SHORT COMMUNICATION

Role of stem cells in arteriovenous access: perspective from Lower Middle Income Countries

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Abstract

Adequately created well functional haemodialysis access is an important part for the physical and mental wellbeing of renal failure patients. Every effort should be made to enhance the patency of these accesses. Recently, stem cell treatment modalities have opened new avenues in the better patency of arteriovenous fistula. Use of mesenchymal stromal cells (MSC) to prevent venous neointimal hyperplasia have been studied with good success rates. Adopting such costly treatment modalities in low middle income class country like Pakistan is associated with significant challenges. This short report discusses the current role of stem cells in arteriovenous access and how this exciting modality can be utilized in our country.

Keywords: Dialysis access, arteriovenous fistula, Stem cell, Mesenchymal stromal cell.

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Introduction

Globally there are more than 850 million individuals who are living with chronic kidney disease (CKD), acute kidney injury (AKI), and renal replacement therapy (RRT), of these more than 4 million people have end stage kidney disease (ESKD) in which chronic dialysis is required for survival.[1] For vascular access in these individuals The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) recommends using arteriovenous fistulas (AVF) rather than arteriovenous graft (AVG) or central venous catheter (CVC), as these two have been associated with a higher rate of complications and risk of mortality when compared to AVFs.[2,3] Kenneth Appell successfully made the first subcutaneous anastomosis between the radial artery and the cephalic vein in 1965, following its ideation by James E. Cimino and Michael J. Brescia as shown in figure 1. This pioneering surgery was named arteriovenous fistula which got published in 1966.[4] The anastomosing of an artery to a nearby vein enables blood to skip the capillary network and directly move from the artery into the vein, this high pressure and flow of arterial blood causes arterialization of the vein over time (Figure1).[5]

In the recent years there has been a large shift to upper arm AVFs due to NKF-KDOQI's clinical practice guidelines.[7] However 60 % of AVFs are unable to mature owing to the formation of VS, following venous neointimal hyperplasia (VNH), in the venous outflow tract.[8] It is suggested that aberrant shear force, hypoxic damage, inflammatory cytokines, matrix deposition, and other variables all contribute to the pathogenesis of VNH/VS.[8] In the United States, the yearly cost of placing and maintaining dialysis VA surpasses a billion dollars.[9] Targeting vascular remodelling and healing surrounding the arteriovenous anastomosis after AVF construction is critical to reducing stenosis development since juxta anastomotic is the most frequent site for AVF stenosis to develop.[10] Numerous researches have focussed on creating local therapeutics to prevent VNH development, these include gene therapies, recombinant elastase,

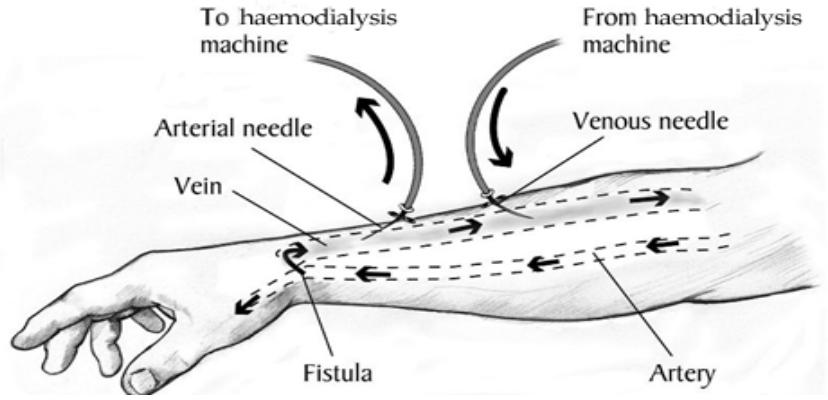

Figure: radio cephalic arteriovenous fistula (AVF). 6

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biologic small molecule inhibitors, and stem cells.[11–15] In this short report, we aim to discuss the evolving role of stem cells for better patency of AVF, implementation challenges pertaining to low-middle class income countries like Pakistan and future prospects for this treatment modality in resource constraint countries.

Role of stem cell in dialysis access

Stem cell treatment has emerged as a very promising and sophisticated scientific research topic in the past decade or so. The advancements in medical treatment options have sparked high hopes.[16] Stem cells are often categorized according to their differentiation potentials, which include totipotent, pluripotent, multipotent, and unipotent.[17] According to recent studies multipotent mesenchymal stromal cells (MSCs), often referred to as mesenchymal stem cells, are able to differentiate into different cell types from their original tissue under certain circumstances, unlike the previous belief that they are only able to develop into cell types within a single lineage, for this reason they have numerous benefits and applications.[18] MSCs can be isolated from bone marrow or adipose tissue thus are autologous and have a limited risk of tissue rejection and ethical problems as compared to fatal pluripotent stem cells which are acquired from fatal tissues or aborted embryos.[19,20] MSCs also possess anti-inflammatory, anti-apoptotic, and immunomodulatory properties, furthermore they are able to migrate to sites of injuries and inflammation and are able to play an important role in tissue development, repair, and protection.[21,22] In context to the role of MSC in dialysis access surgery, MSCs at the anastomosis may alter late remodelling occurring because of changes in vessel wall shear stress.[23] A study involving an immunodeficient male mice model demonstrated that topical application of 250,000 allogenic adipose tissue-derived MSCs to the adventitial surface of the outflow vein (periadventitial xenotransplantation) during carotid artery to jugular vein AVF construction reduces the formation of VNH/VS, hence increasing patency of AVF by suppressing Mcp-1 gene expression.[24] This gene is responsible for monocyte recruitment and the reduction of CD68 (+) cell infiltration into the vessel wall.[24] At present there is a scarcity of literature on cell transplantation in human AVFs. However, Conte et al. have previously done multi-centre phase 1 and 2 clinical trials that evaluated the safety of human (allogenic) endothelial cell implants (Vascugel) following the formation of arteriovenous access for dialysis purposes. In the second phase, 57 individuals (27 AVF and 30 AVG) were recruited and were randomly selected for Vascugel or placebo (control matrices) during operation. Since no significant difference was found in early complication rates among the Vascugel and placebo groups at four weeks, this trial met its primary objective of safety. Later on, the complications reported were mainly vascular access-related issues or ESKD-related comorbidities. At 24 weeks, there was no statistically significant difference in patency amidst the control and treatment group (AVFs and AVGs); nevertheless, the study might not be sufficiently powered to establish a statistically significant difference. The results suggest that, as compared to alternative cell therapies, MSCs likely have a substantial role in extending dialysis AVF longevity.[25] Recent studies like the one done by Piryani et al. has examined the efficacy of human adipose-derived MSCs in averting AVF failure by limiting VNH.[26]

Past studies have reported the use of stem cells and progenitor cells for aiding in vascular remodelling and endothelial regeneration.[14,24] In a bovine model, autologous late outgrowth endothelial cells administration to the anastomosis site following insertion of polytetrafluoroethylene grafts for dialysis reduces venous stenosis (VS).[13] Another study demonstrated coculturing endothelial progenitor cells and fibroblasts decreased fibroblasts conversion to myofibroblasts during hypoxic damage in cell culture.[27] Forte et al. documented MSCs to have decreased carotid artery stenosis following arteriotomy in a rat model as the luminal area was 36% larger in carotid arteries treated with MSC compared to arteries of individuals in the control group.[28] Although many studies have assessed the role of stem cell on different aspects of arteriovenous access, Table 1 summarize some of the important studies done in this area.

Barriers for stem cell research and therapy

Stem cell therapy implementation faces a lot of barriers in a developing country like Pakistan, these include socioeconomic, religious and infrastructural challenges.[29] Pakistan's healthcare system facilities are inadequate to fulfil the demands of its people. On average, one hospital bed exists for more than 1,680 individuals.[30] Considering 40% of the country lives under the poverty line, gross enrolment numbers in secondary schools is below 23%; neonatal mortality rates of 40.4 per 1000 live births and an unemployment rate of 6.3%, so a great majority of households are unable to fund stem cell therapies due to insufficient earnings and financial constraints.[31] Other challenges concerning stem cell therapies and its expansion include low levels of education, a shortage of qualified human resources, struggle to stay up-to-date with technological advances, a dearth of information, an absence of civic infrastructure, an absence of medical insurance, exorbitant private healthcare and

Table-1: Summary of some studies done on the role of different types of stem cell in dialysis access surgeries

Study	Year	Type of stem cell interventions	Outcome assessed
Yang B et al [24]	2016	250,000 allogenic adipose tissue-derived MSCs MSCs to the adventitial surface of the outflow vein (periadventitial xenotransplantation)	Venous neo intimal hyperplasia, venous stenosis
Conte et al [25]	2009	of human (allogenic) endothelial cell implants (Vascugel	Patency of AVF and AV grafts
Piryani et al [26]	2021	human adipose-derived MSCs	Limit venous neointimal hyperplasia
Hughes D et al[13]	2009	endothelial cells administration to the anastomosis	Reduced stenosis in PTFE grafts
Nieves Torres EC et al[27]	2014	coculturing endothelial progenitor cells and fibroblasts	decreased fibroblasts conversion to myofibroblasts
Brahmbhatt A et al[15]	2014	Role of lex-1 gene	Venous Neointimal Hyperplasia

pharmaceutical costs, challenges in following up, an absence of social workers, rehabilitative help, inadequate freshwater availability, and poor sanitation and cleanliness.[32] There is currently no official Islamic stance on stem cell studies. However, a few Muslim leaders support stem cell research on the rationale that an embryo in the early stages of gestation lacks a soul, whereas others say that aborting a foetus at any point of gestation is ethically wrong.[33] More importantly in Pakistan there is spread of misinformation and extremism which have contributed to by social inequality, narcotics trafficking, religious oppression, as well as psychological factors.[34] All the above mentioned limitations gets even more complicated by the fact that available literature on the role of stem cell in dialysis access procedures is scarce and do not conclusively support the long term beneficial role of stem cell therapy.

Conclusion

Despite all these challenges, prospect of stem cell treatment in dialysis access surgeries are very bright and every effort should be made to address the above-mentioned issues by creating adequate social awareness, proper networking and collaboration at national and international level, seeking funding opportunities for such projects, acquiring human and infrastructural resources like state-of-the-art labs with trained personnel and aiming to develop policies which support such endeavours.

There seems to be great possibilities for therapeutic intervention with MSCs, with no notable side effects. Nevertheless, it will take a good amount of time before MSCs can actually come in common use in inpatient beds or physician practices globally let alone in Pakistan. There are presently more than 1,130 registered Clinical Trails (CTs) mentioned on clinicaltrials.gov for MSCs of these 35 have been completed and are published, with favourable outcomes and no major complications. This figure is set to increase in the near future. The growing number of CTs, especially MSCs, will aid in assessing the clinical efficacy and potential of these intriguing biological reservoirs.

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References

1. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. Kidney Int 2019;96:1048-50. doi: 10.1016/j.kint.2019.07.012.
2. Hemodialysis Adequacy 2006 Work Group. Clinical practice guidelines for hemodialysis adequacy, update 2006. Am J Kidney Dis 2006;48(Suppl 1):s2-90. doi: 10.1053/j.ajkd.2006.03.051.
3. Dhingra RK, Young EW, Hulbert-Shearon TE, Leavey SF, Port FK. Type of vascular access and mortality in U.S. hemodialysis patients. Kidney Int 2001;60:1443-51. doi: 10.1046/j.1523-1755.2001.00947.x.
4. Murea M, Geary RL, Davis RP, Moossavi S. Vascular access for hemodialysis: A perpetual challenge. Semin Dial 2019;32:527-34. doi: 10.1111/sdi.12828.
5. Conn J Jr, Roguska J, Bergan JJ. Venous arterialization for hemodialysis. Am J Surg 1968;116:813-7. doi: 10.1016/0002-9610(68)90446-7.
6. National Institute of Diabetes and Digestive and Kidney Diseases (NIH). Forearm with an AV fistula and tubes inserted, with labels. [Online] [Cited 2022 September 28]. Available from URL: https://www.niddk.nih.gov/news/media-library/18306
7. Pisoni RL, Zepel L, Fluck R, Lok CE, Kawanishi H, Süleymanlar G, et al. International Differences in the Location and Use of Arteriovenous Accesses Created for Hemodialysis: Results From the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2018;71:469-78. doi: 10.1053/j.ajkd.2017.09.012.
8. Brahmbhatt A, Remuzzi A, Franzoni M, Misra S. The molecular mechanisms of hemodialysis vascular access failure. Kidney Int 2016;89:303-16. doi: 10.1016/j.kint.2015.12.019.
9. Pantelias K, Grapsa E. Vascular access today. World J Nephrol 2012;1:69-78. doi: 10.5527/wjn.v1.i3.69.
10. Takahashi EA, Harmsen WS, Misra S. Endovascular Arteriovenous Dialysis Fistula Intervention: Outcomes and Factors Contributing to Fistula Failure. Kidney Med 2020;2:326-31. doi: 10.1016/j.xkme.2020.02.004.
11. Kilari S, Cai C, Zhao C, Sharma A, Chernogubova E, Simeon M, et al. The Role of MicroRNA-21 in Venous Neointimal Hyperplasia: Implications for Targeting miR-21 for VNH Treatment. Mol Ther 2019;27:1681-93. doi: 10.1016/j.ymthe.2019.06.011.

12. Singh AK, Cai C, Kilari S, Zhao C, Simeon ML, Takahashi E, et al. 1α,25-Dihydroxyvitamin D3 Encapsulated in Nanoparticles Prevents Venous Neointimal Hyperplasia and Stenosis in Porcine Arteriovenous Fistulas. J Am Soc Nephrol 2021;32:866–85. doi: 10.1681/ASN.2020060832.
13. Hughes D, Fu AA, Puggioni A, Glockner JF, Anwer B, McGuire AM, et al. Adventitial transplantation of blood outgrowth endothelial cells in porcine haemodialysis grafts alleviates hypoxia and decreases neointimal proliferation through a matrix metalloproteinase-9-mediated pathway--a pilot study. Nephrol Dial Transplant 2009;24:85-96. doi: 10.1093/ndt/gfn433.
14. Cai C, Kilari S, Zhao C, Simeon ML, Misra A, Li Y, van Wijnen AJ, et al. Therapeutic Effect of Adipose Derived Mesenchymal Stem Cell Transplantation in Reducing Restenosis in a Murine Angioplasty Model. J Am Soc Nephrol 2020;31:1781-95. doi: 10.1681/ASN.2019101042.
15. Brahmbhatt A, NievesTorres E, Yang B, Edwards WD, Roy Chaudhury P, Lee MK, et al. The role of Iex-1 in the pathogenesis of venous neointimal hyperplasia associated with hemodialysis arteriovenous fistula. PLoS One 2014;9:e102542. doi: 10.1371/journal.pone.0102542.
16. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. Stem Cell Res Ther 2019;10:68. doi: 10.1186/s13287-019-1165-5.
17. Smith A. A glossary for stem-cell biology. Nature 2006;441:1060. Doi: 10.1038/nature04954.
18. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8:315-7. doi: 10.1080/14653240600855905.
19. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell 2002;13:4279-95. doi: 10.1091/mbc.e02-02-0105.
20. Lee T. Novel paradigms for dialysis vascular access: downstream vascular biology--is there a final common pathway? Clin J Am Soc Nephrol 2013;8:2194-201. doi: 10.2215/CJN.03490413.
21. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 2005;105:1815-22. doi: 10.1182/blood-2004-04-1559.
22. Kossl J, Bohacova P, Hermankova B, Javorkova E, Zajicova A, Holan V. Antiapoptotic Properties of Mesenchymal Stem Cells in a Mouse Model of Corneal Inflammation. Stem Cells Dev 2021;30:418-27. doi: 10.1089/scd.2020.0195.
23. Yuan L, Sakamoto N, Song G, Sato M. Low-level shear stress induces human mesenchymal stem cell migration through the SDF-1/CXCR4 axis via MAPK signaling pathways. Stem Cells Dev 2013;22:2384-93. doi: 10.1089/scd.2012.0717.
24. Yang B, Brahmbhatt A, Nieves Torres E, Thielen B, McCall DL, Engel S, et al. Tracking and Therapeutic Value of Human Adipose Tissue-derived Mesenchymal Stem Cell Transplantation in Reducing Venous Neointimal Hyperplasia Associated with Arteriovenous Fistula. Radiology 2016;279:513-22. doi: 10.1148/radiol.2015150947.
25. Conte MS, Nugent HM, Gaccione P, Guleria I, Roy-Chaudhury P, Lawson JH. Multicenter phase I/II trial of the safety of allogeneic endothelial cell implants after the creation of arteriovenous access for hemodialysis use: the V-HEALTH study. J Vasc Surg 2009;50:1359-68.e1. doi: 10.1016/j.jvs.2009.07.108.
26. Piryani AK, Kilari S, Takahashi E, DeMartino RR, Mandrekar J, Dietz AB, et al. Rationale and Trial Design of MesEnchymal Stem Cell Trial in Preventing Venous Stenosis of Hemodialysis Vascular Access Arteriovenous Fistula (MEST AVF Trial). Kidney360 2021;2:1945-e52. doi: 10.34067/KID.0005182021.
27. Nieves Torres EC, Yang B, Brahmbhatt A, Mukhopadhyay D, Misra S. Blood outgrowth endothelial cells reduce hypoxia-mediated fibroblast to myofibroblast conversion by decreasing proangiogenic cytokines. J Vasc Res 2014;51:458-67. doi: 10.1159/000369929.
28. Forte A, Finicelli M, Mattia M, Berrino L, Rossi F, De Feo M, et al. Mesenchymal stem cells effectively reduce surgically induced stenosis in rat carotids. J Cell Physiol 2008;217:789-99. doi: 10.1002/jcp.21559.
29. Kumar VA, Chandrasekaran V, Brahadeeswari H. Prevalence of smartphone addiction and its effects on sleep quality: A cross-sectional study among medical students. Ind Psychiatry J 2019;28:82-5. doi: 10.4103/ipj.ipj_56_19.
30. Pakistan Institute of Development Economics (PIDE). In: ul Haque N, Durr-e-Nayab, eds. PIDE: COVID 19, E-Book. Islamabad, Pakistan: PIDE; 2020.
31. Finance Division, Government of Pakistan. Pakistan Economic Survey 2021-22. [Online] 2022 [Cited 2022 December 26]. Available from URL: https://www.finance.gov.pk/survey/chapter_22/Economic%20Survey%202021-22.pdf
32. Anwar M. Bone marrow transplant in Pakistan: indications and economics. J Coll Physicians Surg Pak 2003;13:549-51.
33. Syed IB. An Islamic Perspective on Stem Cell Research in Brief. [Online] 1988-2009 [Cited 2022 October 01]. Available from URL: http://www.irfi.org/articles/articles_1_50/an_islamic_perspective_on_stem_c.htm
34. Naz A, Khan W, Daraz U, Hussain M, Khan T. Militancy: A Myth or Reality - An Exploratory Study of the Socio-Economic and ReligiousForces Behind Militancy in Khyber Pakhtunkhwa, Pakistan. [Online] 2012 [Cited 2022 October 01]. Available from URL: https://papers.ssrn.com/abstract=2083024