

Heart valve treatment in rheumatic heart disease and plausible role of stem cell therapy

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ABSTRACT

Rheumatic heart disease (RHD) is a global health concern and is a neglected disease relative to its prevalence in developing nations. RHD is a result of recurrent ARF episodes and the abnormal immune response against the host proteins. The primary and secondary interventions are highly recommended for patients with ARF but the patients with a confirmed diagnosis and chronic case of RHD undergo either valve repair or depending on the severity of the cases. According to the reports, surgical intervention has been the mainstay in the treatment of chronic cases of rheumatic heart disease. The fundamental issue with the current treatment strategy is the lack of fast-paced degradation due to the lack of self-renewing cells. The promising solution to this challenge can be the tissue-engineered cardiac valves by combining stem cells and biomaterials. Although tissue engineering has been explored for valve repair and replacement in severe cardiac disease, this strategy has not been studied and explored in RHD. In this review, we have discussed the plausible role of stem cells and tissue-engineered cardiac valves in the treatment of RHD.

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INTRODUCTION

Acute rheumatic fever (ARF) results from an immunological reaction to pharyngitis brought on by infection with *Streptococcus pyogenes*, the group A streptococcus (GAS) species. Joint discomfort, swelling, cardiac valve regurgitation with a chance of subsequent heart failure, chorea, skin and subcutaneous manifestations, and fever are all manifestations of the sickness that results from acute rheumatic fever (ARF). Rheumatic heart disease is the term used to describe the long-term harm that ARF may cause to the heart valves. This harm might come from a single, severe episode or numerous recurrent occurrences of the illness ARF ¹.

1. Prevalence and risk factors of rheumatic heart disease

1.1. Epidemiology

Although RF and RHD are uncommon in developed nations, they continue to pose serious public health issues for children and young people in underdeveloped nations. In 2019, there were approximately 2.79 million RHD incidents worldwide, an increase of 49.70 percent since 1990 ². Additionally, it is thought to be responsible for 3,06,000 deaths worldwide, with a median age of 28.7 years. It appears that RHD mostly affects younger individuals ³. The age group 10 to 14 years had the greatest rate of RHD incidents in 2019, while the 50 to 54 age group was the only one with declining percentage due to changes in the number of cases between 1990 and 2019 ⁴. RHD has the highest mortality rates in South Asia, Oceania, and sub-Saharan Africa. Even while the age-standardized prevalence has increased much more slowly, demonstrating that young, growing populations predominate, the prevalence of RHD worldwide has continued to climb each year. The prevalence of RHD has increased more rapidly than its incidence rate, which indicates a decrease in early death. Notably, since 1996, India has continuously outperformed the world average for the number of RHD cases and deaths. However, the age-standardized RHD mortality rate was found to be lowered from 9.2 in 1990 to 4.8 in 2015 ^{2,5}.

1.2. Risk factors

The main risk factors for RHD are a lack of access to antibiotics, crowded living conditions, and inadequate cleanliness. The Middle East, Africa's sub-Saharan region, the Indian subcontinent, and some parts of South America all have higher rates of it. Oceania has experienced an increase in frequency, particularly among the native populations of New Zealand and Australia. National rates have decreased because of better living standards in transitional countries like China and Russia. However, the poorest segments in those countries, including the indigenous communities there, continue to have high rates of RHD ^{2,6,7}.

2. Molecular and antigenic similarities

The primary consequence of rheumatic fever (RF) is rheumatic heart disease (RHD), which strikes children (3–19 years old) 4–8 weeks after the initial acute RF (ARF) episode. In people with a genetic vulnerability, the condition is brought on by autoimmune responses caused by an untreated *S. pyogenes* throat infection that causes significant valvular damage ⁸.

It has been documented that the streptococcal M protein and several cardiac proteins have several molecular similarities (mimicry), which causes immune-mediated damage to cardiac tissue and serve as the foundation for ARF. The non-cardiac symptoms of ARF are due to molecular mimicry in other tissues like synovium (joints) and nervous tissue. Group A Streptococcus (GAS) strains that cause rheumatoid arthritis (RA), genetically vulnerable people, and an abnormal host immune response are attributable to the pathophysiology of RHD ⁹.

3. Pathophysiology

The underlying mechanism RHD is primarily an immunological reaction, characterized by cellular and humoral components, triggered by exposure to *Streptococcus pyogenes*, commonly following a throat infection ¹⁰. The pathophysiology of RHD is thought to be based on the "Rheumatogenic Triad" which speculates that an exposure to a virulent strain of group A streptococcus, a genetic predisposition in the host, an aberrant immune response, molecular mimicry, and an atypical immune system are the fundamental factors that lead to the development of RHD ^{11,12}.

The precise genetic basis for susceptibility to RHD remains elusive, with no definitive HLA haplotype or combination being consistently associated with the disease. However, recent research has highlighted the potential involvement of HLA type II molecules in the development of RHD. These molecules play a crucial role in antigen presentation to T-cell receptors and have been found to be more closely associated with an increased risk of RHD compared to class I molecules. Additionally, evidence has emerged supporting a potential autoimmune component in the development of RHD, as the interaction of antibodies against group A streptococcus with human heart preparations has been observed ¹³.

The initiation of inappropriate T-cell activation is triggered by specific HLA complexes binding to antigenic peptides ^{2,14}. This process is further exacerbated by the phenomenon of molecular mimicry between Streptococcal M protein and a variety of cardiac proteins such as cardiac myosin, tropomyosin, keratin, laminin, and vimentin. This molecular mimicry leads to the cross recognition of T-cell antigens across different patterns, highlighting the complexity of the underlying mechanism ¹⁵. As a soluble pathogen recognition receptor, MBL (mannose-binding lectin) serves as an acute phase inflammatory protein. MBL plays a significant role in innate immunity because of its capacity to connect with a variety of sugars found on the surface of pathogens. Mannose-binding lectin (MBL) has the capacity to improve the phagocytosis of pathogens and activate the complement cascade via the lectin pathway. Acute rheumatic fever is hypothesized to arise as a result of the generation of inflammatory cytokines such as IL-1 and IL-6, tumor necrosis factor (TNF), and others. TNF has been shown to be present in close vicinity to the major histocompatibility complex (MHC) area, but it is yet unknown if this linkage is connected to any other genetic variables that may increase the likelihood of acquiring the illness.

4. Rheumatic heart disease: chronic consequences

Tricuspid, pulmonic, mitral, and aortic are the four valves present in the heart. They work to prevent the backflow of blood and maintain pressure gradients thus ensuring proper working of the heart. The regurgitation of the valves causes backflow causing equalization of pressure inhibiting proper cardiovascular function. Contrarily, stenosis of the valves causes increased pressure behind the blockage and insufficient pressure ahead of the blockage. RHD is widely associated with pathological changes in the mitral valve, characterized by a combination of morphological alterations including thickening of the valve leaflets, thickening of the subvalvular

apparatus, shortening of the chordae tendineae, fusion of the commissures, calcification, and restricted leaflet mobility. These changes are the hallmarks of the disease and are frequently observed in patients with RHD. In the early phases of RHD, the most frequent valvular lesion in patients is mitral valve incompetence (subclinical RHD) ^{8,9}. In virtually all RHVD (Rheumatic Heart Valve Disease) cases, the mitral valve is damaged, with regurgitation in the early stages and stenosis in the later stages ¹⁶. Mitral stenosis often begins with a protracted period of asymptomatic behavior and is then followed by progressive dyspnea upon exercise and the presence of right heart failure and pulmonary hypertension. The typical mitral valve area is 4-6 cm² and the size of the mitral valve has been observed to be smaller than 1 cm² in size during severe mitral stenosis ¹⁷.

The progression and severity of RHD can present significant challenges in terms of surgical intervention, particularly in cases of advanced myocardial dysfunction. Unfortunately, a lack of access to adequate information and healthcare resources often results in patients seeking treatment at a late stage, particularly in remote or under-served regions. Stem cells, characterized by their ability to self-renew indefinitely and differentiate into a wide range of cell types, offer a promising avenue for treatment. These cells can be sourced from various sources such as bone marrow, placenta, tooth pulp, and adipose tissue. To meet the increasing demand for new treatment options for heart regeneration, various stem cell-based techniques for cardiac tissue engineering have been explored. The development and utilization of stem cell-based mitral valve constructs, which have the capability of growth and regeneration, hold significant potential for improving outcomes for patients suffering from RHVD. This approach offers a promising alternative for addressing the unmet needs of this patient population.

5. Treatment

5.1 Valve Surgery

RHD patients normally need surgery between the ages of 20 and 25, while in low- and middle-income countries (LMICS), about 50% of such patients show the requirement before the age of 20 ¹⁸. In Africa more than 60% of the operated cases required mechanical prosthetic valve, long-term anti-coagulant management, and follow-up ¹⁹. The main issues that have arisen with the prosthetic were, thrombosis, thromboembolism, and bleeding, and all of them were predominantly anticoagulation-related issues. A mismatch between the patient and the prosthesis can also be

problematic, especially in younger patients. To the other side, even the use of bio-prosthetic was not rewarding. Bioprosthetic mitral prosthetic valves degenerated quickly in younger patients and reproductive women, and hence the need of early reoperation ²⁰. Further, they are also more expensive than a mechanical valve. In 3-4% of patients prosthetic valve endocarditis occurred within five years of the index surgery (both mechanical or bioprosthetic valve scenarios) ²¹. Mitral valve repair is therefore desirable for the above-stated reasons, but the RHD valves get worse with time, and hence require more experience, confidence, and advanced skills to achieve a favorable operative result in view of the complex repair process ²².

While various surgical techniques are available for the treatment of RHD in younger patients, previous studies have highlighted the significant challenges presented by rheumatic mitral regurgitation, particularly in terms of repair of the mitral valve. This is due to the extensive fibrosis and distortion of the valve leaflets and sub-valvular apparatus. Despite these difficulties, experienced surgeons have reported successful repair outcomes in a substantial proportion of cases, with rates of up to 75% reported for rheumatic mitral regurgitation ²².

On the other hand, well-performed valve repair has several advantages as compared to typical valve replacement, particularly in terms of avoiding anticoagulation, which may be essential given the prevalence of illness among women who are of reproductive age. In high-volume practices and resource-constrained settings, the availability of extended operating room time may present a challenge for the surgical treatment of complex cases. Additionally, in cases where moderate or severe tricuspid regurgitation is present, it is recommended to perform tricuspid valve repair in conjunction with mitral valve surgery ²³. Minimally invasive surgery (MIS) has increasingly been utilized as an alternative to traditional open surgery, offering several advantages such as reduced cost, faster recovery, improved cosmetic outcomes, and greater comfort for patients. Therefore, the use of MIS should be considered as a viable option for patients of both mitral regurgitation and stenosis ²⁴.

5.2 Catheter-based interventions

For severe isolated rheumatic mitral stenosis balloon mitral valvuloplasty having relatively low cost can be usually performed quickly relatively safely ^{25,26}. Outcomes of surgical mitral commissurotomy and BMV have largely replaced surgery as long-term outcomes are similar ^{27,28}. In cases where recurrent mitral stenosis occurs following a previous successful balloon treatment,

repeat procedures can be a requirement which contributes to increased risk and additional cost. This can be performed even in individuals with mild concomitant mitral regurgitation. However, it should be noted that in 2-5% of such procedures, the need for urgent surgery may arise, making it imperative that surgical backup is available within the same institution ²⁹.

5.3. Stem-cell-based approach for heart valve repair

Stem cells are unspecialized human body cells. They have the ability to self-renew and can develop into any cell in an organism. Stem cells can be stimulated to differentiate into a specific cell type needed to heal, damaged or destroyed tissues. When the demand for transplantable tissues and organs exceeds the available supply, stem cells appear to be a suitable option ³⁰. Bone marrow, the placenta, tooth pulp, and adipose tissue are just a few of the places where stem cells can be extracted. Bone marrow and skin stem cells multiply and repair damaged tissues under physiological settings, but certain pathological circumstances are necessary for this process to occur in the pancreas or the heart tissue. The differentiation of stem cells into specific cell types such as fibroblasts, smooth muscle cells, cardiomyocytes, or endothelial cells can be facilitated through the manipulation of experimental conditions. This is typically achieved through the application of specific biological signals, including growth factors, changes in the redox environment, and magneto-electric stimulation. Such techniques hold the potential to provide a source of functional cells for tissue regeneration and repair ³¹.

The choice of stem cell source is a crucial determinant of the efficiency and viability of micro-engineered tissue in regenerative medicine ³². Utilizing autologous stem cells, as opposed to allogeneic stem cells, offers the benefit of immune compatibility ³³. Induced pluripotent stem cells (iPSCs) are obtained from adult cells, such as skin fibroblasts, through the application of stem cell transcription factors ³⁴. iPSCs are considered to be a favorable source for tissue engineering due to their plasticity and pluripotency ³⁵. Despite the potential of regenerative medicine to treat Rheumatic Heart Disease, conventional medical and surgical therapies remain the foundation of efforts aimed at reducing mortality, particularly in underdeveloped countries where such treatments are often cost-prohibitive

According to current estimates, around 182,000 heart valve replacement procedures are performed annually in the United States ³⁶. Contemporary biological heart valves are typically constructed

from porcine or bovine pericardium. A major challenge with these valves is their rapid degradation resulting from the absence of self-renewing cells. Tissue engineering, which involves the use of stem cells and biomaterials, holds promise as a potential solution to this problem, enabling the production of heart valves with improved longevity and functionality³⁷.

Valvar tissue engineering aims to replicate the functional and structural elements of physiological heart valves through the integration of three-dimensional extracellular scaffolds that provide mechanical support and leaflet motion, along with two key types of cells, namely valvular interstitial cells and endothelial cells, which are responsible for maintaining structural integrity and promoting vascular homeostasis, respectively. The current challenge in valvular tissue engineering is the identification of the optimal cell-scaffold combination that can ensure long-term sustainability, particularly in terms of resistance to degeneration and preservation of vascular homeostasis. Extensive research is being conducted on natural and synthetic materials that can create an ideal microenvironment for stem cell growth and differentiation to achieve this goal³⁸. The development of bioengineered heart valves employs a number of strategies, such as hydrogel-based scaffolds, 3D bioprinting, and decellularization platforms.

Emmert's prospective method of transcatheter, stem cell based TEHV implantation into the site of the aortic valve within a one-step intervention in a sheep model showed that it is most feasible. This study demonstrates that the stem cell-based TEHV technique could be the next-generation heart valve idea since its long-term functioning has been established. The study also suggests that the ideal concept for clinically applicable heart valve tissue engineering (HVTE) would include minimally invasive methods for both cell collection and valve implantation, and the notion of HVTE and transapical administration into the pulmonary location of adult sheep is technically feasible³⁹. An alternative method of valvar tissue engineering was demonstrated by Driessen-Mol et al. in which a homologous decellularized valve was employed to create a functional heart valve in sheep. The study observed the satisfactory functioning of the valve with matrix remodeling and host cell repopulation at the conclusion of a 24-week follow-up period, providing a promising indication of the potential for long-term success using this approach⁴⁰. Jolanda et al.⁴¹ used synthetic materials to exhibit an excellent heart valve design; they created an innovative supramolecular elastomer to create a fibrous valvular scaffold that allows endogenous cells to enter and build a matrix. This tissue-engineered valve demonstrated continued performance for a full

year while gradually accumulating ECM⁴¹. Stassen et al. and Mendelson et al. have undertaken a comprehensive review of the challenges involved in the development of functional, live tissue-engineered heart valves using stem cells, including the integration of these valves with native cardiac tissue to ensure long-term functionality. The review highlights the complexities and difficulties encountered in this field of research, underscoring the ongoing need for further developments in the area^{42,43}

CONCLUSION

In conclusion, it is expected that the utilization of biological porcine or bovine heart valves currently employed in the treatment of mitral valve in RHD, which might eventually be superseded by tissue-engineered heart valves tailored to the individual patient, as advancements in both RHD research, and stem cell technology continue to evolve. This holds the potential to significantly improve the outcomes and longevity of RHD treatment.

Declaration of conflicting interests

The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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