REVIEW

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Human umbilical cords mesenchymal stem cells for kidney diseases

Dianita Halimah Harahap[1*], Gampo Alam Irdam[1]

[1]Department of Urology, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia;

*Corresponding author:
Dianita Halimah Harahap;
Department of Urology, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia;
uro.dianita.fkui@gmail.com

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ABSTRACT

Stem cell therapy is an emerging therapy in the medical field. Recent studies show that stem cell therapy gives promising results. One of the stem cell sources is the human umbilical cord that has many potential, not only for therapy alone but also for banking. Human umbilical cord mesenchymal stem cells (HUCMSCs) have greater advantages than bone marrow and adipose tissue-derived stem cells in isolating the cells and the shortest culture period. Studies on animal models showed improvement of kidney disease in the various mechanism. Human studies regarding human umbilical cord mesenchymal stem cells as therapy for kidney disease have not been conducted on a large scale, but MSC therapy appears safe.

Keywords: human umbilical cord mesenchymal stem cells; kidney disease; efficacy; safety.
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INTRODUCTION

Cell therapy is a newly emerging field, which leads to many scientific disciplines such as stem cell biology, molecular biology, immunology, tissue engineering, regenerative medicine and clinical research. The use of stem cells keeps developing between years to meet the needs of alternative medicine for kidney diseases.[1] In Indonesia, chronic kidney disease is one of the highest prevalence for uncommunicable diseases, with around 0.2%.[2] Chronic kidney disease (CKD) is characterized by an irreversible and progressive deterioration of renal function until it reaches end-stage renal disease (ESRD). The etiology of this condition could be classified based on the location, such as at the glomerular (diabetes mellitus, glomerulonephritis), tubulointerstitial (systemic infection, autoimmune, stone obstruction), vascular disease (hypertension, vasculitis, atherosclerosis), and cyst or congenital diseases (renal dysplasia).[3,4]

When the patient reaches end-stage renal disease, the patient should get renal replacement therapy as in hemodialysis, continuous ambulatory peritoneal dialysis (CAPD) or renal transplantation. These therapies will greatly burden the patient's financial and social aspects of life. Therefore, we need other alternatives in managing kidney disease to prevent the progression leading to end-stage renal disease.

Stem Cells

The stem cell is a pluripotent fibroblast-like cell that could renew itself and go through multilineage differentiation. Aside from bone marrow, the mesenchymal stem cell can be derived from umbilical cord blood, umbilical cord wall, amniotic fluid, peripheral blood, skeletal muscle, adipose tissue, kidney, and dental pulp (Figure 1). Only stem cells derived from bone marrow, umbilical cord, amniotic fluid, and adipose tissue have been widely used to treat many diseases.[5] In Cipto Mangunkusumo National Hospital, the umbilical cord-derived mesenchymal stem cells have been used widely in orthopedic, neurologic, and endocrine treatments.

Human Umbilical-Cord Mesenchymal Stem Cells (HUCMSCs)

The umbilical cord is one of many sources of mesenchymal stem cells. It produces embryonic stem cells that can differentiate into almost all types of cells in the body or call pluripotent. Stem cells can be isolated from Wharton's Jelly, cord lining, and perivascular region. The HUCMSCs with theirs pluripotent capabilities can differentiate to mesoderm (adipocytes, osteocytes, cartilage), ectoderm (neuron, astrocytes, glial cells), and endoderm (liver, islet cells) (Figure 2).[6]

HUCMSCs and Kidney Diseases

Multiple stem cell types have been for their advantages in treating kidney disease. A choice between autologous or non-autologous stem cells is also important before the transplantation. Non-autologous stem cells have to face host immunologic reactions. Bone marrow was the first reported source of stem cells and used to treat many diseases. However, it has its disadvantages: the highly invasive procedure in the donation process, deterioration of cells number, and decrease in its differentiation potential with increasing age. Nonetheless, many studies were trying to find another better source. There are significant differences regarding morphology and immune phenotype of the MSCs between stem cells derived from bone marrow, umbilical cord blood and adipose tissue. Umbilical cord blood stem cells show a lower success rate on isolating MSCs. However, it shows the highest proliferation capacity, shortest culture period, no adipogenic differentiation capacity, and it could be expendable to higher numbers.[7] Collins et al. reported that human MSCs from

healthy bone marrow and umbilical cord significantly improved renal disease in mice, while lupus bone marrow only delayed disease progress. Aside from the effect of stem cells in treating kidney diseases, this study described that the source of stem cells should be selectively chosen.[8]

Many studies have been conducted using HUCMSCs for kidney diseases, particularly using animal models. Most of the studies showed that implantation of HUCMSC shows positive results for kidney diseases. A meta-analysis from Wang et al. analyzed the route of delivery, number of MSC, type of injury and MSC type. It described various types of delivery routes, such as intravenous, intrarenal, intraperitoneal, and via renal artery or carotid artery. Route of delivery was one of many factors influencing the cells' capacity for homing and engraftment.[9] Direct implantation to renal artery shows approximately 4-15% retention rates compared to engraftment rate of intravenously implanted MSC in non-human primates ranging from 0,1 to 2,7%. The Intraparenchymal/intrarenal route is also proven to give renoprotective effects, but it was not easy to implement in humans.[10] Number of MSC used in many studies ranged from 7,5 x 10^4 to 9 x 10^6 cells with sources from rat bone marrow-derived MSC, human MSC from fetal membranes, and human bone marrow-derived MSC.

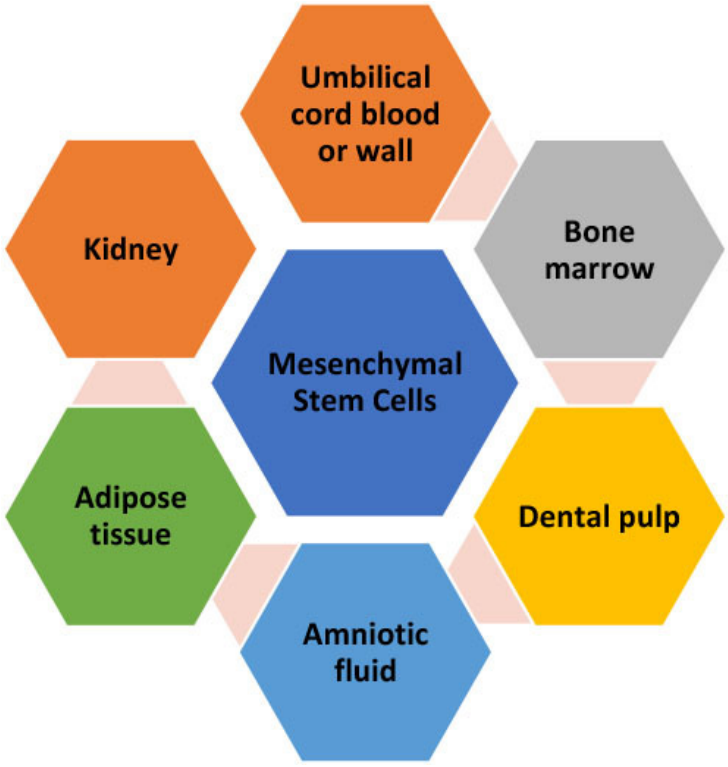

Figure 1. Sources of Mesenchymal Stem Cells.

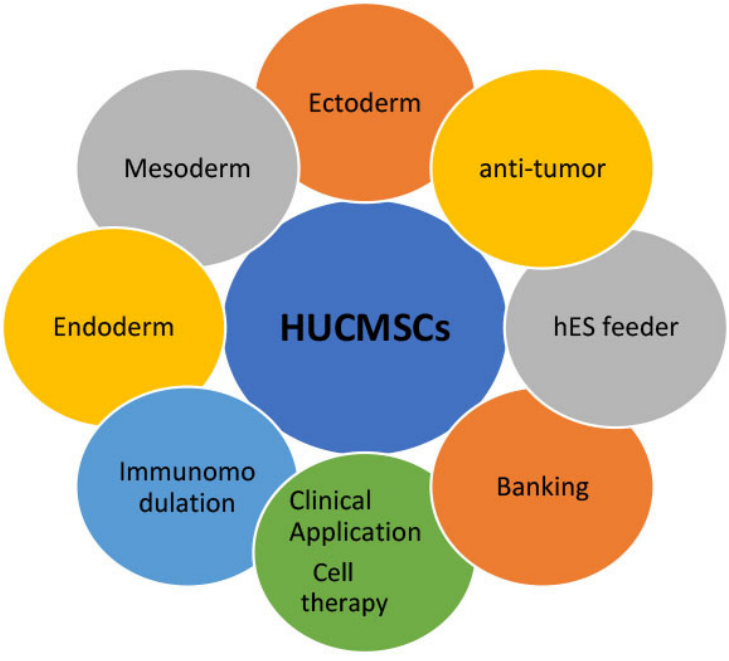

Figure 2. Illustration of the differentiation capability and the utility of HUCMSCs.

To make a similar condition with the diseases, researchers create an injury intentionally with toxic antibodies, toxic-ischemic, ischemia-reperfusion injury, chronic injury, sepsis, and cellular rejection. It concluded that MSC therapy improved impaired renal function with more obvious results in the early stage of renal injuries after arterial delivery. It might have happened because the artery is rich in blood flow and blood velocity, and it could promote MSCs to enter the damaged site more quickly, efficiently and homogenously.[11]

Studies of HUCMSCs have also been conducted in larger animals, such as swine and cats. In these studies, bone marrow-derived MSC could inhibit or delay the chronic kidney disease progression induced by renal fibrosis in swine.[12] Not only for swine but studies on porcine showed that MSC or its derivation could attenuate renal inflammation and improve glomerular and tubular function, leading to renal recovery.[13,14] The efficacy and safety of MSC are also supported by research in cats. Feline allogenic mesenchymal stem cells have renoprotective effect and improve renal function in cats with CKD.[15] However, contradictive results

Table 1. Studies of Human Umbilical Cord mesenchymal stem/stromal cell (MSC) therapy in animal models to impaired renal function.

Author	Subjects	Conditions	Dosage	Results
Chang et al., 2011[25]	mice	Lupus Nephritis	1 x 10^6 cells	Reduced severity of proteinuria and progression of renal function deterioration, reduced anti-ds DNA antibody levels, prolonged the life span of the mice, reduced mesangial proliferation and sclerosis in renal pathology, changed Th cytokine polarization, inhibited lymphocyte and splenocyte proliferation
Park et al., 2012[26]	rats	Diabetic renal injury	5x10^5 cells suspended in 1 ml of 1mg.ml CM-Dil	Improvement in kidney injury of diabetic rats, engrafted in diabetic kidneys, inhibited TGF-beta1-induced EMT dan ECM upregulation in NRK-52E cells.
Fahmy et al., 2017[27]	rats	Renal ischemia/reperfusion injury	1 x 10^6 cells	Enhancement of kidney function via anti-oxidant activity decreasing serum levels of creatinine, urea, and uric acid
Liu et al., 2015[28]	rats	Gentamicin induced acute kidney injury	Uses of UC-MSCs-IGF-1	Better recovery of biochemical variables in serum or urine associated with renal function, histological injury and renal apoptosis
Zhou et al., 2013[29]	rats	Cisplatin-induced renal oxidative stress and apoptosis	200 micrograms exosomes	Repairment of cisplatin-induced AKI in rates and NRK-52E cell injury, promoting cell proliferation
Qiu et al., 2014[30]	rats	Renal ischemia-reperfusion injury in rats	1 x 10^6 cells	Inhibit the upregulation of renal ICAM-1 and protect the kidney from ischemia-reperfusion injury
Ju et al., 2015[31]	rats	Ischemic acute kidney injury	microvesicles	Acceleration of cell dedifferentiation and regeneration.
Fang et al., 2012[32]	mice	Diabetic kidney injury	10^6 cells	Reducing apoptosis and promoting proliferation in renal tubular cells.
Park et al.,[33]	rats	Diabetic kidney injury	1 x 10^6 bells	Reducing proteinuria, renal fibronectin, alfa SMA up-regulation.
Jang et al., 2014[34]	mice	Renal ischemia-reperfusion injury	1 x 10^6 cells	Attenuation of early renal injury during the initial injury phase of IRI.
Gu et al., 2010[35]	mice	Lupus nephritis	1 x 10^6 cells	Inhibition MCP-1 and HMGB-1 production
Chen et al., 2011[36]	rats	Acute kidney injury	1x 10^6 cells	Amelioration for ischemia-reperfusion induced renal injury
Cao et al., 2010[37]	rats	Acute kidney injury	1 x 10^6	Relief of hyperemia and inflammation
Perico et al., 2017[38]	mice	Cisplatin-induced acute kidney injury	5 x 10^5 cells	Renoprotection, facilitating renal repair
Wang et al., 2016[39]	rats	Cisplatin-induced acute kidney injury	200 micrograms HUCMSCs-exosome	Relieve the nephrotoxicity
Ma et al., 2013[40]	rats	Focal segmental glomerulosclerosis	2 x 10^6 cells	Improvement from kidney fibrosis and modulation of inflammatory response
Li, 2017[41]	rats	Chronic renal failure	8 x 10^6 cells + icariin	Decreasing in inflammatory responses, upregulation of expression of growth factors, protection of injured renal tissues

were still found where other studies show only a little effect of MSC implantation, thus needing longer time to follow up and assess factors influencing the effect.[16,17]

Aside from trials in animal models, human studies concerning the effect of HUCMSCs have been conducted (**Table 1**). Salim et al. used injection HUCMSCs intrathecally and intravenously for the patient who was previously diagnosed with spinal cord entrapment with chronic kidney disease as comorbidity. This paper reported an improvement in patients' movement and kidney function.[18] Deng et al. did a study to evaluate the efficacy of HUCMSCs for lupus nephritis. They concluded that even HUCMSCs did not show any obvious additional effects on lupus nephritis, but it have been demonstrated clear results on other conditions such as graft versus host disease.[19] Despite that MSC has been used for kidney disease, the implantation of MSC is more widely used in other aspects, such as cardiovascular, neurological, oncological/hematological, and gastrointestinal diseases.[20] MSC-based clinical trials for kidney disease only accounted for 1,8% of 493 MSC-based clinical trials. Despite studies with animal models showing promising results, MSC-based clinical trials for kidney disease remain in early phases, determining the safety and efficacy of the implantation of allogeneic MSC.[21] Current clinical trials conducted worldwide using MSC to treat kidney diseases mostly use allogeneic or autologous bone marrow MSC and adipocyte-derived MSC. The use of allogeneic umbilical cord MSC is not as frequent as the other types of MSC. Currently, HUCMSCs are used to treat lupus nephritis and systemic lupus erythematous. However, MSC from many sources shows us wide applicability for kidney diseases, from acute kidney injury, chronic kidney injury, focal segmental glomerular sclerosis, diabetic kidney disease, autoimmune disease, and kidney transplantation.[22] For example, kidney transplants require MSC injection several days before the transplantation to induce tolerance before the engraftment and prevent graft-versus-host disease.[23,24]

The efficacy and the safety of HUCMSCs implantation remain controversial. There are some reports regarding the safety of HUCMSCs implantation, such as nephrotic syndrome in patient with acute lymphoblastic leukemia and thromboembolism. However, these conditions can be treated well.[42,43] Lalu et al. conducted a meta-analysis which concluded that MSC therapy via intravascular appears safe, but further studies are needed to ensure the results, particularly larger randomized controlled trials. Generally, primary adverse events were fever, organ dysfunction, graft versus host disease, and death. However, in this study, we have not found any studies concerning the adverse event of MSCs in chronic kidney disease therapy.

CONCLUSION

Transplantation of HUCMSCs for renal diseases shows promising results. However, further studies were needed to ensure the safety of the treatment.

DISCLOSURE

Author Contribution

All authors contributed equally in writing and editing this article.

Ethical Consideration

None.

Conflict of Interest

All authors stated no conflict of interest regarding writing and publishing this article.

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