IN THE NAME OF GOD

TREATMENT STRATEGIES IN MANAGEMENT OF CHRONIC KIDNEY DISEASE FROM PERSPECTIVE OF BIOLOGICAL REGENERATIVE MEDICINE

Dr.Leila Akhondzadeh,MD Internist

GUMS

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CHRONIC KIDNEY DISEASE

Progressive loss of the number of functional nephrons leads to chronic kidney disease (CKD) and eventually end stage renal disease(ESRD), requiring renal replacement therapy.

ETIOLOGY

- **Numerous etiological factors have been attributed to the pathogenesis of CKD, leading the list would be the non-communicable diseases namely hypertension and diabetes mellitus.**

ADAPTATION MECHANISMS OF THE CELLS OF THE KIDNEYS TOWARDS VARIOUS INSULTS

- compensatory renal hypertrophy
- cell proliferation
- reprogramming of endogenous renal cells
- renal progenitor cell differentiation
- mesangial cell proliferation and migration
- neoangiogenesis

DISEASE BURDEN

ORIGINAL RESEARCH article

Front. Endocrinol., 01 July 2021 | https://doi.org/10.3389/fendo.2021.672350

Global, Regional, and National Burden of Diabetes-Related Chronic Kidney Disease From 1990 to 2019

Yujiao Deng[1,2†], Na Li[2†], Ying Wu[2], Meng Wang[2], Si Yang[2], Yi Zheng[2], Xinyue Deng[3], Dong Xiang[4], Yuyao Zhu[2], Peng Xu[2], Zhen Zhai[2], Dai Zhang[2], Zhijun Dai[3] and Jie Gao[1*]

[1]Department of Nephrology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China
[2]Department of Oncology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China
[3]Department of Breast Surgery, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China
[4]Celilo Cancer Center, Oregon Health Science Center Affiliated Mid-Columbia Medical Center, The Dalles, OR, United States

DISEASE BURDEN

It is estimated that 6% of total global medical expenses are being spent on CKD and related conditions.

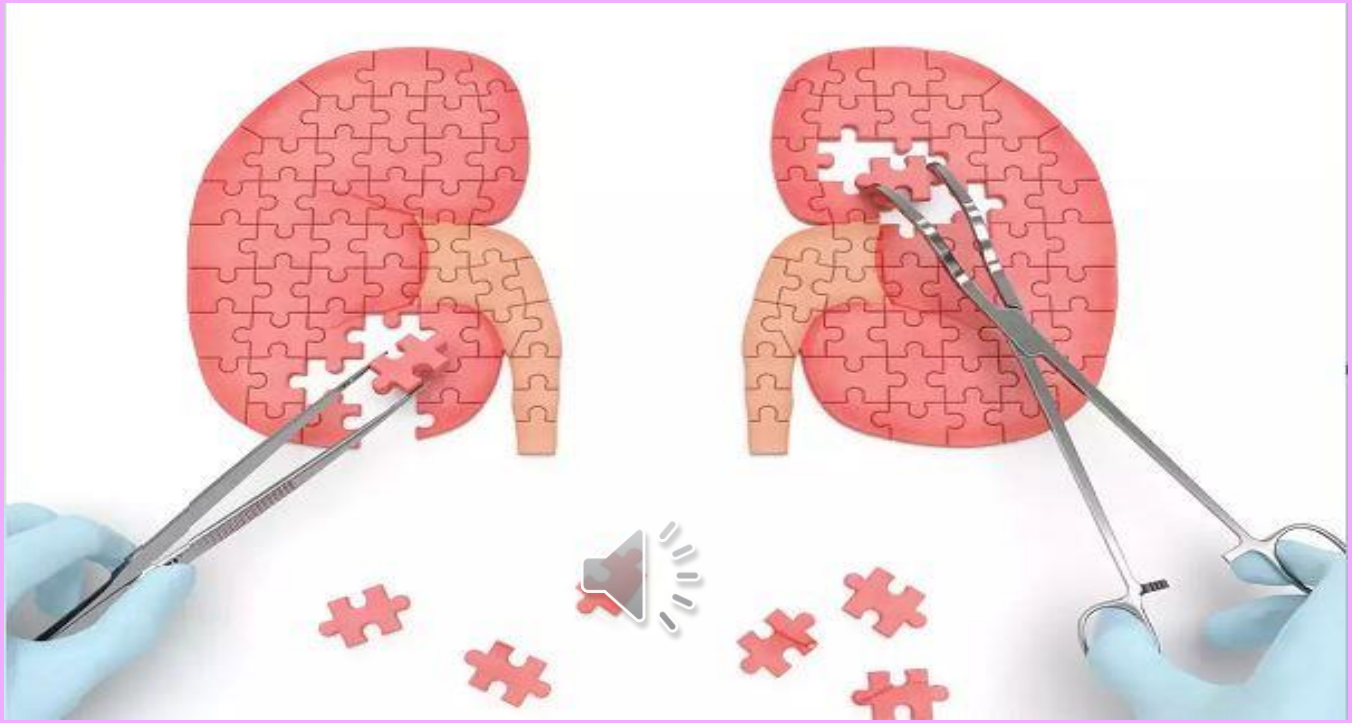
Klokol D, Nallenthiran L, Nalapko Y, et al. Treatment strategies in management of chronic kidney disease from perspective of biological regenerative medicine. J Stem Cell Res Ther. 2020;6(1):1–9.

CURRENT STATUS OF THERAPEUTIC STRATEGIES FOR KIDNEY REGENERATION

Up to date there is no specific method of treatment in severe CKD such as grade more than 3b, but trying conservative measures such as ACE inhibitors or ARB, antihypertensive medicine, kalium lowering agent, phosphate lowering agent, until fall into CKD stage 5, when RRT such as dialysis or kidney transplantation are mandatory.

Kidney International Reports (2020) 5, S1–S392

The advent of regenerative therapies that support repair, regeneration, and restoration of damaged tissues emerged as promising approaches to preserve the structure and function of the kidney.



SUMMARY OF KIDNEY REGENERATIVE MEDICINE STRATEGIES

Approach	Cell source
Self-organization	Kidney progenitors generated from PSCs
Interspecies blastocyst complementation	PSCs
Utilization of xenogeneic organ niche	Kidney progenitors generated from PSCs
Decellularization and repopulation	Kidney-constituent cells
3D bioprinting	Kidney-constituent cells
Cell therapy	MSCs, bone marrow stem cells, autologous kidney cells, and kidney progenitors generated from PSCs

Osafune K. Regenerative treatments for kidney diseases: The closest and fastest strategies to solving related medical and economic problems. Artif Organs. 2021;45:447– 453

TYPES OF STEM CELLS USED IN CKD

- bone-marrow-derived cells (BMDCs)
- embryonic stem (ES) cells
- autologous adipose-derived mesenchymal stem cells (ADMSCs)
- induced pluripotent stem (iPS) cells
- renal progenitor cells

ADIPOSE-DERIVED MESENCHYMAL STEM CELLS

- ADMSCs possess anti-inflammatory and immunomodulating functions and are easily accessible for harvesting and culturing in high volume.

- Unfortunately, these cells have not been proven to actively regenerate into renal cells, hence rendering it not beneficial in treating chronic kidney disease.

BONE-MARROW-DERIVED MESENCHYMAL STEM CELLS

- The bone-marrow-derived mesenchymal stem cells (MSCs) have been the most widely used cell in the treatment of chronic kidney disease and end stage renal failure.

EMBRYONIC STEM CELLS

- **A number of experiments have established that ES cells can differentiate into renal epithelial cells and once introduced directly into developing metanephros can differentiate to tubular epithelia with nearly absolute efficiency.**

- **Unfortunately, studies have also confirmed that this can also give rise to spontaneous teratomas as ES may differentiate into all three types of germ lines.**

Klokol D, Nallenthiran L, Nalapko Y, et al. Treatment strategies in management of chronic kidney disease from perspective of biological regenerative medicine. J Stem Cell Res Ther. 2020;6(1):1–9.

INDUCED PLURIPOTENT STEM CELLS (IPSCS) & RENAL PROGENITOR CELLS

Induced pluripotent stem cells constitute a newly defined stem cell type with similar properties to those displayed by embryonic stem cells (ESCs), in terms of self-renewal and differentiation.

Blocking the proliferative ability of iPSCs with antimitotic agents, such as mitomycin C (MMC) and/or differentiating them into RPCs might be a safer strategy for CKD treatment.

Ribeiro et al. Stem Cell Research & Therapy (2020) 11:530

CELL-FREE APPROACH

MESENCHYMAL STEM/STROMAL CELL–DERIVED EXTRACELLULAR VESICLES

REVIEW

Mesenchymal Stem/Stromal Cell–Derived Extracellular Vesicles for Chronic Kidney Disease: Are We There Yet?

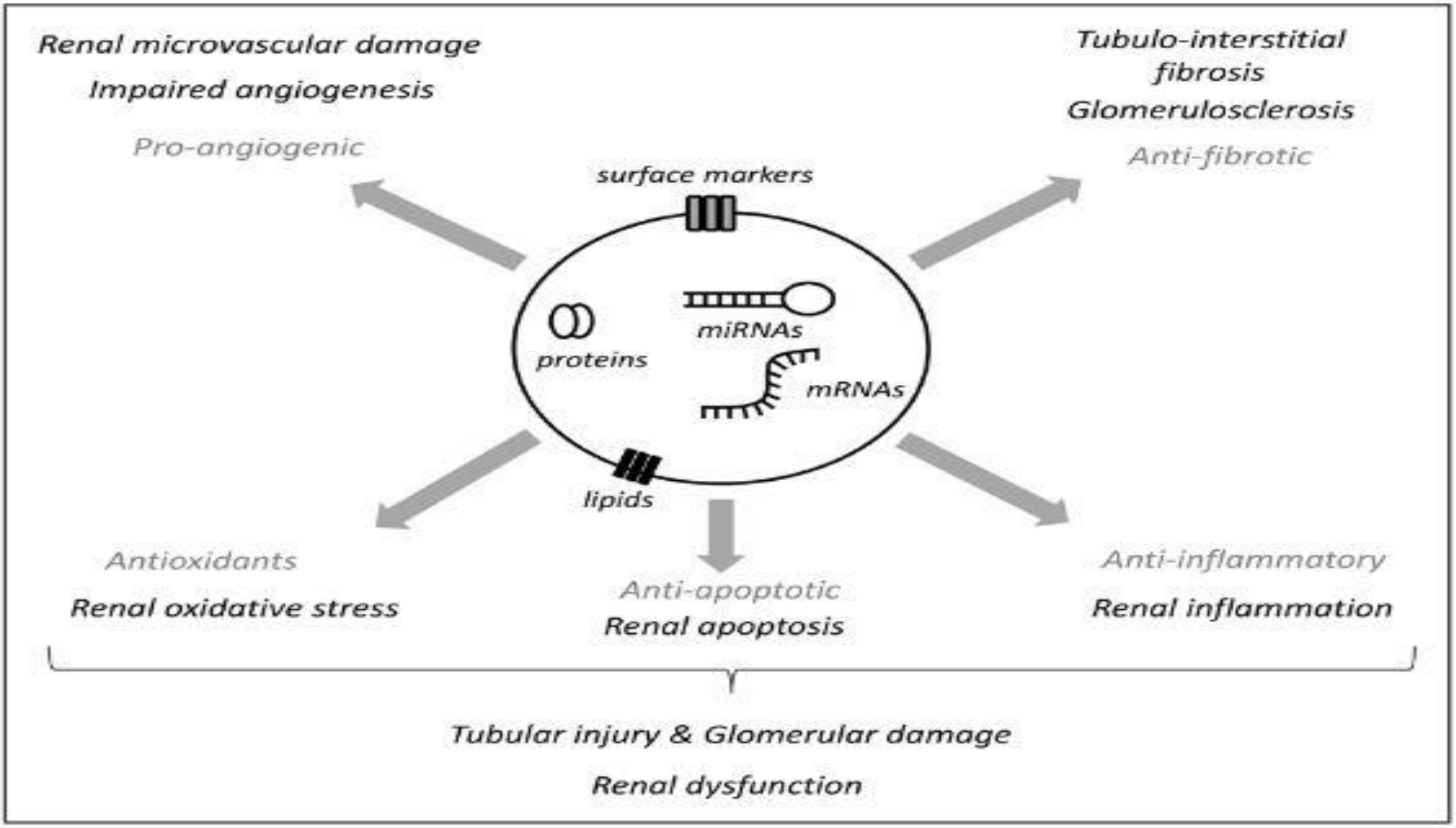
Alfonso Eirin, Lilach O. Lerman

ABSTRACT: Mesenchymal stem/stromal cells (MSCs) are the most utilized cell type for cellular therapy, partly due to their important proliferative potential and ability to differentiate into various cell types. MSCs produce large amounts of extracellular vesicles (EVs), which carry genetic and protein cargo to mediate MSC paracrine function. Recently, MSC-derived EVs have been successfully used in several preclinical models of chronic kidney disease. However, uncertainty remains regarding EV fate, safety, and long-term effects, which might impose important limitations on their path to clinical translation. This review discusses the therapeutic application of MSC-derived EV therapy for renal disease, with particular emphasis on potential mechanisms of kidney repair and major translational barriers. Emerging evidence indicates that the cargo of MSC-derived EVs is capable of modulating several pathways responsible for renal injury, including inflammation, oxidative stress, apoptosis, fibrosis, and microvascular remodeling. EV-induced modulation of these pathways has been associated with important renoprotective effects in experimental studies. However, scarce clinical data are available, and several challenges need to be addressed as we move toward clinical translation, including standardization of methods for EV isolation and characterization, EV fate, duration of EV effects, and effects of cardiovascular risk factors. MSC-derived EVs have the potential to preserve renal structure and function, but further experimental and clinical evidence is needed to confirm their protective effects in patients with chronic kidney disease.

MESENCHYMAL STEM/STROMAL CELL–DERIVED EXTRACELLULAR VESICLES

It is now well accepted that MSCs exert their paracrine activity partly by releasing extracellular vesicles (EVs), lipid bilayer-delimited particles.

These include microvesicles (0.1–1 μm diameter, shed by outward blebbing of the plasma membrane) and exosomes (30–100nm released by the fusion of multivesicular bodies with the plasma membrane).



Hypertension. 2021;78:261–269

MSC-DERIVED EVS IN CKD MODELS

In recent years, the renoprotective effects of MSC-derived EVs have been investigated in several in vivo models of CKD, including:

- diabetic and hypertensive nephropathy,
- ischemia-reperfusion injury (IRI),
- unilateral ureteral obstruction (UUO),
- environmental exposure to heavy metals, and
- subtotal nephrectomy

RESEARCH ARTICLE Open Access

Umbilical cord mesenchymal stem cells derived extracellular vesicles can safely ameliorate the progression of chronic kidney diseases

Wael Nassar[1,2*], Mervat El-Ansary[3], Dina Sabry[5], Mostafa A. Mostafa[2], Tarek Fayad[4], Esam Kotb[2], Mahmoud Temraz[1], Abdel-Naser Saad[1], Wael Essa[1] and Heba Adel[3]

Abstract

Background: Bio-products from stem/progenitor cells, such as extracellular vesicles, are likely a new promising approach for reprogramming resident cells in both acute and chronic kidney disease. Forty CKD patients stage III and IV (eGFR 15–60 mg/ml) have been divided into two groups; twenty patients as treatment group "A" and twenty patients as a matching placebo group "B". Two doses of MSC-derived extracellular vesicles had been administered to patients of group "A". Blood urea, serum creatinine, urinary albumin creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) have been used to assess kidney functions and TNF-α, TGF-β1 and IL-10 have been used to assess the amelioration of the inflammatory immune activity.

Results: Participants in group A exhibited significant improvement of eGFR, serum creatinine level, blood urea and UACR. Patients of the treatment group "A" also exhibited significant increase in plasma levels of TGF-β1, and IL-10 and significant decrease in plasma levels of TNF-α. Participants of the control group B did not show significant improvement in any of the previously mentioned parameters at any time point of the study period.

Conclusion: Administration of cell-free cord-blood mesenchymal stem cells derived extracellular vesicles (CF-CB-MSCs-EVs) is safe and can ameliorate the inflammatory immune reaction and improve the overall kidney function in grade III-IV CKD patients.

Keywords: Chronic kidney disease, Extracellular vesicles, Mesenchymal stem cells, Microvesicles

Table. Advantages and Disadvantages of EVs Over MSCs for CKD

Therapy	MSCs	EVs
In vitro		
Half-life (following freezing and thawing)	+	++
Stability (in inflammatory microenvironment)	−	+
Utility (use as off-the-shelf products or delivery carriers)	±	+
In vivo		
Tumorigenicity (ability to give rise to benign or malignant tumors)	±	−
Immunogenicity (ability to induce humoral or cell immune responses)	+	−
Efficacy (preservation of renal structure and function in CKD)	++	++
Efficiency (reaching damaged sites within the nephron)	+	++
Targeting (ability to ensure renal homing)	+	+

Hypertension. 2021;78:261–269

STROMAL VASCULAR FRACTION (SVF)

AUTOLOGOUS SVF MIGHT BE A RESCUE THERAPY EXTENDING TIME TO RRT IN CKD

Yun, H[1], Byung-soo, C*[1], Sung-min, J[1], Won-hee, C[1], Hyun-soon, L[2], Dae yong, K[3]

[1]Dr. Cho's Kidney Center Nephrology Seoul Korea- Republic Of, [2]Korea pathology lab Pathology Seoul Korea- Republic Of, [3]N-BIOTEK Inc Biology Seoul Korea- Republic Of

Introduction: Up to date there is no specific method of treatment in severe chronic kidney disease(CKD) especially due to IgA nephropathy such as grade more than 3b, but trying conservative measures such as ACE inhibitors or ARB, antihypertensive medicine, omega-s, kalium lowering agent, phosphate lowering agent, etc until fall into CKD stage 5, when RRT such as dialysis or kidney transplantation are mandatory. Cell based therapy is an emerging field in nephrology especially adipose derived stem cells (ASCs). The beneficial effects of mesenchymal stem cell occur through differentiation independent pathways include increased cell survival and proliferation, decreased inflammation, immune modulation, tissue regeneration etc.

MITOCHONDRIA AND CKD

Evidence suggests that mitochondrial dysfunction is a key contributor to the pathogenesis of CKD.

Functional significance of mitochondrial dysfunction in promoting inflammation and fibrotic responses in the pathogenesis of tubulointerstitial fibrosis and various forms of CKD, including diabetic nephropathy , IgA nephropathy, membranous nephropathy, and polycystic kidney disease.

MITOCHONDRIA AND CKD

In a mouse model of type 1 diabetes, MitoQ treatment reduced albuminuria and attenuated both interstitial fibrosis and glomerular damage .

(Chacko BK, Reily C, Srivastava A, et al. Prevention of diabetic nephropathy in Ins2(+/)-(AkitaJ) mice by the mitochondria-targeted therapy MitoQ. Biochem J. 2010;432:9–19.)

MitoQ also inhibited cyst formation in an ADPKD mouse model.

(shimoto Y, Inagi R, Yoshihara D, et al. Mitochondrial abnormality facilitates cyst formation in autosomal dominant polycystic kidney disease. Mol Cell Biol. 2017;37:e00337–17.)

MitoQ is being investigated in a Phase IV controlled, double-blind clinical trial in patients with stage 3-5 CKD.

(ClinicalTrials.gov Identifier:NCT02364648)

KIDNEY BIOENGINEERING

ELSEVIER

Tissue and Cell

Volume 74, February 2022, 101699

Kidney bioengineering by using decellularized kidney scaffold and renal progenitor cells

Chih-Yang Hsu [a], Pei-Ling Chi [b], Hsin-Yu Chen [a], Shih-Hsiang Ou [a], Kang-Ju Chou [a], Hua-Chang Fang [a], Chien-Liang Chen [a], Chien-Wei Huang [a], Tzung-Yo Ho [a], Po-Tsang Lee [a]

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KIDNEY BIOENGINEERING

Original Research | Published: 06 October 2020

Decellularization and Recellularization of Rabbit Kidney Using Adipose-Derived Mesenchymal Stem Cells for Renal Tissue Engineering

Shabnam Sabetkish, Nastaran Sabetkish, Masoumeh Ekhtiari, Bahareh Mohammadi Jobani & Abdol-Mohammad Kajbafzadeh

Regenerative Engineering and Translational Medicine volume 6, pages 433–441 (2020)

CLINICAL TRIALS

Bone marrow–mesenchymal stromal cell infusion in patients with chronic kidney disease: A safety study with 18 months of follow-up

Atieh Makhlough [1*], Soroosh Shekarchian [2*], Reza Moghadasali [2, 3], Behzad Einollahi [4], Mona Dastgheib [2], Ghasem Janbabaee [5], Seyedeh Esmat Hosseini [2], Nasrin Falah [2], Fateme Abbasi [2], Hossein Baharvand [2, 3], Nasser Aghdami [2]

Cytotherapy
Volume 20, Issue 5, May 2018, Pages 660-669

Either We Will Find A Way Or WeWill Make One!