

Role of Adipose-Derived Mesenchymal Stem Cells in the Regeneration of Cardiac Tissue and Improvement of Cardiac Function: a Narrative Review

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Abstract: Recent efforts have made in order to novel therapeutic approaches to reduce the heavy cardiovascular burden. The use of cell therapy and applying stem cell-based therapies has received much attention; of particular interest are adipose-derived mesenchymal stem cells (ADSCs). The present review aimed to review the studies which examined and researched various aspects of ADSCs to improve cardiac function. A comprehensive review of all articles assessed and discussed the application of ADSCs in the improvement of cardiac tissue renewing and cardiomyocytes regeneration was planned and conducted by the two reviewers. The initial literature search revealed a total of 153 articles that, of those, 34 were considered eligible. From the perspective of heart tissue regeneration, the inductive role of ADSCs in sensing mechanical stimulation and produce collagen and elastin scaffolds, vascularizing cardiac tissue, and exosomes (vesicles derived from ADSCs) in ADSCs-mediated myocardial protection has indicated. In the process of ADSCs differentiation to cardiomyocyte-like cells, the role of various targeted pathways have been identified that can be influenced by different elements such as TGF-beta1, phorbol myristate acetate, Angiotensin II, Rho-associated kinases, 5-Azaytidine, Sodium valproate, fibrin scaffold and trichostatin A have been highlighted. In the final, from a therapeutic point of view, the effectiveness of ADMSCs differentiation to cardiomyocytes as improving left ventricular functional state has been discussed. Summarizing the studies confirms a significant improvement in cardiac function following direct application of ADSCs or their transformation to cardiomyocytes by stimulating or inhibiting various cellular pathways leading reducing oxidative stress and inflammatory bed, reducing cardiomyocyte apoptosis, attenuating cardiac fibrosis, reducing the infiltration of immune cells and collagen deposition, and enhancing angiogenesis.

Keywords: Mesenchymal stem cells; adipose tissue; cardiology; cell differentiation.

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1. Introduction

Improving live expectancy, as well as reducing disability, is the main goal for clinicians dealing with chronic life-threatening or acute debilitating diseases. Conventional treatments fail in many cases and, therefore, do not succeed in reducing the heavy burden of the diseases [1,2]. In this regard, cardiovascular disease, as the most common cause of morbidity and disability in the world, is at the forefront of diseases that, despite the many successes in their

treatment, continue to fall victim [3]. Even with unfavorable life patterns and sedentary lifestyles, we are faced with an upward trend in these diseases and their adverse consequences [4]. Therefore, recent efforts have made in order to novel therapeutic approaches to reduce the heavy cardiovascular burden. Accordingly, the use of cell therapy and applying stem cell-based therapies has received much attention [5,6]. Of particular interest are mesenchymal stem cells (MSCs) [7,8]. In this regard, different therapeutic approaches have been described in the literature in the use of these types of cells for treatment. In initial experiences, MSCs were initially inserted in the bone marrow with the capacity to regenerate bone and to create the niche for hematopoietic stem cells, known as bone-marrow mesenchymal stem cells [9,10]. In the next attempts, the extraction of such cells from other distinct and specific tissues of the body, such as adipose tissue, skin, musculoskeletal tissues, lungs, and even placenta has been possible [11]. The main feature of these cells is their high potential in differentiating to other specialized tissues, especially connective tissues, and the same feature is used to renew damaged tissues and organs [12]. In this regard, different mechanisms have been described for MSCs - based therapy. First, MSCs can differentiate into the targeted cell types and contribute to regenerate the injured tissue [13]. Second, due to potential secretory role, MSCs can secrete various growth factors and cytokines, facilitating cell proliferation, inducing vascularization, and angiogenesis [14]. Third, MSCs have immunomodulatory role leading control and inhibition of inflammation processes leading tissue injury [15]. Although both adipose-derived mesenchymal stem cells (ADSCs) and bone marrow mesenchymal stem cells (BM-MSCs) are now commonly used for regenerating damaged tissues, ADSCs have more potential advantages. First, ADSCs are more accessible commonly from subcutaneous fat tissue or supra- and infra-patellar fat pads and by lipoaspirates or adipose tissue biopsy, leading to a lower burden of morbidity on patients as well as higher satisfaction [16]. Second, it seems that ADSCs have more immune properties leading to lower risk for rejection and also higher proliferation rate as compared to BM-MSCs [17]. To access ADSCs from fat tissue, following enzymatic digestion process, a stromal vascular fraction can be extracted from the adipose tissue consisting a mixture of regenerative cell types and various immune cells, including preadipocytes, fibroblasts, vascular smooth muscle cells, endothelial cells, resident monocyte, and lymphocytes, but ADSCs make up about 30% of the total mixture extracted [18,19]. ADSCs are naturally located in the capillary and perivascular adventitia of large blood vessels within adipose tissues and are thought to be derived from pericytes [20]. The main potential of ADSCs is to proliferate to stem cells reservoir in the undifferentiated state during life and also to give rise to different types of both mesenchymal cell lines (such as fibrocytes, chondrocytes, and osteocytes) and also non- mesenchymal cell lines (such as hepatocytes, neuronal, and cardiomyocytes) [21,22]. Based on this ability to regenerate cardiomyocytes, the use of these cells has been widely proposed to regenerate myocardial tissue. Moreover, due to immunomodulation, meaning, and anti-inflammatory properties of ADSCs, the induction and promotion of anti-cardiac ischemic-related processes such as new angiogenesis, tissue remodeling, and cell apoptosis are possible. The present review aimed to review the studies which examined and researched various aspects of ADSCs to improve cardiac function.

2. Materials and Methods

A comprehensive review of all articles assessed and discussed the application of ADSCs in the improvement of cardiac tissue renewing and cardiomyocytes regeneration was planned. The primary search was conducted according to the main keywords including “heart”,

“cardiac function”, “myocardium”, “cardiomyocyte”, and “adipose-derived mesenchymal stem cell” using different databases including PubMed, MEDLINE, SCOPUS, Google Scholar, and Cochrane Library. The searching was conducted by the two reviewers, which blinded each other, and finally, their evaluation results were summarized. Eligibility criteria included English-language papers with full-text availability, including both animal and human models, in vivo and in vitro assessments. Exclusion criteria consisted of the clinical or experimental the predominant pathologies except for the cardiovascular system, multiple publications of a single trial, case studies, or reviews. The initial literature search revealed a total of 153 articles that of those, 34 were considered eligible and included in this review (Table 1). Data from all papers deemed relevant was extracted then independently reviewed by investigators.

Table 1. Summary of the studies.

Author, year	Type of study	Target cells/disease	Main issue	Main results
Bagheri, 2020 [34]	Exp./ <i>in vitro</i>	Differentiation of ADMSCs to cardiomyocyte	Cell differentiation	5-Azaytidine can induce hADSCs to differentiate into cardiomyocytes.
Bao, 2020 [27]	Exp./ <i>in vitro</i>	Cardiac transplantation	Tissue regeneration	Toll-Like Receptor 3 activator preconditioning enhances modulatory function of ADMSCs in heterotopic heart transplantation
Zhang, 2020 [51]	Exp./animal model	Acute myocardial infarction	Therapy	ADMSCs can promote the resolution of cardiac inflammation after ischemia-reperfusion via enhancing efferocytosis of neutrophils
Gao, 2020 [52]	Exp./animal model	Acute myocardial infarction	Therapy	Cardio-renal exosomes deliver miR-1956 and activate paracrine proangiogenic VEGF signaling in ADMSCs used for cardiac regeneration after myocardial infarction
Qayyum, 2019 [53]	Human clinical trial	Chronic Ischemic Heart Disease	Therapy	ADMSCs therapy could not improve myocardial perfusion, functional parameters or amount of scar tissue
Chai, 2019 [54]	Exp./animal model	Ischemia-reperfusion injury	Therapy	Combined cold water-exosome therapy improves myocardial function and reduces oxidative and inflammatory effects following ischemia-reperfusion injury
Qiao, 2019 [55]	Exp./animal model	Acute myocardial infarction	Therapy	Combining ADMSCs and myocardial decellularized extracellular matrix has synergistic effects on cardiac repair
Deng, 2019 [26]	Exp./ <i>in vitro</i>	Acute myocardial infarction	Tissue regeneration	Exosomes from ADMSCs ameliorate cardiac damage after myocardial infarction by activating S1P/SK1/S1PR1 signaling and promoting macrophage M2 polarization
Pan, 2019 [25]	Exp./ <i>in vitro</i>	Acute myocardial infarction	Tissue regeneration	Exosomes derived from miR-146a-modified ADMSCs attenuate myocardial damage via down-regulation of early growth response factor 1 (EGR1)
Sheu, 2019 [56]	Exp./animal model	Acute myocardial infarction	Therapy	Transplantation of ADMSCs resulted in smaller infarcts and rescued cardiac function by improving left ventricular function and reducing inflammation and apoptosis
Najafipour, 2019	Exp./ <i>in vitro</i>	Differentiation of ADMSCs to cardiomyocyte	Cell differentiation	Sodium valproate can increase cardiomyogenesis in ADMSCs
Zhang, 2018 [57]	Exp./ <i>in vitro</i>	Differentiation of ADMSCs to cardiomyocyte	Cell differentiation	ADMSCs differentiation to cardiomyocyte can be enhanced by TGF-β1 effect on increased

Author, year	Type of study	Target cells/disease	Main issue	Main results
				phosphorylation of the Smad signaling pathway
Abd Emami, 2018 [44]	Exp./animal model	Acute myocardial infarction	Therapy	Scar size reduction and recovery of left ventricular function after transplantation of ADMSCs
Mori, 2018 [45]	Exp./animal model	Ischemic Cardiomyopathy	Therapy	Improving systolic and diastolic function by implantation of allogeneic ADMSCs in cardiac tissue
Morrissett, 2018 [24]	Exp./in vitro	Vascular tissue repair	Tissue regeneration	Combining ADMSCs with ventricular cardiomyocytes facilitate the formation of vascularized cardiac tissues
Bagheri, 2018	Exp./in vitro	Differentiation of ADMSCs to cardiomyocyte	Cell differentiation	Fibrin scaffold with a compressive stress of 107.74 kPa allows a higher differentiation of ADMSCs into cardiomyocyte-like cells treated with 50 μ M 5-Aza.
Bagheri, 2018	Exp./in vitro	Differentiation of ADMSCs to cardiomyocyte	Cell differentiation	The combination of fibrin scaffold and trichostatin A for differentiation of ADMSCs into cardiomyocyte-like cells
Fikry, 2017 [46]	Exp./animal model	Acute myocardial infarction	Therapy	ADMSCs can attenuate cardiac fibrosis induced by methotrexate
Cui, 2017 [58]	Exp./animal model	Ischemia-reperfusion injury	Therapy	Exosomes ADMSCs protect the myocardium against Injury through Wnt/ β -Catenin signaling pathway
Wystrychowski, 2016 [33]	Exp./in vitro	Differentiation of ADMSCs to cardiomyocyte	Cell differentiation	Epicardial ADMSCs has higher cardiomyogenic potential as compared with pericardial and omental
Han, 2016 [50]	Exp./animal model	Acute myocardial infarction	Therapy	Melatonin facilitates ADMSCs to repair the murine infarcted heart via the SIRT1 signaling pathway
Ammar, 2015 [49]	Exp./animal model	Acute myocardial infarction	Therapy	ADMSCs is effective in mitigating cardiac damage by promoting angiogenesis, decreasing the infiltration of immune cells and collagen deposition
Liu, 2015 [48]	Exp./animal model	Acute myocardial infarction	Therapy	Priming of ADMSCs with curcumin improve tolerance to oxidative stress injury and resulted in enhancement of therapeutic potential of ADMSCs for myocardial repair.
Han, 2015 [47]	Exp./animal model	Acute myocardial infarction	Therapy	Intramyocardial injection of ADMSCs combining with ghrelin inhibits cardiomyocyte apoptosis, reduced fibrosis, and improved cardiac function through PI3K/Akt pathway
Zhao, 2014 [32]	Exp./in vitro	Differentiation of ADMSCs to cardiomyocyte	Cell differentiation	Rho-associated protein kinases enhance ADMSCs differentiation into cardiomyocytes
Li , 2014 [43]	Exp./animal model	Dilated cardiomyopathy	Therapy	Improving left ventricular function and ventricular dilatation remodeling by differentiating ADMSCs to myocardial cells
Preda, 2014 [42]	Exp./animal model	Ischemia-reperfusion injury	Therapy	Transplantation of ADMSCs resulted in smaller infarcts and improved cardiac function
Song, 2013 [31]	Exp./in vitro	Differentiation of ADMSCs to cardiomyocyte	Cell differentiation	Angiotensin II can induce ADSCs into cardiomyocyte-like cells
Li , 2013 [30]	Exp./in vitro	CD73+ ADMSCs	Cell differentiation	High capacity of CD73+ ADMSCs capacity for differentiation into cardiomyocytes
Zhang, 2013 [41]	Exp./animal model	Acute myocardial infarction	Therapy	Rosuvastatin enhances the therapeutic efficacy of ADSCs for MI via PI3K/Akt and MEK/ERK pathways

Author, year	Type of study	Target cells/disease	Main issue	Main results
Chang, 2012 [29]	Exp./ <i>in vitro</i>	Differentiation of ADMSCs to cardiomyocyte	Cell differentiation	Phorbol myristate acetate differentiates ADMSCs into cardiogenic cells
Bagno, 2012 [40]	Exp./animal model	Acute myocardial infarction	Therapy	Improving left ventricular function by administering ADMSCs directly to the myocardium
Cai , 2011 [39]	Exp./animal model	Acute myocardial infarction	Therapy	Combining Atorvastatin with ADMSCs improve more cardiac function after myocardial infarction
Colazzo, 2011 [23]	Exp./ <i>in vitro</i>	Heart valve tissue repair	Tissue regeneration	ADSCs sense mechanical stimulation and produce collagen and elastin, improving heart valve tissue
Lin, 2010 [38]	Exp./animal model	Dilated cardiomyopathy	Therapy	Combining sildenafil and ADMSCs more improve left ventricular function and angiogenesis
Gwak, 2009 [28]	Exp./ <i>in vitro</i>	Differentiation of ADMSCs to cardiomyocyte	Cell differentiation	TGF-beta1 can induce ADMSCs cardiomyogenic differentiation

3. Results and Discussion

The studies reviewed with the goal of assessing the role of ADSCs in the improvement of cardiac function can be categorized into three subgroups according to the study design and target issue as 1) experimental in-vitro studies with the focus on the role of ADSCs in heart tissue regeneration; 2) experimental in-vitro studies with the aim of assessing the pathways and mediators for the transformation of ADSCs to specific heart cells; and 3) experimental animal modeling study (only one study included human model) assessing the therapeutic efficacy of ADSCs in a clinical setting. In this regard, our review focuses on the details of each subcategory separately.

3.1. ADSCs and cardiac tissue regeneration.

The ability of ADSCs in tissue regeneration has been primarily proposed by Colazzo *et al.* in 2011 [23]. They showed that ADSCs could sense mechanical stimulation and produce collagen and elastin, leading to improving heart valve tissue. This process was mediated by the upregulation of COL3A1 gene followed by producing collagen and elastin cross-linking and also uniformly populated collagen scaffolds shortly after ADSCs induction. In the next effort, as shown by Morrisett *et al.* in 2018 [24], Combining ADMSCs with ventricular cardiomyocytes could facilitate the formation of vascularized cardiac tissues, and thus the application of ADSCs led to promote functional vascular tissue engineering for cardiac regenerative goals. Since 2019, the critical role of exosomes for cardiac tissue regeneration was highlighted. In this regard, the obtained evidence by Pen *et al.* in 2019 [25]. They emphasized that exosomes (30-100 nm small membrane vesicles derived from ADSCs) could play a crucial role in ADSCs-mediated myocardial protection. In their study, it was demonstrated that some miRNAs (such as miR-146a) could promote exosome-mediated cardioprotective effect, and therefore, the link between novel miRNAs and exosomes derived from ADSCs in cardiac tissue regeneration has been explained. In another study by Deng *et al.* [26]. And in parallel to the previous observation, it was shown that exosomes derived from ADMSCs could ameliorate cardiac damage after myocardial infarction by activating S1P/SK1/S1PR1 signaling and promoting macrophage M2 polarization. In recent studies, the regenerative role of ADSCs as a cardioprotective element, even following cardiac transplantation, has also been revealed. In a recent study by Bao *et al.* in 2020 [27], Toll-Like Receptor 3 activator preconditioning

was shown to be an enhancer for the modulatory function of ADMSCs in heterotopic heart transplantation. The pointed study could find that ADSCs had the highest efficiency in inhibiting lymphocyte proliferation, which was correlated with the upregulation of fibrinogen-like protein 2, leading to longer survival of cardiac allografts in transplantation.

3.2. ADSCs and differentiation to cardiac tissue.

The initial evidence on the pathways responsible for the differentiation of ADMSCs to heart cells was presented by Gwak *et al.* in 2009 by the assessment of the molecular pathways for differentiation of ADMSCs to cardiomyocytes. They focused on a specific cytokine (TGF-beta1) as a mediator the pointed cellular differentiation and could show that TGF-beta1 could induce the mRNA expression of cardiac-specific genes helping cardiac myosin heavy chain (MHC) and alpha-sarcomeric actin regeneration [28]. Thereafter, Chang *et al.* in 2012 [29] introduced phorbol myristate acetate, a protein kinase C (PKC) activator, as an important element for differentiation of ADMSCs into cardiogenic cells. Their experiment could successfully show that cardiomyocytes producing by ADMSCs in the induction of phorbol myristate acetate led to markedly reducing infarct size, interstitial fibrosis, and apoptotic index and ultimately improving cardiac functional state. Further studies could discover more mediators and pathways that induced ADSCs differentiation to cardiac tissue. As indicated by Li *et al.* in 2013 [30], CD73+ ADMSCs had the highest capacity among other cellular subtypes for differentiation into cardiomyocytes. Song *et al.* in 2013 [31] introduce Angiotensin II as a potential mediator for differentiating ADMSCs to cardiomyocyte-like cells. Zhao *et al.*, in 2014, in another *in-vitro* study in 2014 [32] showed that some protein kinases enhance ADMSCs differentiation into cardiomyocytes. According to their observations, Rho-associated kinases (ROCKs) could control actin cytoskeleton reorganization, the main pathway for the production of cardiomyocytes. As an interesting result obtained by Wystrychowski *et al.* in 2016 [33], the affinity and potential of ADMSCs for differentiating to cardiomyocytes is significantly different in three layers of cardiac tissue. Based on their finding, epicardial ADMSCs had higher cardiomyogenic potential as compared with pericardial, and thus this finding opened up the prospect of the fact that ADMSCs derived from different adipose tissue depots may exert a diverse multi-potency in differentiating to cardiomyocytes. In order to facilitate such cellular differentiation, some authors focused their experiments on elements inducing and accelerating differentiation of ADMSCs to cardiomyocytes. In this regard, the use of 5-Azaytidine[34], Sodium valproate[35], fibrin scaffold[36] and trichostatin A [37]as the accelerators for such cellular differentiation was assessed and demonstrated through *in-vitro* experiments. However, the pathways involved in this mediating role should be further studied.

3.3. ADMSCs and therapeutics.

In recent years, special attention has been paid to the effectiveness of ADMSCs differentiation to cardiomyocytes or even its direct-injection, especially in combination with other therapeutics to improve cardiovascular function. In this regard, combining ADMSCs with different cardiac and even non-cardiac drugs could improve cardiac function. A primarily shown by Lin *et al.* in 2010 [38], combining sildenafil and ADMSCs could improve left ventricular ejection fraction along with the progression of myocardial-related angiogenesis in the background of dilated cardiomyopathy. In a similar animal study by Cai *et al.* in 2011 [39],

applying ADMSCs in combination with atorvastatin as a main cardioprotective statin could be more efficient in recovering ischemic cardiac tissue following acute myocardial infarction. In an interesting experimental study by Bagno *et al.* in 2012 [40], administering ADMSCs directly to the myocardium could effectively improve left ventricular systolic dysfunction. Zhang *et al.* [41]. In 2013 could firstly describe the pathways through which statins improve cell therapeutic effects. According to their experiments, rosuvastatin could promote the therapeutic effect of ADMSCs via PI3K/Akt and MEK/ERK pathways in the sample suffering an acute myocardial infarction. Later, some studies could also reveal that the direct transplantation of ADMSCs could reduce infarct size in ischemic myocardium leading to the improvement of left ventricular functional state and [42] and ventricular dilatation remodeling [42,43]. On what mechanism is also effective in improving cardiac function after ADMSCs transformation, some studies were performed. In this regard, the inducing role of ADMSCs transformation or its direct implantation on inhibiting cardiomyocyte apoptosis, reduced fibrosis, and improved cardiac function through activation of PI3K/Akt pathway [44-47], improving tolerance to oxidative stress injury [48], mitigating cardiac damage by promoting angiogenesis and decreasing the infiltration of immune cells and collagen deposition [49], and repairing damaged myocardium by activating the SIRT1 signaling pathway (by melatonin) [50] have been discussed. In recent experimental studies, the protective role exosomes derived from ADMSCs to protect the injured myocardium against some destructive tissue pathways such as Wnt/ β -Catenin signaling pathway has also been studied. However, none of the studies focusing therapeutic effects of ADMSCs alone or in combination with other drugs have performed in the human level needing expansion of the studies at the level of clinical trials.

4. Conclusions

Reviewing the literature ultimately shows that directly transformation of ADMSCs to cardiomyocytes alone, embedded in platelet-rich fibrin, or along with administration of other therapeutics such as statins, melatonin, curcumin, or ghrelin can effectively improve left ventricular cardiac function by cardiac tissue regeneration. This process can be mediated by activation of some molecular pathways such as paracrine proangiogenic VEGF signaling pathway, S1P/SK1/S1PR1 signaling pathway (leading) promoting macrophage M2 polarization, phosphorylation of the Smad signaling pathway, SIRT1 signaling pathway, PI3K/Akt pathway, MEK/ERK pathway, or inactivation of some other pathways such as growth response factor 1 producing pathway and Wnt/ β -Catenin signaling pathway. The effects of ADMSCs as a therapeutic inducer on the pointed pathways are ultimately marked by reducing oxidative stress and inflammatory bed, reducing cardiomyocyte apoptosis, attenuating cardiac fibrosis, decreasing the infiltration of immune cells and collagen deposition, and enhancing angiogenesis that all lead to improvement of left ventricular remodeling and ejection fraction. Overall, it seems that the described in-vitro and animal studies should be evidenced by human-based studies so that its applications can be clinically productive.

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Conflicts of Interest

The authors declare no conflict of interest.

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