Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 3776-3785 | ISSN:2251-6727

Cardiovascular Renaissance: Unveiling the Promise of Hydrogel Tissue Engineering

Uppuluri Varuna Naga Venkata Arjun M. Pharm[1*], Santhosh Krishnamoorthy B. Pharm[2], Sandhiya Saravanan B. Pharm[3], Sanjay Rajendran B. Pharm[4]

[1*]Assistant Professor, Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS)

[2,3,4]Department of pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai-600117.

(Received: 17 February 2024 Revised: 04 April Accepted: 30 April)

KEYWORDS

Cardiac tissue defect, Hydrogel, Tissue Engineering, Polymers, and Bioactive molecules.

ABSTRACT:

Hydrogel-based cardiac tissue engineering, a promising avenue for addressing cardiovascular disease challenges, can potentially revolutionize cardiovascular medicine. This review explores the diverse aspects of hydrogel designing, fabrication, and its applications in cardiac tissue engineering. From the intricate interplay of cells and hydrogels to optimizing mechanical and structural properties, each aspect contributes to developing functional cardiac constructs with the potential for clinical translation. While challenges such as achieving integration with the host tissue and ensuring long-term stability exist, the future perspectives discussed in this review offer a glimpse into the exciting possibilities of advancing the field toward personalized therapeutic interventions. Hydrogel-based cardiac tissue engineering represents a transformative approach that could significantly improve patient outcomes and advance cardiovascular medicine.

1. Introduction

Cardiovascular diseases (CVDs) are a significant health burden worldwide. Conditions such as heart failure and myocardial infarction (MI) result in significant morbidity and mortality. Conventional treatments for these conditions, including pharmacotherapy and surgical interventions, often provide symptomatic relief but fail to address the underlying cause of tissue damage or degeneration. Consequently, there is a pressing need for innovative therapeutic strategies that can restore cardiac function and improve patient outcomes. Cardiac tissue engineering is an emerging approach to regenerate damaged myocardium and promote functional recovery, promising to address the limitations of current treatments. At its core, cardiac tissue engineering seeks to harness the principles of biomaterials science, cellular biology, and bioengineering to develop bioengineered constructs capable of mimicking the structure and function of native cardiac tissue. By integrating biocompatible scaffolds, cells, and bioactive molecules, tissue engineers aim to create three-dimensional (3D) cardiac constructs that can replace or repair damaged myocardium and restore normal heart function.[1]

The design and development of biomaterial scaffolds play a crucial role in cardiac tissue engineering, providing the architectural framework for cell attachment, proliferation, and differentiation. Among the various biomaterials explored for this purpose, polymeric hydrogels stand out due to their unique properties and versatility. Hydrogels, three-dimensional networks of hydrophilic polymer chains, can retain large amounts of water while maintaining structural integrity. These materials offer several advantages for cardiac tissue engineering, including tunable mechanical properties, biocompatibility, and the ability to encapsulate bioactive molecules for controlled release. Significant strides have been made in designing and optimizing polymeric hydrogels for cardiac tissue engineering applications in recent years. Researchers have explored a variety of

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 3776-3785 | ISSN:2251-6727

synthetic and natural polymers and hybrid materials to tailor the physical, mechanical, and biochemical properties of hydrogel scaffolds for specific therapeutic goals. Moreover, advancements in fabrication techniques, such as 3D bioprinting and microfluidic patterning, have enabled the precise control of scaffold architecture and cellular organization, further enhancing the functionality of engineered cardiac tissues. These advancements underscore the progress and potential in polymeric hydrogel design for cardiac tissue engineering, inspiring further exploration and innovation.[2]

Despite these advancements, several challenges remain to be addressed before hydrogel-based cardiac constructs can be translated into clinical therapies. These include optimizing hydrogel scaffolds' biocompatibility and degradation kinetics, improving cell survival and integration within the engineered tissue, and promoting vascularization to ensure adequate nutrient supply and waste removal. Additionally, hydrogel-based therapies' long-term safety and efficacy must be rigorously evaluated in preclinical models and clinical trials. In this review, we aim to provide a comprehensive overview of the role of polymeric hydrogels in cardiac tissue engineering, encompassing their design principles, fabrication techniques, properties, and applications. We seek to contribute to the ongoing efforts to develop effective cardiac repair and regeneration strategies by critically examining the field's current state and highlighting recent advancements and challenges. Ultimately, polymeric hydrogel-based approaches will shape the future of cardiovascular medicine and offer new hope for patients with debilitating cardiac conditions.[3]

2. Importance of Biomaterials in Cardiac Regeneration

Biomaterials, the backbone of cardiac regeneration, play a pivotal role by providing the necessary support and cues for cells' growth, organization, and function within damaged cardiac tissue. Unlike traditional therapies that merely manage symptoms or rely on organ transplantation, biomaterial-based approaches can promote tissue repair and regeneration by creating a conducive microenvironment for endogenous or exogenously delivered cells. The selection of appropriate biomaterials is crucial as they can influence various aspects of tissue engineering, including scaffold architecture, mechanical properties, degradation kinetics, and biological interactions. This underscores the importance of your work in the field of biomaterials in cardiac regeneration. One key advantage of biomaterials in cardiac regeneration is their ability to mimic the extracellular matrix (ECM) – the complex network of proteins and polysaccharides that provides structural support and biochemical cues to cells in native tissues. By recapitulating the native ECM's composition and architecture, biomaterial scaffolds can guide cell behavior, including adhesion, migration, proliferation, and differentiation. For example, natural polymers such as collagen, fibrin, and gelatin closely resemble components of the cardiac ECM and have been extensively used to fabricate scaffolds for cardiac tissue engineering. These biomimetic scaffolds promote cell attachment and organization, facilitating the formation of functional cardiac tissue constructs.[4]

Another vital aspect of biomaterials in cardiac regeneration is their ability to deliver bioactive molecules, such as growth factors, cytokines, and small molecules, in a spatiotemporally controlled manner. These bioactive cues can modulate cellular responses, including proliferation, differentiation, and angiogenesis, to enhance tissue repair and regeneration. For instance, biomaterial-based delivery systems can protect sensitive bioactive molecules from degradation, prolong their release kinetics, and target specific cell populations within the injured myocardium. This targeted delivery of bioactive molecules can promote cardiomyocyte survival, stimulate angiogenesis, and modulate inflammatory responses, thereby promoting tissue regeneration and functional recovery. Furthermore, biomaterial scaffolds provide mechanical support to the injured myocardium, preventing adverse remodeling and promoting tissue integration and maturation. The mechanical properties of biomaterials, such as stiffness, elasticity, and viscoelasticity, can be tailored to match those of native cardiac tissue, thereby minimizing mechanical mismatch and enhancing cell-matrix interactions. For instance, polymeric hydrogels with tunable mechanical properties have been engineered to mimic the elasticity of native myocardium, allowing them to withstand cardiac mechanical forces while

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 3776-3785 | ISSN:2251-6727

providing a supportive matrix for cell growth and tissue formation.[5]

In addition to their role as structural and biochemical cues, biomaterials also serve as carriers for cells in cardiac regeneration strategies. Various cell types, including cardiomyocytes, endothelial cells, and stem cells, have been encapsulated or seeded onto biomaterial scaffolds for transplantation into the injured myocardium. Biomaterial carriers protect transplanted cells from immune rejection, promote their retention and engraftment within the host tissue, and provide a supportive microenvironment for their survival, proliferation, and differentiation. By enhancing cell delivery and integration, biomaterial-based approaches can augment the therapeutic efficacy of cell-based therapies for cardiac regeneration. Biomaterials are multifaceted in cardiac regeneration as structural scaffolds, biochemical reservoirs, mechanical supports, and cell carriers. Their versatility and tunability make them indispensable tools for designing innovative strategies to repair and regenerate damaged myocardium, offering new hope for patients with cardiovascular diseases. By harnessing the unique properties of biomaterials, researchers can continue to advance the field of cardiac tissue engineering and develop clinically viable therapies for improving heart function and patient outcomes.[6]

3. Design Considerations for Cardiac Tissue Engineering Hydrogels

The design of hydrogel scaffolds for cardiac tissue engineering requires careful consideration of various factors to ensure optimal performance and therapeutic efficacy. Several key design parameters, including biomaterial selection, scaffold architecture, mechanical properties, and bioactive molecule incorporation, play critical roles in determining the success of hydrogel-based approaches for repairing and regenerating damaged myocardium. Biomaterial selection is fundamental to hydrogel design, as it dictates the scaffold's biocompatibility, degradation kinetics, and biochemical properties. Natural polymers, such as collagen, fibrin, and hyaluronic acid, are commonly used in cardiac tissue engineering due to their inherent biocompatibility and resemblance to the native extracellular matrix (ECM). For example, collagen-based hydrogels closely mimic the structural and biochemical cues present in native cardiac tissue, promoting cell adhesion, migration, and differentiation. Synthetic polymers, such as polyethylene glycol (PEG) and poly(lactic-co-glycolic acid) (PLGA), offer advantages in terms of tunable mechanical properties and degradation kinetics, allowing for precise control over scaffold design and performance. Scaffold architecture is another crucial design consideration, as it influences cellular behavior, tissue organization, and mechanical stability. Hydrogel scaffolds can be fabricated using various techniques, including physical crosslinking, chemical crosslinking, and 3D bioprinting, to create structures with controlled pore size, interconnectivity, and geometry. For instance, electrospinning and microfabrication techniques enable the fabrication of hydrogel scaffolds with precise spatial organization and hierarchical structures, resembling the complexity of native cardiac tissue. These advanced scaffold architectures promote cell infiltration, vascularization, and tissue integration, enhancing the functional properties of engineered cardiac constructs.[7]

Mechanical properties are paramount in hydrogel design, as they influence cell-matrix interactions, tissue remodeling, and overall scaffold performance. The mechanical properties of hydrogels can be tuned to match those of native cardiac tissue by adjusting parameters such as polymer concentration, crosslinking density, and swelling ratio. For example, hydrogels with stiffnesses in the 10-20 kPa range closely resemble the mechanical properties of a healthy myocardium, promoting cardiomyocyte alignment, contractility, and maturation. Conversely, hydrogels with higher stiffnesses can mimic the mechanical properties of fibrotic or diseased myocardium, providing insights into pathological processes and potential therapeutic interventions. Incorporation of bioactive molecules is another essential aspect of hydrogel design, as it enables the controlled release of growth factors, cytokines, and small molecules to modulate cellular behavior and tissue development. Bioactive molecules can be encapsulated within hydrogel matrices or tethered to polymer chains to achieve spatiotemporal control over their release kinetics. For example, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) can be incorporated into hydrogel scaffolds to stimulate angiogenesis and improve vascularization within

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 3776-3785 | ISSN:2251-6727

engineered cardiac tissues. Similarly, small molecules such as microRNAs and small interfering RNAs (siRNAs) can be delivered via hydrogel carriers to regulate gene expression and cellular responses, offering potential therapeutic benefits for cardiac repair and regeneration. In summary, the design of hydrogel scaffolds for cardiac tissue engineering requires careful consideration of biomaterial selection, scaffold architecture, mechanical properties, and bioactive molecule incorporation. By addressing these design considerations, researchers can develop hydrogel-based approaches that mimic the native cardiac microenvironment, promote cell survival and function, and enhance tissue regeneration to treat cardiovascular diseases.[8]

4. Synthesis and Fabrication Techniques of Hydrogels

Hydrogels can be synthesized and fabricated using various techniques, each offering unique advantages regarding control over scaffold properties, structure, and functionality. These techniques range from conventional methods, such as physical and chemical crosslinking, to advanced approaches, including 3D bioprinting and microfluidic patterning, enabling the precise engineering of hydrogel scaffolds for cardiac tissue engineering applications. One of the most common methods for hydrogel synthesis is physical crosslinking, which involves the formation of physical bonds between polymer chains through non-covalent interactions, such as hydrogen bonding, electrostatic interactions, or hydrophobic interactions. For example, temperature-responsive hydrogels based on poly(N-isopropyl acrylamide) (PNIPAAm) undergo reversible sol-gel transitions in response to changes in temperature, making them suitable for minimally invasive injectable therapies. Similarly, self-assembling peptide hydrogels can be formed via molecular self-assembly of peptide amphiphiles, offering precise control over scaffold structure and mechanics. Chemical crosslinking represents another common approach for hydrogel synthesis, involving the formation of covalent bonds between polymer chains through chemical reactions, such as photopolymerization, enzymatic crosslinking, or click chemistry. Photopolymerization, for instance, relies on photoactive molecules, such as photoinitiators and photocrosslinkers, to initiate polymerization upon exposure to light, allowing for spatial and temporal control over hydrogel formation. Enzymatic crosslinking, on the other hand, utilizes enzymes, such as transglutaminase or tyrosinase, to catalyze the formation of covalent bonds between polymer chains, offering biocompatible and cytocompatible hydrogel synthesis routes.[9]

In recent years, 3D bioprinting has emerged as a powerful technique for fabricating complex hydrogel structures with precise spatial control over cell and biomaterial deposition. 3D bioprinters deposit bioinks, consisting of cells suspended in hydrogel precursors, layer by layer to create 3D constructs with defined architectures and compositions. For example, cardiac patches composed of alginate-based bioinks containing cardiomyocytes, endothelial cells, and supporting cells have been fabricated using 3D bioprinting, demonstrating the potential of this technology for engineering functional cardiac tissues. Microfluidic patterning represents another advanced fabrication technique for creating hydrogel scaffolds with precise spatial organization and control over scaffold properties. Microfluidic devices generate controlled flows of hydrogel precursors, allowing for the precise patterning of hydrogel structures at the microscale. For instance, microfluidic channels can pattern hydrogel scaffolds with spatially defined chemical gradients or cell-laden compartments, enabling the study of cell-cell interactions and tissue morphogenesis in vitro. Overall, hydrogel synthesis and fabrication techniques continue to evolve, offering increasingly sophisticated approaches for engineering biomimetic scaffolds for cardiac tissue engineering. By harnessing these techniques, researchers can create hydrogel-based constructs that closely mimic the structure and function of native cardiac tissue, providing new opportunities for treating cardiovascular diseases.[10]

5. Biocompatibility and Biodegradability of Polymeric Hydrogels

The biocompatibility and biodegradability of polymeric hydrogels are critical considerations in their application for cardiac tissue engineering, as these properties influence interactions with host tissues, cellular responses, and long-term outcomes. Polymeric hydrogels

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 3776-3785 | ISSN:2251-6727

must be compatible with biological systems to minimize adverse immune reactions, inflammation, and cytotoxicity while exhibiting controlled degradation to support tissue remodeling and regeneration. Several factors contribute to the biocompatibility of polymeric hydrogels, including their chemical composition, surface properties, and degradation products. Natural polymers, such as collagen, gelatin, and hyaluronic acid, are inherently biocompatible due to their resemblance to extracellular matrix components (ECM). These polymers support cell adhesion, migration, and proliferation, facilitating tissue integration and regeneration. Synthetic polymers, such as polyethylene glycol (PEG) and poly(lactic-co-glycolic acid) (PLGA), can also be engineered to enhance biocompatibility by modifying their surface chemistry or incorporating cell-adhesive motifs.[11]

Moreover, the degradation behavior of polymeric hydrogels plays a crucial role in determining their long-term biocompatibility and tissue response. Hydrogels can degrade via various mechanisms, including hydrolysis, enzymatic cleavage, and surface erosion, depending on their chemical composition and structure. Biodegradable hydrogels, such as those based on PLGA or poly(lactic acid) (PLA), undergo gradual degradation into biocompatible byproducts, such as water, carbon dioxide, and metabolizable monomers, which are safely metabolized or excreted from the body. Examples of biocompatible and biodegradable polymeric hydrogels used in cardiac tissue engineering include injectable hydrogels based on hyaluronic acid derivatives, such as hyaluronic acid methacrylate (HAMA) or thiolated hyaluronic acid, which form stable hydrogel networks in situ upon cross-linking. These hydrogels have been utilized for minimally invasive delivery of cells and bioactive molecules into the myocardium, promoting tissue repair and regeneration following myocardial infarction (MI). Similarly, poly(ethylene glycol) diacrylate (PEGDA)-based hydrogels, crosslinked via photopolymerization, offer tunable mechanical properties and degradation kinetics, making them suitable for engineering cardiac patches and scaffolds with tailored properties for myocardial repair.[12]

Furthermore, natural polymers such as gelatin and fibrin have been extensively used in cardiac tissue engineering due to their biocompatibility and ability to support cell growth and tissue formation. For example, fibrin-based hydrogels, formed by enzymatic crosslinking of fibrinogen and thrombin, have encapsulated cardiomyocytes and endothelial cells to fabricate engineered cardiac tissues with improved vascularization and contractile function. Overall, the biocompatibility and biodegradability of polymeric hydrogels are essential considerations in their application for cardiac tissue engineering. By selecting appropriate biomaterials, optimizing scaffold properties, and controlling degradation kinetics, researchers can develop hydrogel-based approaches that promote tissue regeneration and functional recovery following cardiac injury, offering new hope for patients with cardiovascular diseases.[13]

6. Mechanical and Structural Properties of Hydrogels for Mimicking Cardiac Tissue

Hydrogels' mechanical and structural properties are crucial in cardiac tissue engineering as they influence cell behavior, tissue organization, and overall scaffold performance. Mimicking the mechanical properties of native cardiac tissue is essential for promoting cell-matrix interactions, supporting tissue development, and enhancing functional outcomes in engineered cardiac constructs. Several fundamental mechanical and structural properties, including stiffness, elasticity, anisotropy, and hierarchical organization, must be carefully considered when designing hydrogel scaffolds that closely resemble the native myocardium. Stiffness, or the resistance of a material to deformation, is a critical mechanical property that significantly impacts cell behavior and tissue function. The myocardium exhibits a stiffness range of approximately 10-20 kPa in healthy adult hearts, while pathological conditions, such as fibrosis or myocardial infarction, can alter tissue stiffness. Therefore, hydrogel scaffolds for cardiac tissue engineering should ideally mimic the mechanical properties of healthy or diseased myocardium to promote cell alignment, contractility, and maturation. For example, polyacrylamide hydrogels with tunable stiffness have been used to investigate the effects of substrate stiffness on cardiomyocyte behavior and contractile function, providing insights into the mechanobiology of cardiac tissue development and disease progression.[14]

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 3776-3785 | ISSN:2251-6727

Elasticity, or the ability of a material to return to its original shape after deformation, is another important mechanical property for mimicking cardiac tissue behavior. The myocardium exhibits viscoelastic behavior, meaning it can deform and recover in response to mechanical forces, such as contraction and relaxation. Hydrogel scaffolds with elastic properties similar to native cardiac tissue can enhance cell-matrix interactions, facilitate cell alignment, and promote tissue contractility. For instance, polyethylene glycol (PEG)--based hydrogels with tunable elasticity have been engineered to mimic the viscoelastic properties of the myocardium, supporting cardiomyocyte alignment and contractile function in vitro. Anisotropy, or the directional dependence of mechanical properties, is a characteristic feature of native cardiac tissue, where cardiomyocytes align along preferential directions to facilitate synchronous contraction and electrical conduction. Hydrogel scaffolds with anisotropic mechanical properties can guide cell alignment and organization, recapitulating the structural and functional architecture of native myocardium. For example, electrospun fibrous scaffolds from natural or synthetic polymers can provide topographical cues that promote cardiomyocyte alignment and anisotropic tissue formation, enhancing contractile function and electrical propagation in engineered cardiac constructs. Furthermore, the hierarchical organization of hydrogel scaffolds, from the nanoscale to the macroscale, is critical for mimicking the complex architecture of native cardiac tissue. Hierarchical structures, such as aligned nanofibers, microgrooves, or macroscopic patterns, can guide cell behavior, tissue organization, and functional integration in engineered cardiac constructs. For instance, micro-engineered hydrogel scaffolds with precisely controlled microscale features have promoted cardiomyocyte alignment and tissue assembly, enhancing contractile function and electrical coupling in vitro and in vivo. In summary, hydrogels' mechanical and structural properties play essential roles in mimicking the complex architecture and function of native cardiac tissue. By engineering hydrogel scaffolds with appropriate stiffness, elasticity, anisotropy, and hierarchical organization, researchers can create biomimetic platforms for studying cardiac development, modeling disease pathogenesis, and developing regenerative heart repair and regeneration therapies (Figure 1).[15]

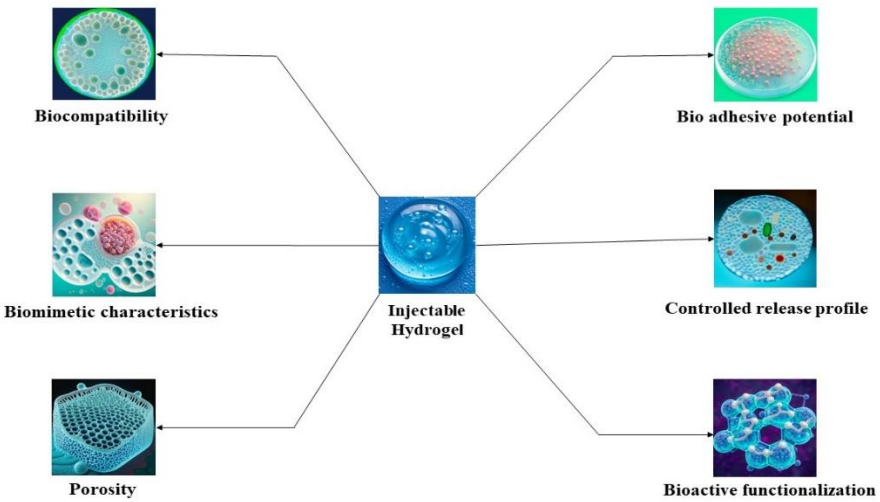

Figure 1. Represents the characteristics of the injectable hydrogels that plays a significant role in the cardiac regeneration.

7. Cell-Hydrogel Interactions and Cell Fate in Cardiac Tissue Engineering

Cell-hydrogel interactions play a crucial role in cardiac tissue engineering by influencing cell behavior, fate, and, ultimately, the functional properties of engineered cardiac constructs. Various factors, including biochemical cues, mechanical properties, and scaffold architecture, mediate cell interactions and hydrogel scaffolds. These collectively determine cell adhesion, proliferation, differentiation, and tissue formation within the engineered constructs. One key aspect of cell-

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 3776-3785 | ISSN:2251-6727

hydrogel interactions is the presentation of biochemical cues within the hydrogel matrix that regulate cellular behavior and fate. Hydrogel scaffolds can be functionalized with bioactive molecules, such as growth factors, cytokines, and extracellular matrix (ECM) proteins, to mimic the native cardiac microenvironment and promote specific cellular responses. For example, hydrogels functionalized with cardiomyocyte-specific ECM proteins, such as laminin or fibronectin, can enhance cardiomyocyte adhesion, alignment, and maturation within the scaffold. Similarly, the controlled release of growth factors, such as insulin-like growth factor (IGF) or transforming growth factor-beta (TGF-β), from hydrogel matrices can stimulate cardiomyocyte proliferation, differentiation, and tissue remodeling, leading to improved functional outcomes in engineered cardiac constructs. Moreover, the mechanical properties of hydrogel scaffolds play a critical role in modulating cell behavior and fate in cardiac tissue engineering. Hydrogels' stiffness, elasticity, and viscoelasticity can influence cellular mechanotransduction pathways, leading to cell morphology, gene expression, and tissue phenotype changes. For instance, hydrogels with stiffnesses similar to native cardiac tissue can promote cardiomyocyte alignment, sarcomere organization, and contractile function. In contrast, hydrogels with higher stiffness may induce fibroblast activation and ECM remodeling. By tuning the mechanical properties of hydrogel scaffolds, researchers can modulate cellular responses and guide cell fate toward desired phenotypes in engineered cardiac tissues.[16]

Furthermore, scaffold architecture is crucial in cell-hydrogel interactions and cell fate determination in cardiac tissue engineering. Hydrogel scaffolds can be engineered to mimic the hierarchical organization of native cardiac tissue, providing spatial cues that guide cell alignment, organization, and tissue assembly. For example, micro-engineered hydrogel scaffolds with predefined microscale features, such as grooves, channels, or patterns, can promote cardiomyocyte alignment and anisotropic tissue formation, enhancing contractile function and electrical coupling within the engineered constructs. Similarly, 3D bioprinting techniques enable the fabrication of complex hydrogel structures with precise spatial control over cell and biomaterial deposition, facilitating the creation of multicellular cardiac tissues with controlled architecture and composition. Cell-hydrogel interactions play a pivotal role in cardiac tissue engineering by modulating cell behavior, fate, and tissue development within engineered constructs. By engineering hydrogel scaffolds with appropriate biochemical cues, mechanical properties, and scaffold architecture, researchers can create biomimetic platforms for studying cardiac biology, modeling disease pathology, and developing regenerative therapies for heart repair and regeneration (Figure 2).[17]

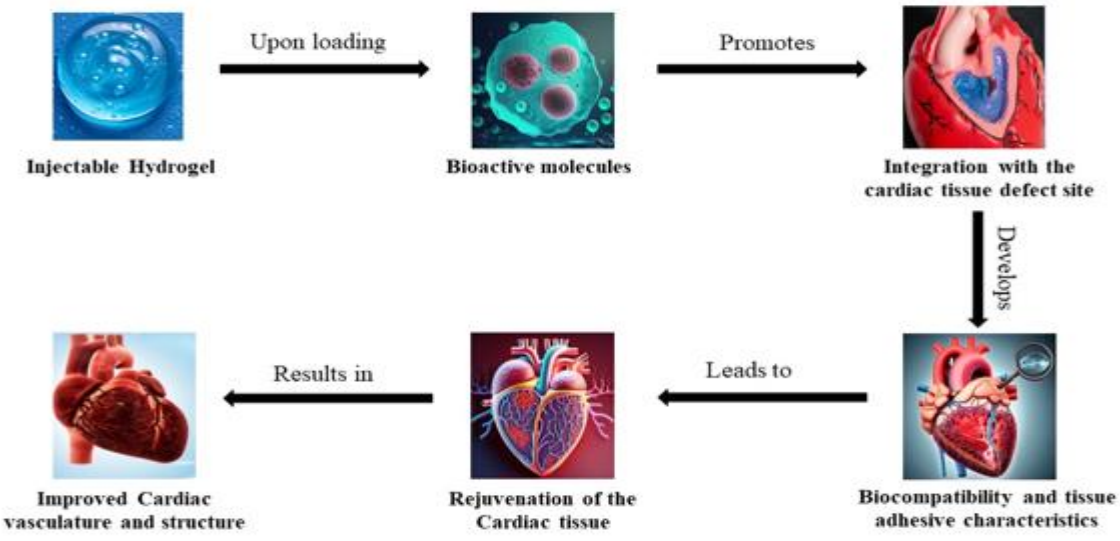

Figure 2. Depicts the importance of the injectable hydrogels in cardiac tissue regeneration.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 3776-3785 | ISSN:2251-6727

8. Challenges and Future Directions in Hydrogel-Based Cardiac Tissue Engineering

Despite significant advancements, hydrogel-based cardiac tissue engineering still faces several challenges that must be addressed to translate laboratory research into clinical applications successfully. These challenges range from scaffold design and functionalization to integration with host tissues and long-term performance. Overcoming these hurdles requires interdisciplinary collaboration, innovative strategies, and refinement of continuous biomaterials and fabrication techniques. One of the primary challenges in hydrogel-based cardiac tissue engineering is achieving functional integration with the host myocardium upon transplantation. While hydrogel scaffolds can support the growth and organization of cardiac cells in vitro, promoting their engraftment and integration within the native tissue remains a significant hurdle. Enhancing integration includes improving scaffold-cell interactions, promoting vascularization, and modulating immune responses to prevent rejection and promote tissue remodeling. For example, incorporating cell-adhesive motifs or angiogenic factors within hydrogel scaffolds can enhance cell retention and vascular network formation, facilitating nutrient supply and waste removal within engineered cardiac tissues. Another challenge is recapitulating the complex architecture and electromechanical properties of native cardiac tissue within hydrogel constructs. While hydrogels can mimic certain aspects of the myocardium, such as stiffness, elasticity, and biochemical composition, replicating the intricate cellular organization and electrical coupling in native tissue remains challenging. Advanced fabrication techniques, such as 3D bioprinting and microfluidic patterning, offer promising avenues for creating multicellular cardiac tissues with defined architectures and functional properties. By precisely controlling cell deposition, scaffold structure, and electrical stimulation, researchers can develop engineered cardiac constructs that closely resemble the native myocardium in terms of morphology, function, and electrophysiology.[18]

Moreover, achieving long-term stability and functionality of hydrogel-based cardiac constructs remains a significant hurdle for clinical translation. Hydrogel scaffolds often degrade over time, leading to loss of mechanical integrity, cell viability, and tissue function. Strategies to improve scaffold durability include optimizing degradation kinetics, enhancing crosslinking density, and incorporating reinforcement materials, such as nanofibers or nanoparticles, to enhance mechanical strength and stability. Additionally, developing non-invasive monitoring techniques, such as imaging modalities or biosensors, can enable real-time assessment of scaffold performance and tissue integration in vivo, facilitating the development of personalized therapeutic strategies and improving patient outcomes. In the future, advances in biomaterials science, stem cell biology, and tissue engineering techniques hold great promise for overcoming these challenges and advancing hydrogel-based cardiac tissue engineering toward clinical applications. By addressing critical issues related to scaffold design, functionalization, integration, and long-term performance, researchers can develop innovative therapies for repairing and regenerating damaged myocardium, ultimately improving the prognosis and quality of life for patients with cardiovascular diseases.[19]

9. Conclusion and Perspectives

In conclusion, hydrogel-based cardiac tissue engineering holds great promise for addressing the limitations of current treatments for cardiovascular diseases and advancing the field toward clinically viable solutions for heart repair and regeneration. Through interdisciplinary collaboration and innovative research efforts, significant progress has been made in developing biomimetic hydrogel scaffolds that support cardiac cell growth, organization, and function and promote tissue regeneration. These advancements have led to developing engineered cardiac constructs with improved structural, mechanical, and functional properties, offering new hope for patients with heart failure, myocardial infarction, and other cardiac conditions. Looking ahead, several essential perspectives and directions can further propel the hydrogel-based cardiac tissue engineering field toward clinical translation and widespread adoption. First, continued optimization of hydrogel scaffolds, including their mechanical properties, biochemical composition, and degradation kinetics, is essential to enhance their compatibility with host tissues, promote tissue integration, and improve long-term performance. Second, advancements in stem

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 3776-3785 | ISSN:2251-6727

cell biology and tissue engineering techniques, such as 3D bioprinting and organ-on-a-chip platforms, offer exciting opportunities for creating more complex and functional cardiac tissues that better mimic the native myocardium. Additionally, developing non-invasive monitoring techniques, such as imaging modalities and biosensors, can provide valuable insights into scaffold performance, tissue maturation, and therapeutic outcomes in vivo, facilitating the translation of hydrogel-based cardiac therapies from bench to bedside. Furthermore, addressing regulatory and translational challenges, such as scalability, standardization, and safety, is critical to facilitating the clinical translation and commercialization of hydrogel-based cardiac therapies, ultimately benefiting patients worldwide. In conclusion, hydrogel-based cardiac tissue engineering represents a promising approach for developing innovative therapies to repair and regenerate damaged myocardium, improve heart function, and enhance patient outcomes in cardiovascular medicine. By harnessing the unique properties of hydrogel scaffolds and advancing our understanding of cardiac biology and tissue engineering principles, researchers can continue pushing the boundaries of what is possible in cardiac regeneration and contribute to developing transformative therapies for cardiovascular diseases.

Acknowledgments: The authors are thankful to Vels Institute of Science, Technology & Advanced Studies (VISTAS), Chennai, for the facilities extended.

Ethical Issues: This article does not contain any animal experimentation performed by any of the authors.

Conflict of interest: The authors declare that they have no conflict of interest.

References

[1] Shaito A, Thuan DTB, Phu HT, Nguyen THD, Hasan H, Halabi S, Abdelhady S, Nasrallah GK, Eid AH, Pintus G. Herbal Medicine for Cardiovascular Diseases: Efficacy, Mechanisms, and Safety. Front Pharmacol. 2020;11:422. doi: 10.3389/fphar.2020.00422.

[2] Roacho-Pérez JA, Garza-Treviño EN, Moncada-Saucedo NK, Carriquiry-Chequer PA, Valencia-Gómez LE, Matthews ER, Gómez-Flores V, Simental-Mendía M, Delgado-Gonzalez P, Delgado-Gallegos JL, Padilla-Rivas GR, Islas JF. Artificial Scaffolds in Cardiac Tissue Engineering. Life (Basel). 2022;12(8):1117. doi: 10.3390/life12081117.

[3] El-Sherbiny IM, Yacoub MH. Hydrogel scaffolds for tissue engineering: Progress and challenges. Glob Cardiol Sci Pract. 2013; 2013(3):316-42. doi: 10.5339/gcsp.2013.38.

[4] Vasu S, Zhou J, Chen J, Johnston PV, Kim DH. Biomaterials-based Approaches for Cardiac Regeneration. Korean Circ J. 2021;51(12):943-960. doi: 10.4070/kcj.2021.0291.

[5] Eugenis I, Wu D, Rando TA. Cells, scaffolds, and bioactive factors: Engineering strategies for improving regeneration following volumetric muscle loss. Biomaterials. 2021;278:121173. doi: 10.1016/j.biomaterials.2021.121173.

[6] Li J, Liu L, Zhang J, Qu X, Kawamura T, Miyagawa S, Sawa Y. Engineered Tissue for Cardiac Regeneration: Current Status and Future Perspectives. Bioengineering (Basel). 2022;9(11):605. doi: 10.3390/bioengineering9110605.

[7] Echeverria Molina MI, Malollari KG, Komvopoulos K. Design Challenges in Polymeric Scaffolds for Tissue Engineering. Front Bioeng Biotechnol. 2021;9:617141. doi: 10.3389/fbioe.2021.617141.

[8] Zhu J, Marchant RE. Design properties of hydrogel tissue-engineering scaffolds. Expert Rev Med Devices. 2011;8(5):607-26. doi: 10.1586/erd.11.27.

[9] Ali F, Khan I, Chen J, Akhtar K, Bakhsh EM, Khan SB. Emerging Fabrication Strategies of Hydrogels and Its Applications. Gels. 2022;8(4):205. doi: 10.3390/gels8040205.

[10] Gungor-Ozkerim PS , Inci I , Zhang YS , Khademhosseini A , Dokmeci MR . Bioinks for 3D bioprinting: an overview. Biomater Sci. 2018;6(5):915-946. doi: 10.1039/c7bm00765e.

[11] Radulescu DM, Neacsu IA, Grumezescu AM, Andronescu E. New Insights of Scaffolds Based on Hydrogels in Tissue Engineering. Polymers (Basel). 2022;14(4):799. doi: 10.3390/polym14040799.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 3776-3785 | ISSN:2251-6727

[12] Kharkar PM, Kiick KL, Kloxin AM. Designing degradable hydrogels for orthogonal control of cell microenvironments. Chem Soc Rev. 2013;42(17):7335-72. doi: 10.1039/c3cs60040h.

[13] Sanz-Horta R, Matesanz A, Gallardo A, Reinecke H, Jorcano JL, Acedo P, Velasco D, Elvira C. Technological advances in fibrin for tissue engineering. J Tissue Eng. 2023;14:20417314231190288. doi: 10.1177/20417314231190288.

[14] Saludas L, Pascual-Gil S, Prósper F, Garbayo E, Blanco-Prieto M. Hydrogel based approaches for cardiac tissue engineering. Int J Pharm. 2017;523(2):454-475. doi: 10.1016/j.ijpharm.2016.10.061.

[15] Mierke CT. Viscoelasticity, Like Forces, Plays a Role in Mechanotransduction. Front Cell Dev Biol. 2022;10:789841. doi: 10.3389/fcell.2022.789841.

[16] Vunjak-Novakovic G, Tandon N, Godier A, Maidhof R, Marsano A, Martens TP, Radisic M. Challenges in cardiac tissue engineering. Tissue Eng Part B Rev. 2010;16(2):169-87. doi: 10.1089/ten.TEB.2009.0352.

[17] Mantha S, Pillai S, Khayambashi P, Upadhyay A, Zhang Y, Tao O, Pham HM, Tran SD. Smart Hydrogels in Tissue Engineering and Regenerative Medicine. Materials (Basel). 2019;12(20):3323. doi: 10.3390/ma12203323.

[18] Sharma V, Dash SK, Govarthanan K, Gahtori R, Negi N, Barani M, Tomar R, Chakraborty S, Mathapati S, Bishi DK, Negi P, Dua K, Singh SK, Gundamaraju R, Dey A, Ruokolainen J, Thakur VK, Kesari KK, Jha NK, Gupta PK, Ojha S. Recent Advances in Cardiac Tissue Engineering for the Management of Myocardium Infarction. Cells. 2021;10(10):2538. doi: 10.3390/cells10102538.

[19] Peña B, Laughter M, Jett S, Rowland TJ, Taylor MRG, Mestroni L, Park D. Injectable Hydrogels for Cardiac Tissue Engineering. Macromol Biosci. 2018;18(6):e1800079. doi: 10.1002/mabi.201800079.