st 2025. Articles written in English and published within the last ten years (2015 – 2025) that addressed human-derived stem cells and their use in clinical translation were included in the study. While, abstracts of conferences, congresses, meetings, letters, and comments were not included. For this evaluation, the abstracts of study were reviewed on the use of stem cells for clinical trials, underlying diseases, the type of stem cells employed in the study, study types, sample sizes, infusion methods, clinical outcomes, and adverse events. Data were analyzed and written up in a descriptive manner.

3. CLINICAL STUDIES ON STEM CELL THERAPY FOR KIDNEY DISEASES

Stem cell therapy has become a promising treatment option for a number of kidney diseases with its ability to reduce inflammation, promote tissue regeneration, and halt the progression of the disease. The application of MSCs and other regenerative therapies to different kidney diseases has been the subject of an increasing number of clinical trials. These studies have investigated various patient groups, administration methods, stem cell types, safety and tolerability of stem cells, and the serious adverse events with differing degrees of effectiveness. Although stem cell therapy’s safety has been widely established, investigations into its clinical efficacy remains an ongoing area of research. We have reviewed 13 recent clinical studies in the field arranged by disease category while

emphasizing the study design, primary and exploratory clinical outcomes, adverse events, and serious adverse events.

Chronic kidney disease (CKD) is the most studied disease in kidney regeneration, where the conventional treatment frequently fails to stop the disease progression. Utilizing BM-MSCs in patients with CKD, Makhlough et al. (2018) demonstrated that the treatment was safe, but there were only slight improvements in kidney function during an 18-months of follow-up period (Makhlough et al., 2018). Similarly, Zheng et al. (2022) examined the safety and feasibility of an allogeneic adipose-derived MSC treatment and found that 58% of participants experienced minor improvements in eGFR, while there was no apparent reduction in proteinuria (Zheng et al., 2022). Another study harnessing adipose-derived MSCs reported a slight decrease in proteinuria, but no obvious impact on the recovery of kidney function (Villanueva et al., 2019). These results collectively demonstrate the wide range of responses to MSC therapy, indicating that future research should focus more on refining cell types, administration methods, dosage regimens, and patient selection criteria in order to optimize clinical advantages. Unlike other studies that mostly harnessing MSCs, a phase-1 clinical trial by Lee et al. (2017) tested autologous peripheral blood-derived CD34+ cells or known as peripheral blood stem cells (PBSCs), in CKD patients through intra-renal artery transfusion after G-CSF stimulation. The study confirmed the safety and tolerability of CD34+ cells but failed to show improvement in eGFR. Interestingly, the treatment could stabilize the creatinine levels compared to that of baseline after 12-month follow up (Lee et al., 2017).

Additional to common CKD, chronic kidney disease of unknown cause (CKDu), also known as Mesoamerican Nephropathy, has drawn notice as a new public health emergency, especially among agricultural laborers who are subjected to intense heat and dehydration. Therefore, a first-in-human research testing autologous stromal vascular fraction (SVF) cells was conducted in patients with CKDu. The study showed that kidney function stabilization was attained in those with eGFR>30, whereas those with more advanced disease continued to decline (Carstens et al., 2023). The study used bilateral renal artery catheterization for direct SVF cell injection, a targeted-administration strategy that might improve vascular repair mechanisms. Despite these promising results, further research is required to determine whether SVF therapy could be applied as an early intervention approach for high-risk groups.

Whereas CKD involves slow disease progression, acute kidney injury (AKI) presents a rapid onset and high mortality risk, facing urgent clinical challenge. A study by

Swaminathan et al. (2018) performed an allogeneic BM-MSCs treatment in a post-cardiac surgery AKI in a Phase II randomized trial. Unfortunately, the study was terminated early since it was unable to show a significant reduction in recovery time (Swaminathan et al., 2018). Building on this finding, 4 years after the former study, they developed a cutting-edge ex vivo bioreactor system integrated with continuous renal replacement therapy (CRRT) intended to improve immunomodulatory effects of MSCs in AKI patients with systemic inflammation. However, the treatment did not reduce mortality or dialysis dependance despite its potential anti-inflammatory effects (Swaminathan et al., 2021). The possible reasons for these unfavorable results of the study are the complex disease conditions and variability in the onset and pathophysiology of the disease (Makris & Spanou, 2016). This underlines the need for more MSC delivery strategy improvement in AKI conditions.

In addition to CKD and AKI, several studies have investigated MSC-based approaches to slow the progression of diabetic kidney disease (DKD). Packham et al. (2016) investigated allogeneic mesenchymal precursor cells in DKD patients in a randomized, dose-escalation experiment. They found that while the therapy was well tolerated, it only produced minor improvements, with no notable rise in eGFR (Packham et al., 2016). Seven years later, Perico et al. (2023) assessed a next generation BM-MSC therapy called ORBCEL-M in a randomized, placebo-controlled experiment. They showed that the treatment significantly reduced the decline in eGFR when compared to the placebo group, demonstrating improvement in clinical benefit of the therapy (Perico et al., 2023). However, both studies emphasized the need for larger trials and longer-term follow-up to fully assess MSC therapeutic potential, even current results have implied that it may have kidney protective effects in DKD.

Researchers have also studied the clinical applications of stem cells for atherosclerotic renovascular disease (ARVD) which is characterized by reduced blood supply to the kidney, leading to progressive renal failure. In order to assess adipose-derived MSCs in ARVD patients, Saad et al. (2017) carried out Phase I/IIa trials, revealing that intra-arterial MSC infusion may stabilize kidney perfusion along with improving renal blood flow (Saad et al., 2017). Moreover, a further study supported the potential benefit of targeted intra-arterial MSC delivery versus systemic treatment, demonstrating that MSC therapy could increase renal tissue oxygenation and achieve modest eGFR improvement in targeted intra-arterial fashion (Abumoawad et al., 2020).

In 2017, Makhlough et al. explored stem cell ability to slow the cyst growth in autosomal dominant polycystic kidney disease (ADPKD). They conducted a Phase I clinical investigation to evaluate the safety of autologous BM-MSC infusion in patients with ADPKD. The study revealed that the treatment was well tolerated without serious adverse events, but no significant impact on kidney function over a 12-month follow-up period (Makhlough et al., 2017). These results imply that MSC treatment is unlikely to stop the growth of cysts immediately, suggesting more investigation into different regenerative strategies tailored to the pathophysiology of ADPKD. Furthermore, employing stem cell treatment in lupus nephritis poses a distinct challenge from ADPKD since it is an autoimmune disease with intricate immunological dysregulation which is genetically acquired. A randomized, double-blind, and placebo-controlled study was performed by Deng et al. (2017) to evaluate the application of hUC-MSCs in lupus nephritis patients. The trial resulted in little to no difference in remission rate of kidney function markers between treatment groups. The study concluded that although hUC-MSCs therapy was safe and well-tolerated, it failed to offer any additional advantages over conventional immunosuppressive medication (Deng et al., 2017). These findings also highlight the heterogeneity of lupus nephritis as indicating more challenges to develop effective MSC therapy. Therefore, future trials may need to include biomarkers for patient stratification to determine which patients are most likely to benefit from stem cell-based therapies.

4. CHALLENGES IN CLINICAL TRANSLATION AND FUTURE DIRECTIONS

Based on key findings from 13 clinical studies, MSCs are being considered for kidney regeneration because of their unique biological characteristics in comparison to other stem cell types such as iPSCs and ESCs. Unlike ESCs which have ethical concerns and the potential to form teratomas, and iPSCs which require complex reprogramming and may display genomic instability, MSCs provide a more practical and safer alternative to apply in a clinical setting. There is strong evidence that MSC therapy can reduce kidney damage, enhance renal function, and restore vascular integrity based on studies conducted in mice, pigs, and primates (An et al., 2019; Eirin et al., 2018; Moghadasali et al., 2015; Nagaishi et al., 2016). Unfortunately, human clinical trials have often failed to demonstrate significant benefits, especially in patients with ESRD, despite these encouraging results in animal studies (Makhlough et al., 2018; Swaminathan et al., 2018). This disparity demonstrates the complexity of renal repair processes and raises the possibility that MSC

therapy may not be able to fully reverse permanent kidney damage in ESRD, although beneficial in early stages of the disease.

Preclinical studies using models from non-human primates, swine, and mice have consistently shown that MSCs can enhance renal function when given in the early phases of kidney damage. Moghadasali et al. (2015) showed that intra-renal MSC infusion successfully decreased renal inflammation and histological damage in a rhesus macaque model of CKD (Moghadasali et al., 2015). However, the study found that treatment in late-stage fibrosis failed to restore structural damage, suggesting that MSC therapy was successful only when given shortly after kidney injury onset. In a primate model of DKD, An et al. (2019) demonstrated that repeated infusions of human umbilical cord-derived MSCs (hUC-MSCs) enhanced renal function and glycemic management, resulting in decreased glomerular hypertrophy and a reduction in albuminuria (An et al., 2019). Interestingly, the study found that MSCs may have kidney protective effects through a unique mechanism that is similar to the pharmacological activity of sodium-glucose cotransporter 2 (SGLT2), an inhibitor used to treat DKD.

Eirin et al. (2018) provided more molecular insights in a pig model of metabolic renovascular disease, showing that EVs derived from MSCs enhanced glomerular filtration rate (GFR) and repaired renal microvascular structure. Significantly, EV-treated swine showed elevated expression of VEGF and Notch-1, indicating that MSCs improve angiogenesis and endothelium repair (Eirin et al., 2018). This finding is particularly relevant given that capillary and vascular dysfunction are major factors in the development of CKD. In addition, Nagaishi et al. (2016) demonstrated that MSC-derived exosomes decreased inflammation and fibrosis in mice with diabetic nephropathy, confirming the idea that paracrine signalling is the main mechanism of MSC-mediated healing rather than direct cellular differentiation (Nagaishi et al., 2016).

Despite the potent immunomodulatory properties of MSCs, a number of unresolved issues remain challenges in applying MSC in a clinical setting. First, timing seems to be a crucial component in determining the efficacy of MSC (An et al., 2019; Moghadasali et al., 2015). While infusions in late-stage disease may not be able to cure existing fibrosis, preclinical studies indicate that early MSC delivery produces more favorable results. This is consistent with the findings of human trials, which showed that MSC infusion had little to no benefit for patients with advanced CKD or ESRD (Makhlough et al., 2017; Swaminathan et al., 2018). Second, the effectiveness of treatment may be affected by the method used to deliver MSCs. Although intravenous infusion is the most often used

method, intrarenal arterial distribution may be more effective, especially in the case of vascular injury (Eirin et al., 2018; Moghadasali et al., 2015). Third, there are still problems with MSC MSC heterogeneity and variability in cell differentiation. Several factors such as MSC donor age, passage number, and culture conditions can greatly impact the success of the treatment, highlighting the necessity of standardized cell preparations and quality control procedures.

Those challenges in clinical translation require further investigations through large-scale clinical trials, biomarker-based patient selection, and optimization of the dose and method of therapy administration in order to harness stem cells to treat kidney diseases such as DKD, CKD, AKI, and ARVD. RCT-based studies have shown that stem cell therapy is generally safe with treatment-unrelated cases of serious adverse events (Packham et al., 2016; Perico et al., 2023). In ARVD and CKD, patients with certain biomarker levels showed better therapy responses, supporting the importance of more specific patient selection. In addition, multi-center studies are necessary to increase external validity, although there are still issues such as discrepancy in patient profiles and regulations. In order to increase the efficacy of therapy, research should also be performed on optimizing the dosage and delivery mechanism.

As discussed earlier, EVs-derived MSC play a significant role in MSC-mediated healing rather than the direct cell differentiation. Through GDNF/RET signaling pathways, EVs decrease fibrosis and promote angiogenesis to accelerate renal tissue recovery. Consequently, they have been developed as a safer alternative to direct cell transplantation for renal regenerative therapy (Lee et al., 2017). Furthermore, it has been demonstrated that preconditioning MSCs with melatonin improves their therapeutic effects when paired with EVs, protects against oxidative stress and post-transplant hypoxia, as well as increases MSC viability and regenerative capacity (Zahran et al., 2020; Zhao et al., 2020).

Furthermore, the advancement of combining stem cells and biomaterials scaffolds that support cell growth and differentiation has emerged as a viable approach to kidney tissue regeneration. Without the need of external differentiation factors, PLGA-based scaffolds enhanced with extracellular matrix, magnesium hydroxide, and zinc oxide have been created to boost the viability of IM cells and promote the development of renal progenitors (Willerth & Sakiyama-Elbert, 2019). Biomaterial scaffolds have been demonstrated to preserve renal tubular shape and vascularization. However, problems with uneven cell distribution and functionality continue to be significant barriers to their use (Remuzzi et al., 2017). Therefore, new approaches are still required to increase the

effectiveness of recellularization with the combination of 3D printing and stem cell-based regeneration for upcoming clinical use.

5. CONCLUSION

Overall, these clinical trials demonstrate the important developments in stem cell research for kidney disorders, exhibiting a range of delivery methods, differing levels of effectiveness, and consistent positive safety profile. While intravenous infusion remains a widely used administration method, a more targeted delivery technique such as intra-renal artery infusion and the use of an ex vivo bioreactor system supporting immobilized cells are showing promise to promote kidney function. These clinical studies establish a solid basis for future research, which should concentrate on improving patient selection, refining infusion procedures, and incorporating MSC therapy with potential advance treatment strategy. As research progresses with more favourable results, stem cell therapy might soon move from experimental approach to practical clinical intervention for kidney diseases.

The advancement strategies of MSCs, EVs, biomaterial-based scaffolds, and melatonin preconditioning has demonstrated significant promise in improving the effectiveness of renal regeneration therapy as research advances. MSCs-derived EVs provide an alternative for renal tissue regeneration without direct cell transplantation. Although biomaterial scaffolds constitute a significant advancement in kidney tissue creation, recellularization issues still need to be evaluated. This strategy is progressively demonstrating its promise as a more potent therapy and is prepared for upcoming clinical applications with the combination of 3D printing technology and stem cell-based regeneration techniques.

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