

Novel strategies for the management of renal replacement – A review

T. Lakshmi^{1*}, Thirumalaikumaran Rathinam², D. Ezhilarasan¹

¹Department of Pharmacology, Saveetha Dental College and Hospitals, Saveetha University, Chennai, Tamil Nadu, India, ²Department of Pharmacognosy, College of Pharmacy, Sri Ramachandra Medical College & Research Institute, Sri Ramachandra University, Chennai, Tamil Nadu, India.

Correspondence: T. Lakshmi, Department of Pharmacology, Saveetha Dental College and Hospitals, Saveetha University, Chennai - 600 077, Tamil Nadu, India. E-mail: Lakshmi085@gmail.com

ABSTRACT

End-stage renal disease (ESRD) is the last stage of kidney disease, and it is life threatening and often causes fatal complications such as cardiovascular disease. ESRD is a growing public health issue with prominent increase and prevalence in developed and developing countries with high rates of morbidity and mortality. It worsens the quality of life. The life expectancy of these patients is up to 4-5 years. Interleukin-6 is a major factor responsible for the mortality in ESRD patients. Treatment cost for renal replacement therapy in ESRD patients is too high annually. Strategies are developed to overcome to minimize the medical expenditure. Novel innovative strategies were developed for ESRD include wearable kidney, nanotechnology, and regenerative medicine. This article focuses on the different advanced strategies such as transplantation of bioengineered kidney, kidney regeneration and cell replacement, wearable kidney – dialysis machine, continuous dialysis therapy at home, and micro-Chinese osmotherapy.

Keywords: End-stage renal disease, hemodialysis, renal replacement therapy, transplantation.

Introduction

Chronic kidney disease (CKD) is a common condition most commonly occurs in the elderly population which results in end-stage renal failure.^[1-5] CKD in younger patients is associated with loss of kidney function, but of patients over 65 years of age with CKD, 30% do not have a progressive disease with loss of kidney function over time. CKD is associated with an increased risk of cardiovascular disease and chronic renal failure.^[3-5, 6-13] Kidney disease is the 9th leading cause of death in the United States. Patients with CKD Stages 1-3 (glomerular filtration rate [GFR] >30 mL/min/1.73 m²) are generally asymptomatic. Mostly in Stages 3 and 4, endocrine/metabolic derangements or disturbances in water or electrolyte balance become clinically manifest. Imaging studies such as renal ultrasonography, retrograde pyelography, computed tomography, magnetic resonance imaging, and radionuclide scanning will diagnose CKD (Figure 1).



Figure 1: End-stage renal disease

Pathologic manifestations include anemia, hypophosphatemia, hypocalcemia, hyperparathyroidism, and metabolic acidosis.^[6, 7, 14-21]

Different stages of CKD are as follows:

- **Stage 1:** Kidney damage with normal or increased GFR (>90 mL/min/1.73 m²)
- **Stage 2:** Mild reduction in GFR (60-89 mL/min/1.73 m²)

Access this article online

Website: www.japer.in

E-ISSN: 2249-3379

How to cite this article: T. Lakshmi, Thirumalaikumaran Rathinam, D. Ezhilarasan. Novel strategies for the management of renal replacement – A review. J Adv Pharm Edu Res 2017;7(1):1-4.

Source of Support: Nil, Conflict of Interest: None declared.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

- **Stage 3:** Moderate reduction in GFR (30-59 mL/min/1.73 m²)
- **Stage 4:** Severe reduction in GFR (15-29 mL/min/ 1.73 m²)
- **Stage 5:** Kidney failure (GFR <15 mL/min/1.73 m² or dialysis)

Stage 5 is termed as end-stage renal disease (ESRD), in which the kidneys stop working totally. There will be a permanent kidney failure which is a fixed one in nature.

ESRD is a growing public health issue with prominent increase and prevalence in developed and developing countries. It worsens the quality of life.^[8, 9, 22-27] Treatment cost for renal replacement therapy (RRT) in ESRD patients is too high annually. Strategies are developed to overcome to minimize the medical expenditure.

ESRD and high potassium level

Majority of the ESRD patients are living with high potassium level which results in irregular heartbeat and weakness, hence reducing the potassium level shall keep away these risks. Potassium level in blood vessels most commonly increases when the kidneys stop excreting extra potassium level effectively.^[10, 28] Damaged residual nephrons are another cause for electrolyte disorder.

Diabetes and ESRD

Low socioeconomic status is associated with an increased risk of ESRD due to diabetes.

Mortality and morbidity of ESRD patients

Sudden death in ESRD patients is due to hyperkalemia followed by missed dialysis. The another cause is cardiovascular disease and cardiovascular mortality,^[11] which is more higher in dialysis patients. ESRD patients at every age have increased the mortality comparatively with nondialysis patients.

Materials and Methods

Literature review was done extensively using various sources like PUBMED, SCOPUS, MEDLINE, EMBASE.

Novel innovative strategies for ESRD.

Transplantation of bioengineered kidney

The study published by Song *et al.*, 2013, states a novel strategy about the success of Transplantation of the bioengineered kidney by creating a transplantable graft to permanently replace kidney function. These innovative findings shall address the donor organ shortage and the morbidity associated with immunosuppression (Figure 2).^[12, 29-34]

Such a bioengineered graft possesses the kidney's architecture and function and permits perfusion, filtration, secretion, absorption, and drainage of urine. These transplantable grafts produced rudimentary urine *in vitro* when perfused through their intrinsic vascular bed. When transplanted in an orthotopic position in rat, the grafts were reported to be perfused by the recipient's circulation and produced urine through the ureteral conduit *in vivo*. In light of the above study, it is suggested that transplantable bioengineered graft is an alternative remedy for RRT.

Kidney regeneration and cell replacement

Induced pluripotent stem cells for disease modeling and drug therapy

The induced pluripotent stem cells used for the reprogramming process of the kidney from mesangial cells. This is a novel strategy in ESRD patients. According to Sharon *et al.*, enormous amount of somatic cells can be efficiently reprogrammed into induced pluripotent cells and simultaneously redifferentiated into other cell types that recapitulate disease phenotypes. In this view, the induced pluripotent stem cells aids *in vitro* modeling system that could absolutely lead to novel drug development and testing. The induced pluripotent stem cell technology in kidney disease modeling offers an opportunity to develop self-renewing models that will facilitate mechanistic aspect of the disease (Figure 3).^[13, 35-40]

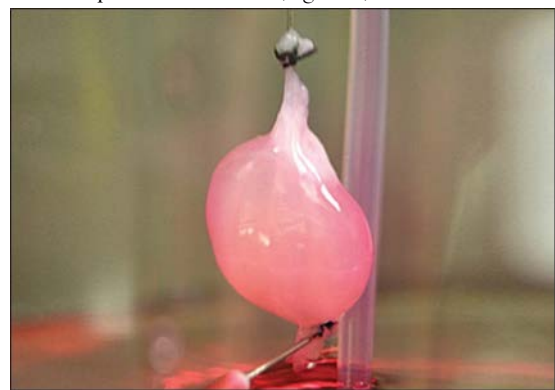


Figure 2: Bioengineered graft/rat

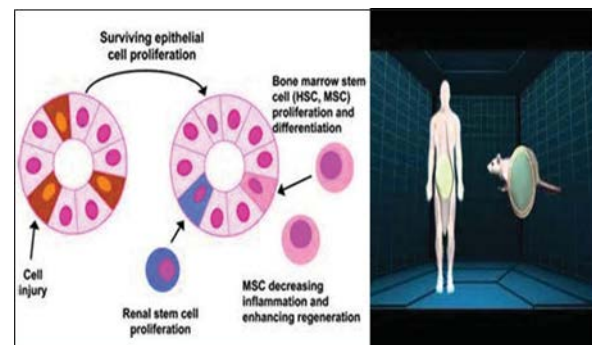


Figure 3: Kidney regeneration and cell replacement

Wearable kidney – Dialysis machine

Dialysis on daily basis will be uncomfortable and cumbersome issue to implement. Miniaturized ambulatory continuous renal replacement device approved by FDA is available for end-stage renal failure patients that they can wear permanently. This can be worn as a belt operated with batteries of weight <5 lbs. The development of such a strategy will reduce the cost and increase the survival rate by reducing the mortality in ESRD patients.^[14, 41]

Continuous ambulatory peritoneal dialysis (CAPD)

RRT with dialysis and transplantation is the only option of prolonging life for patients with ESRD. Although transplantation is the treatment of choice, the number of donor kidneys is limited and transplants may fail. Hence, many patients require prolonged or even life-long dialysis. CAPD is an alternative to hospital or home hemodialysis for patients with ESRD (Figure 4).^[15, 16]



Figure 4: Wearable kidney

Traditional Chinese medicine

Micro-Chinese medicine osmotherapy

Micro-Chinese medicine osmotherapy is an advanced natural therapy which is based on Chinese Herbal Medicine. It is an external application and is used for kidney disease. The core technology of micro-Chinese medicine osmotherapy is to make the effective herbs of kidney disease superfinely shattered.^[17] Then, with the help of effective penetrant and osmosis devices, the effective medicines are permeated into kidney lesions by external application, thus achieving the goal of treating kidney disease. Clinical practices have been proved that this application method is both effective and convenient. Micro-Chinese medicine osmotherapy can improve kidney functions; thereby, it does help patients to increase the chance to get rid of dialysis (Figure 5).



Figure 5: Continuous dialysis therapy

Conservative management of ESRD

Conservative (non-dialytic) management of ESRD includes careful attention to fluid balance, treatment of anemia, and correction of acidosis and hyperkalemia. Blood pressure and calcium/phosphorus metabolism must also be managed.^[18, 19]

There is emerging evidence that dietary modifications may be helpful in prolonging life and decreasing symptoms.^[20, 42-46]

Providing palliative care is essential for prolonging the quality of life for ESRD patients (Figure 6).^[21]



Figure 6: Micro-Chinese osmotherapy

Conclusion

ESRD is a growing public health issue with prominent increase and prevalence in developed and developing countries. It worsens the quality of life. Treatment cost for RRT in ESRD patients is too high annually. Strategies are developed to overcome to minimize the medical expenditure. These recent advances such as bioengineered graft, wearable kidney, CAPD, and micro-Chinese osmotherapy throw a light on the management of ESRD and minimize the RRT.

Acknowledgment

The authors wish to acknowledge various database, research/review articles from where the source of the article has been utilized for compilation

References

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39 2 Suppl 1: S1-266.
2. Abboud H, Henrich WL. Clinical practice. Stage IV chronic kidney disease. *N Engl J Med* 2010; 362:56-65.
3. Eddy AA, Neilson EG. Chronic kidney disease progression. *J Am Soc Nephrol* 2006; 17:2964-6.
4. Ferrans CE, Powers MJ. Quality of life index: Development and psychometric properties. *ANS Adv Nurs Sci* 1985; 8:15-24.
5. Harwood L, Wilson B, Locking-Cusolito H, Sontrop J, Spittal J. Stressors and coping in individuals with chronic kidney disease. *Nephrol Nurs J* 2009; 36:265- 75, 301.
6. Jablonski A. The multidimensional characteristics of symptoms reported by patients on hemodialysis. *Nephrol Nurs J* 2007; 34:29-37.
7. Groop PH, Thomas MC, Moran JL, Wadén J, Thorn LM, Mäkinen VP, et al. The presence and severity of chronic kidney disease predicts all-cause mortality in Type 1 diabetes. *Diabetes* 2009; 58:1651-8.
8. Royston P. Explained variation for survival models. *Stata J* 2006; 6:83-96.
9. Taal MW. Screening for chronic kidney disease: Preventing harm or harming the healthy? *PLoS Med* 2012;9: e1001345.
10. Tuomilehto J, Jousilahti P, Rastenyte D, Moltchanov V, Tanskanen A, Pietinen P, et al. Urinary sodium excretion and cardiovascular mortality in Finland: A prospective study. *Lancet* 2001; 357:848-51.
11. McCarron DA, Stern JS, Gradual N. Public policy and dietary sodium restriction. *JAMA* 2010; 303:1916.
12. Song JJ, Guyette JP, Gilpin SE, Gonzalez G, Vacanti JP, Ott HC. Regeneration and experimental orthotopic transplantation of a bioengineered kidney. *Nat Med* 2013; 19:646-51.
13. O'Neill AC, Ricardo SD. Human kidney cell reprogramming: Applications for disease modeling and personalized medicine. *J Am Soc Nephrol* 2013; 24:1347-56.
14. Gura V, Beizai M, Ezon C, Polaschegg HD. Continuous renal replacement therapy for end-stage renal disease. The wearable artificial kidney (WAK). *Contrib Nephrol* 2005; 149:325-33.
15. De Vecchi AF, Dratwa M, Wiedemann ME. Healthcare systems and end-stage renal disease (ESRD) therapies—an international review: Costs and reimbursement/funding of ESRD therapies. *Nephrol Dial Transplant* 1999;14 Suppl 6:31-41.
16. Jain N, Simoyi P. An overview of chronic kidney disease management and CAPD in the home. *Br J Community Nurs* 2008; 13:213-4, 216-8.
17. The Reviews of Micro Chinese Osmotherapy. Available from: <http://www.renaldiseases.org/ckd-treatment/1343.html>. [Last accessed on 2014 Aug 20].

18. Moncrief JW, Decherd JF. Conservative management of end-stage renal failure. *Tex Med* 1975; 71:74-9.
19. Brunori G, Viola BF, Parrinello G, De Biase V, Como G, Franco V, et al. Efficacy and safety of a very-low-protein diet when postponing dialysis in the elderly: A prospective randomized multicenter controlled study. *Am J Kidney Dis* 2007; 49:569-80.
20. O'Hare AM. The management of older adults with a low eGFR: Moving toward an individualized approach. *Am J Kidney Dis* 2009; 53:925-7.
21. Fassett RG, Robertson IK, Mace R, Youl L, Challenor S, Bull R. Palliative care in end-stage kidney disease. *Nephrology (Carlton)* 2011; 16:4-12.
22. Rezaei S, Asgari Mobarake K, Saberi A, Keshavarz P, Leili EK. Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism and post-stroke dementia: a hospital-based study from northern Iran. *Neurol Sci.* 2016 Jun;37(6):935-42. doi: 10.1007/s10072-016-2520-2. Epub 2016 Apr 12.
23. Keshavarz P, Saberi A, Sharafshah A, Asgari K, Rezaei S. Association of BDNF G196A Gene Polymorphism with Ischemic Stroke Occurrence and its 6-Month Outcome in an Iranian Population. *Top Stroke Rehabil.* 2016 Aug;23(4):254-60. doi: 10.1080/10749357.2016.1141491. Epub 2016 Feb 17.
24. Chabok SY, Kapourchali SR, Leili EK, Saberi A, Mohtasham-Amiri Z. Effective factors on linguistic disorder during acute phase following traumatic brain injury in adults. *Neuropsychologia.* 2012 Jun;50(7):1444-50. doi: 10.1016/j.neuropsychologia.2012.02.029. Epub 2012 Mar 5.
25. Saberi A, Nemati S, Shakib RJ, Kazemnejad E, Maleki M. Association between allergic rhinitis and migraine. *J Res Med Sci.* 2012 Jun;17(6):508-12.
26. Ghaffari S, Sohrabi B, Aslanabadi N, Mogadam AR, Sepehrvand N, Pourafkari L, Ghaffari R, Akbarzadeh F, Yaghoobi A. Percutaneous transvenous mitral commissurotomy: with or without heparin? A randomized double blind study. *Kardiol Pol.* 2011;69(5):445-50.
27. Arazpour M, Moradi A, Samadian M, Bahramizadeh M, Joghataei M, Bani MA, Hutchins SW, Mardani MA. The influence of a powered knee-ankle-foot orthosis on walking in poliomyelitis subjects: A pilot study. 2016. *Prosthetics and Orthotics International.* 40(3), pp. 377-383.
28. Shokouhi S, Alavi Darazam I, Sharifi G, Gachkar L, Amirsardari A, Samadian M. Statins and postoperative infections: A randomized clinical trial. 2014. *Jundishapur Journal of Microbiology.* 7(4).
29. Dehnad SV, Ghavimi MA, Ghoreishizadeh A, Falsefi P, Negahdari R, Babalou AR. The Comparison of Job Stress among Dental Professionals of Dentistry Faculty Members of Tabriz University. Volume 8, Supplementary Issue 1, 2016. <https://doi.org/10.18311/ajprhc/2016/7714>.
30. Yazdani J, Hajizadeh S, Ghavimi MA, Pourghasem Gargari B, Nourizadeh A, Kananizadeh Y. Evaluation of changes in anthropometric indexes due to intermaxillary fixation following facial fractures. *J Dent Res Dent Clin Dent Prospects.* 2016 Fall;10(4):247-250. doi: 10.15171/joddd.2016.039.
31. Yazdani J, Ghavimi MA, Jabbari Hagh E, Ahmadpour F. The Role of E-Cadherin as a Prognostic Biomarker in Head and Neck Squamous Carcinoma: A Systematic Review and Meta-Analysis. *Mol Diagn Ther.* 2018 Jul 13. doi: 10.1007/s40291-018-0351-y.
32. Fakhrazadeh V, Eslami H, Nasrollah A P, Negahdari R, Falsafi P, Sabeti M. The Comparison of Dimensional Accuracy of Modified Two-Stage Putty-Wash Condensation S Polyvinyl Molding Method and Distance Two-Stage Putty-Wash Molding Method. *International Journal of Clinical Dentistry.* 2016, Vol. 9 Issue 4, p265-271. 7p.
33. Dehnad SV, Ghavimi MA, Ghoreishizadeh A, Falsefi P, Negahdari R, Babalou AR. The Comparison of Job Stress among Dental Professionals of Dentistry Faculty Members of Tabriz University. Volume 8, Supplementary Issue 1, 2016. <https://doi.org/10.18311/ajprhc/2016/7714>.
34. Pournasrollah A, Fakhrazade V, Eslami H, Negahdari R. Evaluation of shear bond strength between direct composite and zirconia. 2015. *Der Pharmacia Lettre.* <http://localhost:8080/xmlui/handle/123456789/13525>.
35. Fakhrazadeh V, Gaffari T, Hamedirad F, Negahdari R, Nasrollah A. P, Eslami H. Influence of Preparation Design and Restorative Material to Marginal Discrepancy of Ceramic Laminate Veneers. *Biomed Pharmacol J* 2015;8(2).
36. Alamolhoda SH, Kariman N, Hoseinpanah F, Alavi Majd, H. Relationship between maternal hemoglobin level in first trimester with gestational diabetes mellitus. 2010. *Iranian Journal of Endocrinology and Metabolism* 11(6), pp. 661-666+734.
37. Kariman N, Hedayati M, Taheri Z, Fallahian M, Salehpour S, Alavi Majd SHA. Comparison of ELISA and three rapid HCG dipsticks in diagnosis of premature rupture of membranes. 2011. Comparison of ELISA and three rapid HCG dipsticks in diagnosis of premature rupture of membranes. 13(6).
38. Nahidi F, Kariman N, Simbar M, Mojab F. The study on the effects of Pimpinella anisum on relief and recurrence of menopausal hot flashes. *Iranian Journal of Pharmaceutical Research.* Volume 11, Issue 4, 2012, Pages 1079-1085.
39. Alimoradi Z, Kariman N, Simbar M, Ahmadi F. Empowerment of Adolescent Girls for Sexual and Reproductive Health Care: A Qualitative Study. *Afr J Reprod Health.* 2017 Dec;21(4):80-92. doi: 10.29063/ajrh2017/v21i4.9.
40. Atarodi-Kashani Z, Kariman N, Ebadi A, Alavi Majd H, Beladi-Moghadam N. Sexual function and related factors in Iranian woman with epilepsy. *Seizure.* 2017 Nov;52:147-153. doi: 10.1016/j.seizure.2017.10.001. Epub 2017 Oct 5.
41. Shahrahmani H, Kariman N, Jannesari S, Rafeiean-Kopaei M, Mirzaei M, Ghalandari S, Shahrahmani N, Mardani G. The effect of green tea ointment on episiotomy pain and wound healing in primiparous women: A randomized, double-blind, placebo-controlled clinical trial. *Phytother Res.* 2018 Mar;32(3):522-530. doi: 10.1002/ptr.5999.
42. Merghati-Khoei E, Pirak A, Yazdkhasti M, Rezasoltani P. Sexuality and elderly with chronic diseases: A review of the existing literature. *J Res Med Sci.* 2016; 21: 136.
43. Ghaffari R, Safale N, Hassanzadeh S, Salek F., Mohammadpour A. Assessment of clinical skills department from medical students' perspectives. 2008. *Rawal Medical Journal.* 33(1), pp. 104-105.
44. Ahmadi S, Ghaffari R, Kabiri N, Amini A, Salek F. Health care systems in selected countries and Iran: A descriptive-comparative study. 2015. *Biosciences Biotechnology Research Asia.* 12, pp. 753-766.
45. Hayati F, Jahani S, Mousavi P, Haghhighizade MH. Association between personal characteristics and health beliefs with pre-mammography anxiety in women referred to mammography centers. *Iranian Journal of Obstetrics, Gynecology and Infertility.* Volume 20, Issue 2, Spring 2017, Article number 4, Pages 31-40.
46. Samad-Soltani T, Rezaei-Hachesu P, Ghazisaeei M. Pervasive decision support systems in healthcare using intelligent robots in social media. (2017) *Iranian Journal of Public Health,* 46 (1), pp. 148-149.