REVIEW ARTICLE

Mesenchymal Stem Cell Therapy in Ischaemic Heart Failure: Hope or Hype?

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Abstract

Ischaemic heart diseases (IHDs) are the leading contributor to mortality worldwide and more than 60% occur in low-to-middle-income countries (LMICs) and 40% of these are specified as premature. Despite notable improvements in treatment options, premature deaths due to IHDs including ischaemic heart failure (IHF) continue to rise in the South Asian population due to prevalent conventional and inherent cardiovascular risk profiles. Stem cell (SCs) therapy has emerged as a potential frontier in regenerative therapy for acute and chronic illnesses. Among various available sources of SCs, the safety and efficacy of mesenchymal stem cells (MSCs) for non-functional cardiomyocytes have been established, but robust evidence necessitates to endorse these preliminary investigations. Little work has been conducted in resource constraints countries and needs immediate attention of all the stakeholders to explore non-conventional cost-effective and sustainable interventions for long term management of IHDs including IHF. This review article provides an overview of basic technical aspects of SCs therapy and a way forward to inspire the scientific community and health authorities to setup priorities via collaborative public and private partnership toward the formulation and execution of sustainable strategies for IHDs to explore the new contextual destination in the field of SCs therapy.

Keywords: Myocytes, Cardiovascular, Myocardial Ischemia, Heart Failure, Mesenchymal Stem Cells.

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Introduction

Ischaemic heart diseases (IHDs) are the leading contributor to mortality and disability-adjusted life years (DALYs) worldwide.[1] More than 60% of these mortalities occur in low-to-middle-income countries (LMICs)[2] and nearly 40% of these are specified as premature.[3] Asians are at a high risk of developing IHDs due to prevalent conventional and inherent cardiovascular risk profiles including diabetes and related metabolic disturbances.[4]

Among IHDs, ischaemic heart failure (IHF) becomes a global epidemic, affecting 26 million people worldwide and about 60% are comprised of ischaemic heart failure (IHF).[5] Though remarkable advancement has been observed in conventional treatment for IHDs, and a dramatic decline in mortality has been observed, but it still persists as top-ranked causes of mortality and disability worldwide.[6] Therapeutic interventions for IHDs include medical management such as thrombolytics, percutaneous intervention (PCI), and surgical revascularization. However, these modalities provide short term survival benefits to the patients and symptoms of IHF often persist even after revascularization for which no other treatments options are available. Heart transplantation is a curative option, but availability, harvesting, matching and overall delicate management, complicated perioperative course and associated prohibitive cost are the main limitations. Despite recent advancement in treatment modalities, it is still challenging to manage heart failure for longer periods.[5] In extreme stages, non-conventional treatment modalities including ventricular assist devices, artificial heart, and heart transplant can be opted but these options are beyond the resources of LMICs, and warranted exploration of cost-effective and durable management of IHDs such as SCs therapy.

Stem cells are a group of undifferentiated cells with an ability to extensively proliferate, usually arise from a single cell, and differentiate into different types of cells and tissue.[7] The knowledge of SCs biology expands significantly during the last decades and exploratory research has been expanded on an exponential rate, particularly in the field of regenerative therapies within medicine and surgical domains. SCs based regenerative therapy is a promising frontier emerged as an alternative therapeutic approach for major chronic diseases including cardiovascular diseases. Extensive translational, preclinical, and early clinical trials have shown an acceptable safety, and efficacy of several types of SCs based therapy, evaluated for regeneration of injured or non-functional myocardium by inhibiting scar formation,

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improved angiogenesis, and enhanced cardiac function. Pre-clinical and clinical trials showed mild to moderate improvement in the cardiomyocytes function, after transplantation of SCs in the target tissue,[8, 9] but mechanism of action of regenerative characteristics remain incomprehensible and require more evidence from robust well designed clinical research.

A substantial progress has been evident during last decade that provide coherent and convincing discoveries of SCs based therapy in IHDs that could be of great interest particularly in LMICs where burden of IHDs is constantly rising. The idea of writing this review was conceptualized by the multi-disciplinary team of experts and started to write this article in the mid of July, 2022 targeting last 10 years published experimental trials, aiming to provide an overview of essential technical aspects of SCs based therapy focussing on Mesenchymal Stem Cells (MSCs) and a way forward to inspire the scientific community and healthcare authorities to setup priorities via collaborative public and private sector partnership towards the formulation and implementation of sustainable management for IHDs to explore the new contextual destination in the field of SCs based therapy.

Injury to Cardiomyocytes

Cardiac muscle cells are specialized cells having intrinsic property of rhythmic contractility using energy supplied through the coronary arteries. These muscles are potentially at risk of dying because of coronary occlusion leading to myocardial and infarction demands for an early intervention for improved outcomes. It is well established that native cardiomyocytes are not sufficient to repair damaged myocardial tissue, as hardly 15% of cardiomyocytes (CMs) are capable to regenerate and undergo division following ischaemic injuries. Cardiac muscle repair after myocardial infarction accompanied by a series of events, begins with intense sterile inflammation and immune cell infiltration, phagocytosis, and shedding of damaged cells from surrounding extracellular matrix tissue. It is followed by a recovery phase which resolves the inflammation through scarring and neovascularization within few days of the cardiac injury.[10] Post MI non-viable muscle cells with the scar tissue results in contractile dysfunction and eventually leads to heart failure.[11]

Sources of SCs

SCs are unique in nature as they can regenerate themselves and differentiate into several types of mature cells and perform the native cell function. SCs are broadly classified into embryonic stem cells (ESCs) and adult stem cells, which can be isolated from various body tissues including cardiac cell, chromospheres, skeletal myoblast, umbilical cord, and adipose tissues. Bone marrow-derived stem cells (BM-MSCs) include haematopoietic (HSCs), endothelial progenitor (EPCs) and mesenchymal stem cells (MSCs), have shown a positive effect on cardiac regeneration process.[12]

ESCs believed to be a controversial source and its clinical application is limited due to ethical implications. BM-MSCs emerged as a breakthrough capability to regenerate and repair cardiomyocytes and endogenous tissues through paracrine signalling and immunomodulatory properties.[13] Subsequently, MSCs have been isolated from various other sources such as adipose tissue, serve as one of the alternatives to bone marrow derived SCs, isolated as a viable and safer source of SCs.[14] They are widely studied source due to abundance, trouble-free operation, proven capability to differentiate into cardiomyocytes, less tendency for tumor formation, immune exemption and free from ethical issues.

Stem Cell Isolation and Route of Delivery

The SCs have been transplanted into patient's heart as autograft (from patients own tissues) or allograft (tissue from another person). SCs based therapy for IHDs consists of cell acquisition, processing, and transplantation into patient's heart.[15] Bone marrow aspirate is processed and cultured to get pure population of MSCs which are then induced by various molecules to differentiate into cardiac progenitor cells[16] that can be transplanted into heart by various approaches.[17] The delivery routes include:

Thoracotomy injection: Transportation of SCs via thoracotomy consists of epicardial, intramyocardial injection and cellular patches. This trans-epicardial intramyocardial injection is most classic cell delivery method in which SCs are directly injected into the target tissue to prevent cell loss. This method is suitable for patients undergoing coronary bypass surgery and concurrent heart valve surgery.[18] Whereas the patch improves cell survival and engraftment, which positively impact on heart function.

System infusion: Systemic infusions, including intracoronary injections, can increase the number of cells entering the ischaemic zone of the myocardium without causing damage compared to direct injection into the myocardium. It is the mostly used method in clinical practice and can be done with percutaneous coronary intervention (PCI) procedure without opening the chest.[19] It is a non-invasive, reproducible, economical, and

practical clinical treatment, but its effectiveness is yet to be established. In the preclinical porcine model of chronic myocardial ischaemia, a combination of intracoronary and intravenous administration has shown good safety and efficacy by improving cardiac function, increase myocardial perfusion and relieve ventricular remodelling. Whether combined transplantation is better than single injection is yet to be explored.

Imaging-Guided Mini-Invasive Injection: This minimally invasive approach includes trans-endocardial and trans-epicardial tans-endocardial intra-myocardial injections guided by Digital Subtraction Angiography (DSA), Magnetic Resonance Imaging (MRI) or three-dimensional (3D) NOGA. The electromechanical mapping system does not require thoracotomy and SCs directly transplanted into the target area, however, this requires specific positioning equipment and devices. Potential risk includes damage to myocardium and arrythmia due to high pressure technology and death of transplanted cell.[20] Recently minimally invasive image-guided injections and triple puncture needle device introduced that allows intramyocardial injection through ultrasound-guided thoracic epicardium. This technique is less traumatic, has fewer complications and multiple transplants can be performed at different time points.

The route of administration appears to have a remarkable influence on the effectiveness of MSCs therapy in both acute and chronic myocardial infarction[21] and has important implications for the design of future studies.[22]

Mechanism of cardiomyocytes repair

Recently, MSCs have been evaluated as a potential cellular substrate for cell therapy, repair, and regeneration. MSCs act as a great source of cytokines and chemokines that play beneficial paracrine actions in tissue repair.[23] After implantation at the targeted site, cardiomyocytes help in reviving cardiac function by actively contracting and promoting angiogenesis.[11] Ni et al. suggested a possible mechanism that include direct regeneration, paracrine effects, immunity regulation, improved microenvironment and promote the endogenous cardiomyocytes.[24] Since myocardial repair is a complex process, the underlying details remain uncovered yet.

Factor Influence on The Survival of Implanted SCs

There are numerous factors that can influence on survival rate and efficacy of transplanted SCs. Adult SCs may exhibit DNA abnormality during a lifetime and often present in only minute quantities due to increasing age, thus difficult to isolate and purify.[12] Therefore, it is important to keep the cell population homogenous. Selection and isolation of pure cardiomyocytes before transplantation is crucial because non-specific cells may be the cause to generate unwanted types of cells like cancerous tumour cells and other related complications such as severe infections, blood clots, stroke, rejection and even death.

The timing of transplantation also plays a critical role in acquiring success. In acute MI, due to non-conducive microenvironment with an overwhelming inflammatory local response, survival, and growth of grafted SCs could be at risk.[25] Since the inflammation reaches its climax around 1-4 days, vascular endothelial growth factor (VEGF), which promotes stem cell migration, reaches at its peak around 7 days after the event. Moreover, left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), and left ventricular end-diastolic volume (LVEDV) have shown improvement if SCs transplanted between 7-10 days of the event. However, further studies warranted to confirm precise duration of transplantation after an index event.[13]

Observed variability in response to SCs treatment may be secondary to comorbidities. Abnormal glucose metabolism and diabetes have been found to affect SCs and angiogenic cells mobilization in diabetic patients. A meta-regression analysis by Fadini et al. indicated that diabetes is the major negative determinant that impairs SCs mobilization, with possible negative implications for IHDs population with diabetes.[26] Apart from diabetes, the findings open the new area of exploratory research to study the influence of other comorbidities such as hypertension, dyslipidaemia, and other risk factors on the efficacy of SCs based therapy in IHDs and IHF. Therefore adjusting baseline risk-specific reprogramming for SCs therapy may predict improved probabilities of success.[12] Other factors may include, underlying heart failure aetiology, type and mode, number of cells (dose) transported and paracrine factors leading to trans-differentiation also influence on the outcomes of SCs therapy.[17]

Overview of RCTs on BM-MSCs in IHF

A sizable number of clinical trials initiated to explore safety and efficacy of BM-MSCs based treatment for IHF, have either been completed or withdrawn due to safety issues or are in progress. The key issues in these trials are heterogeneity in terms of source of SCs, mode of delivery, number of cells transplanted, time of implantation of the cells and allograft vs autograft transplantation.[15] Table-1, summarizes utility and outcomes of major studies on the role of BM-MSCs in IHF and cardiomyopathies. C-Cure,

Table-1: The outcome of RCTs (2013 to date) on Safety and efficacy of Bone Marrow Derived Mesenchymal cell (BM-MSCs) transplantation in ischemic heart failure and cardiomyopathies.

Study	Journal And Publication Year	Design and Phase	Mode Of Delivery	Outcome Variable	Results
C-CURE TRIAL Bartunek et. al	J Am Coll Cardiol,2013	RCT II/III NCT00810238 n=48 Chronic heart failure	AutologousEndo-ventricular injection	Primary: Feasibility and safety (2 years follow-up)Secondary: Cardiac structure/function and performance at 6 months	There was no safety issue reported. An increase in LVEF, decrease in LVESV; while 6-min walk distance and NYHA improved in the standard of care plus lineage-specified stem cells
MSC HF TRIAL Mathiasen et. al	Eur Heart J. 2015	RCT I/II NCT00644410 n=60 2:1	Autologousintra-myocardial injections	Primary: Change in LVEF, LVESV, At 6 months	An increase in LVEF, and a decrease in LVESV.No change in NYHA and 6-min walk distance.
MESAMI 1 Pilot study Guijarro et. al	Int J Cardiol. 2016	RCT I/II NCT01076920 n=10	Autologousintra-myocardial injections	Primary: Feasibility and safetySecondary: LVEF and LVESD(1 year follow up)	Feasibility and safety were met in all patients. An increase in LVEF, decrease in LVESV; 6-min walk distance and NYHA improved in the standard of care plus lineage-specified stem cells.
Trident Study Florea et. al	Circ Res. 2017	RCT-II NCT02013674 n=30	AllogeneicTrans endocardial injectionMSC 20 million vs 100 million	Safety and efficacy (at 1 year)Dose-response to scar reductionChange in LVEF	There were no emergent serious adverse events. With a comparable reduction in Scar size, LVEF improved only in the 100 million group.NYHA class improved in both groups.Highlights the crucial role of cell dose in the responses to cell therapy.
POSEIDON-DCM Trial Hare et. al	J Am Coll Cardiol. 2017	RCT- I/II NCT01392625 n=37 Non-ischemic dilated cardiomyopathy	Autologous vs allogeneic100 millionTrans endocardial stem cell injection	30 days, and 3-, 6-, and 12-months for safetyChange in LVEFNYHA, 6-min walkEndothelial function	Prove to be safe intervention.Increase in Ejection fraction and 6-min walk in Allogeneic group while 6-min walk improved significantly more in Allogeneic group. No change in LVESV or LVEDV ESVSV Allogeneic group showed better efficacy than autologous group. Marginal improvement in NYHA in and significant improvement in endothelial function in Allogenic group
Cardia MP-HF Feasibility study Raval et. al	Int J Cardiol. 2021	RCT-III NCT02438306 n=10	AutologousTrans endocardial injection of 200 million	Change in Scar tissue, LVEF, 6-min walk at 12 months	Improvement in 6-min walk test along with improvement in scar tissue.Change in LVEF and NYHA were comparable in both group

C-HF and MESAMI-1 trials have established safety and efficacy of SCs therapy.[27-29] Patient received autologous intra-myocardial or endo-ventricular injections vs active controls. An increase in LVEF and a decrease in LVESV was evident in MSCs group. However, C-Cure and MESAMI-1 trials showed an improvement in 6-min walk test and NYHA class as well. While MSC-HF did not show any significant difference in 6-min walk test and NYHA class; interestingly, at 4 year follow up, a decrease in hospitalization rates for angina in the MSCs group was evident in the later trial.[30]

Trident trial used allogeneic BM-MSCs and compared dose response of MSCs,[31] (20 million vs 100 million) given via trans-endocardial injection. Primary endpoints were assessed for safety and efficacy at 12 months. Both groups showed a reduction in scar tissue, interestingly LVEF increased by 3.7 units only with 100 million units' arm, this highlight's the role of BM-MSCs dose-response association. Poseidin-DCM trial which compared allogeneic and autologous BM-MSCs on non-ischaemic dilated cardiomyopathy patients[32] and showed desirable efficacy of allogeneic MSCs based therapy. Allogeneic group has shown to be superior to autologous and showed more improvement in LVEF and 6-min walk test. A recent meta-analysis of RCTs including 612 patients by Fan et al. showed a significant reduction in mortality (by 36%), unplanned hospital readmissions (by 34%), improvement in LVEF (by 5.5%) and 6-min walk test in MSCs vs placebo group.[33] Another meta-analysis by Afzal et al. that summarizes efficacy of injectable BM-MSCs therapy in IHDs in 48 eligible trials of 2602 patients. The results showed improvement in LVEF by 2.92% and

reduction in scar size by 2.25%.[34] A recent trial used 200 million autologous cells via trans endocardial injection and demonstrated significant reduction in scar tissue and improvement in 6-min walk test in the intervention arm, however, change in LVEF and NYHA were comparable in both groups.[35]

Most of the clinical trials have confirmed safety of BM-MSCs delivery routes however, the efficacy of SCs in IHF are still questionable. Larger, well-designed phase-III clinical trials are in progress, which may help to establish the outlooks of MSCs therapeutic potentials for IHDs and IHF.

Current Status of Stem cell therapy in Pakistan

In Pakistan, SCs therapy is an emerging field and a beacon of hope for those undergoing end stage heart failure.[36] Multiple preclinical and very few clinical trials conducted in Pakistan have shown desirable feasibility and efficacy of SCs therapy in IHF. In 1995, SCs transplantation was started in Pakistan at Zia-Uddin Hospital Karachi by Dr. Tahir Shamsi,[37] since then, little progress was observed in the field of SCs biology. A total 14 laboratories are associated with SCs research, while only three centres providing the facility for bone marrow transplantation.[38] Several clinical studies are performed for the isolation of Haematopoietic SCs (HSCs) from the bone marrow for transplantation in degenerative sites. Though majority of clinicians are optimistic about SCs therapy, yet no clinical grade SCs propagation, characterization, cell line development and storage facilities are available in Pakistan. Stem cells samples are sent aboard for proliferation to get the desirable number of cells for clinical use.

Compared to Pakistan, neighbouring countries are doing quite well in SCs transplantation. China is the second-best provider of stem cell-based products following USA in the lead. Iran has invested $2.5 billion in SCs research with 34 research centres working in regenerative medicine.[39]

By the end of 2017, India has marketed SCs therapy products worldwide was estimated to be of worth $600 million, which is expected to increase up to $119 billion by 2019 and further increase at a growth rate of 24.2%. Forty research institutes and hospitals are working under the umbrella of nine major SCs research organizations for SCs-based therapy to be translated from bench to bed side.[40]

Indian ministry of health also has setup guidelines for SCs clinical trials, and hence has become a leading provider in SCs-based therapy products to world renowned companies.[41]

Pre-Clinical Research in Pakistan

In Pakistan, initial research work done in the field of cardiac regeneration using SCs based therapy in IHDs. MSCs, mostly used cells obtained from human umbilical cord or rat bone marrow used in preclinical experiments. In one study Khan et al. reported substantial improvement in cardiac function in infarcted myocardium of rat after transplantation of preconditioned MSCs with 2-4, dinitrophenol.[42] It has been observed that transplantation of genetically modified MSCs with interlukin-7 improved the pumping ability of rat's heart. This improvement may be attributed to enhanced fusion with cardiac myocytes and angiogenesis that leads to regeneration of cardiomyocytes.[43] Treatment of MSCs with small molecules like 5-azacytadine and zebularine have successfully differentiated rat BM-MSCs into cardiac cells expressing cardiac gene and protein expression.[44] Studies have reported enhanced survival, homing, angiogenesis and preservation of native myocardium when MSCs were preconditioned with hypoxic stress or certain molecules.[45, 46]

Human umbilical cord derived MSCs also been explored for their role in cardiac muscle regeneration. In one study, umbilical cord derived MSCs differentiated with small molecules 2-deoxycytidine showed enhanced expression of cardiac genes and proteins including myosin heavy chain, alpha actinin, GATA-4, Nkx2.5, cardiac troponin-T, and cardiac troponin-C. These xenogeneic cardiac cells when transplanted in rat myocardial infarction model showed better survival and homing in the infarcted region and results in improved cardiac function and ventricular wall thickness by enhancing cardiac systolic function, promoting angiogenesis and improving ventricle remodelling.[47, 48] The preclinical studies on animal models in Pakistan have shown promising results of MSCs in cardiomyocytes regeneration but its translation into clinical practice is still awaited. In Pakistan, umbilical cord preservation banks are working in different cities mainly in private sectors. There is a dire need to establish a private and public collaborative initiative to store and utilize this rich source of excellent quality MSCs for chronic illnesses.

Clinical Research in Pakistan

Negligible studies have been done on the efficacy of SCs in IHDs and IHF in Pakistan. Nuri et al. injected intracoronary autologous BM-MSCs in patients with recent anterior wall MI.[49, 50] They found the procedure to be simple, safe, and effective. They reported an improved LVEF (by 4%) and myocardial perfusion at 12 weeks of follow up. Large scale double-blind controlled trials are

crucial to endorse safety and efficacy of SCs based therapy for translational clinical application. More randomized clinical trials are essential to explore the beneficial effects of these modalities in our population that have been driven by an epidemiological transition and a surge in the prevalence of etiological factors such as hypertension, diabetes mellitus, dyslipidaemia and obesity. Lifestyle changes, characterized by increasing physical activity and discouraging tobacco use.

Lack of Clinical Benefit: Pot of Gold or Pandora Box

Despite the promising results of preclinical studies, the clinical benefit of SCs therapy is uncertain.[51] Studies have found limited engraftment in the myocardium on long-term follow up.[15] The possible culprits for this failure includes harsh environment at the implanted site like ischaemia, immune reaction and ongoing inflammation.[5] Thus, further exploratory research is warranted to consider various issues to ensure use of correct cell type, dosage, time of transportation, delivery methods and identify actual mechanism of functional improvement. It is not sure how to get pure and fully matured transplantable cardiomyocytes and its integration into the targeted tissue beating in the same rhythm as a healthy cardiomyocyte does. Thus, for feasibility purposes, the ideal SCs based therapy should be convenient, reproducible, consistent, cost effective and available "off-the-shelf" without confounding by comorbid conditions for a large-scale expansion for IHDs research and its application in the LMICs like Pakistan.

Ethical Issue in Stem Cell Therapy

SCs research is a noteworthy and emerging biomedical research that extends promising therapeutic opportunities to treat a wide range of acute and chronic disorders and injuries. Due to the complexity of SCs and the variety of ways in which they used and manipulated, it does not fit within current monitoring frameworks for biological products or medicines and is still a subject of ongoing ethical debate employing a massive challenge for regulatory agencies worldwide particularly LMICs and Muslim countries. Recently, many Muslim countries have dedicated a substantial resource to develop high-quality research institutions for exploring venues in SCs based therapy for acute and chronic diseases. Several national and international organizations and Muslim countries have developed guidelines in the field of SCs-related research and therapies, including Iran, Jordan, Malaysia, Qatar, Saudi Arabia, UAE, and Turkey. National Bioethics Committee in Pakistan has also developed guidelines on SCs research.[52] All such regulatory policies are crucial for uniformity, reproducibility, sustainability in the region that may help to establish collaborative platforms for capacity building and resource efficient initiative for technology transfer and its application on larger scale to mitigate challenges of non-communicable diseases that are now overtaking to infectious diseases in our region.

Way Forward

In Pakistan, a substantial number of researchers are working in the basic stem cells biology. There is an urgent need to bring the clinicians and basic scientists on a common platform, in fact hospital based SCs laboratories for expansion of SCs research should be established for clinical application. The government should invest and establish Good Manufacturing Practice (GMP) facility for cell therapy products in mega cities to facilitate patients particularly with haematological disorders, and degenerative illnesses. Once these facilities start working, the public sector may invest and offer services to the patients on sustainable basis. This will also contribute to the country's economy by medical tourism. However, a strict monitoring body should be established to regulate and evaluate such labs and hospitals which offer safe, efficient, and ethical SCs therapy. This will also lay the foundation for production of biological drugs, vaccines, and gene therapy products. An interdisciplinary endeavour at the scientific, clinical, regulatory authorities' fore part will bring successful results of this innovative and reliable therapy for healing acute and chronic illnesses and may convert what seems now a dream into a reality.

Conclusion

Evidence from preclinical and clinical trials have shown a reduction in mortality and a considerable improvement in cardiac function including LVEF, LVESV and quality of life by SCs therapy. MSCs-based cardiomyopathy have demonstrated as a viable, safe, and effective approach to manage IHDs. However, the mechanism underpinning SCs' ability to regenerate injured cardiac tissues is not entirely known.[53] The clinical evidence often inconsistent in many aspects and require deeper exploration on concealed aspects by conducting more phase-III RCTs. Moreover, information on source and type of SCs and supporting cells used, cell processing, cell dosage, route of admiration, frequency and best timing for transplantation is yet to be optimized.

LMICs, like, Pakistan should initiate to develop a cultural, religious and risk adaptive regenerative translational research models for the management of IHDs by involving stakeholders from all cadre to setup priorities for the long-term sustainable goals towards cost effective

and affordable treatment choices for IHDs including IHF.

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References

1. Wang C, Sun Y, Jiang D, Wang C, Liu S. Risk-Attributable Burden of Ischemic Heart Disease in 137 Low- and Middle-Income Countries From 2000 to 2019. J Am Heart Assoc 2021;10:e021024. doi: 10.1161/JAHA.121.021024.
2. Vardell E. Global Health Observatory Data Repository. Med Ref Serv Q 2020;39:67-74. doi: 10.1080/02763869.2019.1693231.
3. Prabhakaran D, Anand S, Watkins D, Gaziano T, Wu Y, Mbanya JC, et al. Cardiovascular, respiratory, and related disorders: key messages from Disease Control Priorities, 3rd edition. Lancet 2018;391:1224-36. doi: 10.1016/S0140-6736(17)32471-6.
4. Tan ST, Scott W, Panoulas V, Sehmi J, Zhang W, Scott J, et al. Coronary heart disease in Indian Asians. Glob Cardiol Sci Pract 2014;2014:e13-23. doi: 10.5339/gcsp.2014.4.
5. Yu H, Lu K, Zhu J, Wang J. Stem cell therapy for ischemic heart diseases. Br Med Bull 2017;121:135-54. doi: 10.1093/bmb/ldw059.
6. Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low- and middle-income countries. Curr Probl Cardiol 2010;35:72-115. doi: 10.1016/j.cpcardiol.2009.10.002.
7. Kolios G, Moodley Y. Introduction to stem cells and regenerative medicine. Respiration 2013;85:3-10. doi: 10.1159/000345615.
8. Cong XQ, Li Y, Zhao X, Dai YJ, Liu Y. Short-Term Effect of Autologous Bone Marrow Stem Cells to Treat Acute Myocardial Infarction: A Meta-Analysis of Randomized Controlled Clinical Trials. J Cardiovasc Transl Res 2015;8:221-31. doi: 10.1007/s12265-015-9621-9.
9. Henry TD, Pepine CJ, Lambert CR, Traverse JH, Schatz R, Costa M, et al. The Athena trials: Autologous adipose-derived regenerative cells for refractory chronic myocardial ischemia with left ventricular dysfunction. Catheter Cardiovasc Interv 2017;89:169-77. doi: 10.1002/ccd.26601.
10. Frangogiannis NG. Regulation of the inflammatory response in cardiac repair. Circ Res 2012;110:159-73. doi: 10.1161/CIRCRESAHA.111.243162.
11. Razeghian-Jahromi I, Matta AG, Canitrot R, Zibaeenezhad MJ, Razmkhah M, Safari A, et al. Surfing the clinical trials of mesenchymal stem cell therapy in ischemic cardiomyopathy. Stem Cell Res Ther 2021;12:361. doi: 10.1186/s13287-021-02443-1.
12. Nair N, Gongora E. Stem cell therapy in heart failure: Where do we stand today? Biochim Biophys Acta Mol Basis Dis 2020;1866:165489. doi: 10.1016/j.bbadis.2019.06.003.
13. Ma S, Xie N, Li W, Yuan B, Shi Y, Wang Y. Immunobiology of mesenchymal stem cells. Cell Death Differ 2014;21:216-25. doi: 10.1038/cdd.2013.158.
14. Strioga M, Viswanathan S, Darinskas A, Slaby O, Michalek J. Same or not the same? Comparison of adipose tissue-derived versus bone marrow-derived mesenchymal stem and stromal cells. Stem Cells Dev 2012;21:2724-52. doi: 10.1089/scd.2011.0722.
15. Ward MR, Abadeh A, Connelly KA. Concise Review: Rational Use of Mesenchymal Stem Cells in the Treatment of Ischemic Heart Disease. Stem Cells Transl Med 2018;7:543-50. doi: 10.1002/sctm.17-0210.
16. Horwitz EM, Andreef M, Frassoni F. Mesenchymal stromal cells. Curr Opin Hematol 2006;13:419-25. doi:10.1097/01.moh.0000245697.54887.6f.
17. Liu C, Han D, Liang P, Li Y, Cao F. The Current Dilemma and Breakthrough of Stem Cell Therapy in Ischemic Heart Disease. Front Cell Dev Biol 2021;9:e636136. doi: 10.3389/fcell.2021.636136.
18. Hamano K, Nishida M, Hirata K, Mikamo A, Li TS, Harada M, et al. Local implantation of autologous bone marrow cells for therapeutic angiogenesis in patients with ischemic heart disease: clinical trial and preliminary results. Jpn Circ J 2001;65:845-7. doi: 10.1253/jcj.65.845.
19. de Jong R, Houtgraaf JH, Samiei S, Boersma E, Duckers HJ. Intracoronary stem cell infusion after acute myocardial infarction: a meta-analysis and update on clinical trials. Circ Cardiovasc Interv 2014;7:156-67. doi: 10.1161/CIRCINTERVENTIONS.113.001009.
20. van der Spoel TI, Vrijsen KR, Koudstaal S, Sluijter JP, Nijsen JF, de Jong HW, et al. Transendocardial cell injection is not superior to intracoronary infusion in a porcine model of ischaemic cardiomyopathy: a study on delivery efficiency. J Cell Mol Med 2012;16:2768-76. doi: 10.1111/j.1582-4934.2012.01594.x.
21. Fakoya AO. New Delivery Systems of Stem Cells for Vascular Regeneration in Ischemia. Front Cardiovasc Med 2017 24;4:7. doi: 10.3389/fcvm.2017.00007.
22. Kanelidis AJ, Premer C, Lopez J, Balkan W, Hare JM. Route of Delivery Modulates the Efficacy of Mesenchymal Stem Cell Therapy for Myocardial Infarction: A Meta-Analysis of Preclinical Studies and Clinical Trials. Circ Res 2017;120:1139-50. doi: 10.1161/CIRCRESAHA.116.309819.
23. Gnecchi M, Melo LG. Bone marrow-derived mesenchymal stem cells: isolation, expansion, characterization, viral transduction, and production of conditioned medium. Methods Mol Biol 2009;482:281-94. doi: 10.1007/978-1-59745-060-7_18.
24. Ni X, Ou C, Guo J, Liu B, Zhang J, Wu Z, et al. Lentiviral vector-mediated co-overexpression of VEGF and Bcl-2 improves mesenchymal stem cell survival and enhances paracrine effects in vitro. Int J Mol Med 2017;40:418-26. doi: 10.3892/ijmm.2017.3019.
25. Poomani MS, Mariappan I, Perumal R, Regurajan R, Muthan K, Subramanian V. Mesenchymal Stem Cell (MSCs) Therapy for Ischemic Heart Disease: A Promising Frontier. Glob Heart 2022;17:19. doi: 10.5334/gh.1098.
26. Fadini GP, Avogaro A. Diabetes impairs mobilization of stem cells for the treatment of cardiovascular disease: a meta-regression analysis. Int J Cardiol 2013;168:892-7. doi: 10.1016/j.ijcard.2012.10.089.
27. Mathiasen AB, Qayyum AA, Jørgensen E, Helqvist S, Fischer-Nielsen A, Kofoed KF, et al. Bone marrow-derived mesenchymal stromal cell treatment in patients with severe ischaemic heart failure: a randomized placebo-controlled trial (MSC-HF trial). Eur Heart J 2015;36:1744-53. doi: 10.1093/eurheartj/ehv136.
28. Bartunek J, Behfar A, Dolatabadi D, Vanderheyden M, Ostojic M, Dens J, et al. Cardiopoietic stem cell therapy in heart failure: the C-CURE (Cardiopoietic stem Cell therapy in heart failURE) multicenter randomized trial with lineage-specified biologics. J Am Coll Cardiol 2013;61:2329-38. doi: 10.1016/j.jacc.2013.02.071.
29. Guijarro D, Lebrin M, Lairez O, Bourin P, Piriou N, Pozzo J, et al. Intramyocardial transplantation of mesenchymal stromal cells for chronic myocardial ischemia and impaired left ventricular function: Results of the MESAMI 1 pilot trial. Int J Cardiol 2016;209:258-65. doi: 10.1016/j.ijcard.2016.02.016.
30. Mathiasen AB, Qayyum AA, Jørgensen E, Helqvist S, Kofoed KF, Haack-Sørensen M, et al. Bone marrow-derived mesenchymal stromal cell treatment in patients with ischaemic heart failure: final 4-year follow-up of the MSC-HF trial. Eur J Heart Fail 2020;22:884-92. doi: 10.1002/ejhf.1700.
31. Florea V, Rieger AC, DiFede DL, El-Khorazaty J, Natsumeda M, Banerjee MN, et al. Dose Comparison Study of Allogeneic Mesenchymal Stem Cells in Patients With Ischemic

Cardiomyopathy (The TRIDENT Study). Circ Res 2017;121:1279-90. doi: 10.1161/CIRCRESAHA.117.311827.

32. Hare JM, DiFede DL, Rieger AC, Florea V, Landin AM, El-Khorazaty J, et al. Randomized Comparison of Allogeneic Versus Autologous Mesenchymal Stem Cells for Nonischemic Dilated Cardiomyopathy: POSEIDON-DCM Trial. J Am Coll Cardiol 2017;69:526-37. doi: 10.1016/j.jacc.2016.11.009.
33. Fan M, Huang Y, Chen Z, Xia Y, Chen A, Lu D, et al. Efficacy of mesenchymal stem cell therapy in systolic heart failure: a systematic review and meta-analysis. Stem Cell Res Ther 2019;10:150. doi: 10.1186/s13287-019-1258-1.
34. Afzal MR, Samanta A, Shah ZI, Jeevanantham V, Abdel-Latif A, Zuba-Surma EK, et al. Adult Bone Marrow Cell Therapy for Ischemic Heart Disease: Evidence and Insights From Randomized Controlled Trials. Circ Res 2015;117:558-75. doi: 10.1161/CIRCRESAHA.114.304792.
35. Raval AN, Johnston PV, Duckers HJ, Cook TD, Traverse JH, Altman PA, et al. Point of care, bone marrow mononuclear cell therapy in ischemic heart failure patients personalized for cell potency: 12-month feasibility results from CardiAMP heart failure roll-in cohort. Int J Cardiol 2021;326:131-8. doi: 10.1016/j.ijcard.2020.10.043.
36. Ahmad FJ. Regenerative Medicine-an Emerging Therapy in Pakistan. Asian J Allied Health Sci 2021;5:e828. doi: 10.52229/ajahs.v0i0.828.
37. Shamsi Ts, Hashmi K, Adil S, Ahmad P, Irfan M, Raza S, et al. The stem cell transplant program in Pakistan--the first decade. Bone Marrow Transplant 2008;42(Suppl 1):s114-17. doi: 10.1038/bmt.2008.137.
38. Zahra SA, Muzavir SR, Ashraf S, Ahmad A. Stem cell research in pakistan; past, present and future. Int J Stem Cells 2015;8:1-8. doi: 10.15283/ijsc.2015.8.1.1.
39. Nasr V. Forces of Fortune: The Rise of the New Muslim Middle Class and What It Will Mean for Our World. New York, USA: Free Press; 2009.
40. Morulaa Health Tech (P) Ltd. Stem cell research in India, A step forward. [Online] 2017 [Cited 2022 October 01]. Available from URL: https://morulaa.com/news/10080-stem-cell-research-in-india-a-step-forward/
41. Sharma A. Stem cell research in India: emerging scenario and policy concerns. Asian Biotechnol. Dev. Rev 2006;8:43-53.
42. Khan I, Ali A, Akhter MA, Naeem N, Chotani MA, Mustafa T, et al. Preconditioning of mesenchymal stem cells with 2,4-dinitrophenol improves cardiac function in infarcted rats. Life Sci 2016;162:60-9. doi: 10.1016/j.lfs.2016.08.014.
43. Haneef K, Ali A, Khan I, Naeem N, Jamall S, Salim A. Role of interleukin-7 in fusion of rat bone marrow mesenchymal stem cells with cardiomyocytes in vitro and improvement of cardiac function in vivo. Cardiovasc Ther 2018;36:e12479. doi: 10.1111/1755-5922.12479.
44. Naeem N, Haneef K, Kabir N, Iqbal H, Jamall S, Salim A. DNA methylation inhibitors, 5-azacytidine and zebularine potentiate the transdifferentiation of rat bone marrow mesenchymal stem cells into cardiomyocytes. Cardiovasc Ther 2013;31:201-9. doi: 10.1111/j.1755-5922.2012.00320.x.
45. Haneef K, Naeem N, Khan I, Iqbal H, Kabir N, Jamall S, et al. Conditioned medium enhances the fusion capability of rat bone marrow mesenchymal stem cells and cardiomyocytes. Mol Biol Rep 2014;41:3099-112. doi: 10.1007/s11033-014-3170-1.
46. Khan I, Ali A, Akhter MA, Naeem N, Chotani MA, Iqbal H, et al. Epac-Rap1-activated mesenchymal stem cells improve cardiac function in rat model of myocardial infarction. Cardiovasc Ther 2017;35. doi: 10.1111/1755-5922.12248.
47. Ali SR, Ahmad W, Naeem N, Salim A, Khan I. Small molecule 2'-deoxycytidine differentiates human umbilical cord-derived MSCs into cardiac progenitors in vitro and their in vivo xeno-transplantation improves cardiac function. Mol Cell Biochem 2020;470:99-113. doi: 10.1007/s11010-020-03750-6.
48. Mirza A, Khan I, Qazi RE, Salim A, Husain M, Herzig JW. Role of Wnt/β-catenin pathway in cardiac lineage commitment of human umbilical cord mesenchymal stem cells by zebularine and 2'-deoxycytidine. Tissue Cell 2022;77:101850. doi: 10.1016/j.tice.2022.101850.
49. Nuri MM, Hafeez S. Autologous bone marrow stem cell transplant in acute myocardial infarction. J Pak Med Assoc 2012;62:2-6.
50. Nuri MM, Hafeez S. Intracoronary administration of autologous bone marrow stem cell transplant in myocardial infarction. J Pak Med Assoc 2011;61:3-5.
51. Shah VK, Shalia KK. Stem Cell Therapy in Acute Myocardial Infarction: A Pot of Gold or Pandora's Box. Stem Cells Int 2011;2011:536758. doi: 10.4061/2011/536758.
52. Dajani R, Jiwani B, Nanji A, Zoloth L, Ghaly M, İlkılıç İ, et al. Diversifying stem cell debates: Including Muslim contexts and perspectives. Stem Cell Reports 2022;17:1019-22. doi: 10.1016/j.stemcr.2022.03.008.
53. Jeon K-H. Current concepts in stem cell therapy for cardiovascular diseases: what we know and don't know. Hanyang Med Rev 2015;35:242-9. Doi: 10.7599/hmr.2015.35.4.242.