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# Exercise Promotes Mirnas' Change in Cardiac Fibrosis

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**Abstract**

*Cardiac fibrosis is a pathological feature as a key factor in cardiac remodelling, thus progressing to heart failure. MicroRNAs (miRNAs) are crucial intracellular mediators of various biological processes, involved in the regulation of physiological and pathological processes. Recently, it has been shown that miRNAs were found to play a role in exercise-induced cardioprotection. Studies in human and animal subject with variety of acute and chronic exercise were observed. This review highlights impacts of exercise on the miRNA levels associated with cardiac fibrosis.*

## Introduction

Cardiac fibrosis (CF) underlies various heart diseases, this condition occurs due to abnormal proliferation of fibroblast and accumulation of extracellular matrix (ECM) with an excessive amount of collagen. This cause cardiac dysfunction and leads to CHF (Creemers & Van Rooij, 2016). The pathological CF process has been known involved in myocardial infarction (MI), dilated and hypertrophic cardiomyopathies and heart failure (Van Rooij & Olson, 2009). Fibrosis disrupts contacts between cardiomyocytes and this change may cause alterated electrical propagation and slow conduction, escalate the susceptibility of arrhythmia (Stølen et al., 2020). During cardiac remodelling, TGF-β signalling pathway transform fibroblasts into myofibroblasts and regulate the excessive matrix accumulation (Wang et al., 2012). The pathological stimuli will recruit fibrogenic leukocyte subsets in the cardiac interstitium through the activation of pro-inflammatory cytokines and chemokines migration. This process may activate fibroblasts via TGF-β/Smad signaling, resulting in the deposition of matricellular macromolecules and structural extracellular matrix proteins (Russo & Frangogiannis, 2016).

Exercise training increases body performance through various adaptation mechanisms to natural stress conditions. Exercise training induces mechanical stress, growth hormone secretion, and inflammatory cytokines which will trigger changes in signaling pathways in cardiomyocytes (Sun et al., 2022). Regular endurance exercise training enhance aerobic capacity, potentially resulting in cardiac hypertrophy as part of a natural adaptive response. Exercise training was found to supressing fibrosis in cardiac remodeling, leading to a better heart function (Borges et al., 2019; Novoa et al., 2017). The World Health Organization (WHO) recommends that adults should aim for at least 150-300 minutes of moderate aerobic activity per week (or equivalent vigorous activity and the mix of both exercise) to achieve significant health benefits (Pelliccia et al., 2019; Riebe et al., 2018). The intensity plays a crucial role in

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determining the physiological response to exercise. A study found an improved cardiorespiratory fitness level in individuals with high-intensity exercise once a week and a greater result than moderate-intensity physical exercise after two to three times a week exercise routine (Chin et al., 2020).

MicroRNAs (miRNAs) comprise a class of small non-coding single stranded RNAs consist of 19–25 nucleotides. miRs bind to the 3'-untranslated region (3'-UTR) of their target transcript to regulate gene expression on the post-transcriptional level, provoking to degradation or inhibition of translation of the miRs (Bartel, 2009). miRNAs are transported into circulation (c-miRNAs) enclosed within exosomes, protein complexes, or microvesicles. MicroRNAs are transported steadily by these complexes, insulating them from physical and enzymatic deterioration (Barber et al., 2019). MiRNAs play a regulatory role by interacting with their target genes. miRNAs bindings to target mRNA and subsequent gene expression regulation is also influenced by individual's genetic background. Typically, miRNAs have multiple targets and can serve diverse functions within the same organ (Pickrell et al., 2010).

To date, miRNAs play an essential role in angiogenesis (Nemecz et al., 2016; Zhang et al., 2013), mitochondrial metabolism (Li et al., 2016), cardiomyocyte growth (Li et al., 2016),18 remodelling (Liu et al., 2015), and cell death (Wang et al., 2015). Numerous research studies have established a connection between miRNAs and CF. The identification of target genes holds importance in elucidating pathways involved in CF. miR-21 and miR-24 are related to fibroblast proliferation and fibrosis processes (Thum et al., 2008; Wang et al., 2012). miR-21 is highly expressed in cardiac fibroblasts, cardiomyocytes, vascular smooth muscle cells (VSMCs), and endothelial cells, regulating the VEGF and TGF β signaling pathways associated with the inflammation, apoptosis, and fibrosis. A study also found that miR-21 promotes cardiac hypertrophy (Wang et al., 2016). In cardiac remodelling after myocardial infarction (MI), it was discovered that miR-24 may control the transformation of fibroblast to myofibroblasts through its binding to furin mRNA, a protease involed in regulating angiotensin-II induced TGF β activation (Dogar et al., 2011; Luna et al., 2011; Wang et al., 2012).

Collagen production and deposition in the heart and tendons were regulated by miR-29 family (Soci et al., 2011). A study shown that supression of miR-29b activity induces increased collagen expression in the heart (Van Rooij et al., 2008). Xiao et al stated that regular aerobic exercise increases the expression of miR-29a and miR-101a, accompanied by a decrease in the expression of pro-fibrotic proteins (Xiao et al., 2017). miR-30 and miR-133 are well known to regulate ECM gene expression (Duisters et al., 2009). miR-133a is highly expressed in the cardiac muscle. Upregulation of miR-133a prevents fibrosis in a mouse model of diabetes-induced cardiac fibrosis via ERK1/2 and SMAD-2 phosphorylation pathway (Chen et al., 2014). miR-199b was also reported to alleviate fibrosis by targeting calcineurin-NFAT pathway (da Costa Martins et al., 2010). The miR-15 family play a crucial role in cardiac fibrosis. Tijsen et al demonstrated that in vivo inhibition of miR-15b using anti-miRs upregulated pro-fibrotic protein and leads to myocardial fibrosis (Tijsen et al., 2014). Additionaly, Huang et al found that miR-34a was shown to induced cardiac fibrosis after myocardial infarction by targeting Smad4 (Huang et al., 2014).

## Methods

### Search Strategy

Literature search was obtained from the selected electronic database from MEDLINE by Pubmed, SCOPUS, ScienceDirect, Google Scholar and a manual search in references of the selected article. All search strategies were performed in 2023.

### Inclusion And Exclusion Criteria

Studies were eligible for further analysis if the following inclusion criteria were met: 1) Experimental studies, 2) Subject being conditioned to do exercise, 3) Including different groups, compared with control group or other intervention, 4) Subject being assessed for cardiac or/and circulating miRNAs, 5) Studies could be access online in the past 5 years, and 6) Studies were in English or Bahasa. Abstracts, conference papers, case reports, editorial comments, and review articles were excluded from the literature analysis.

### Literature Review Process

After the exclusion of duplicate articles, a screening of the abstract and title from relevant articles were carried out independently by three authors. Each of the authors reviewed the complete articles and made their selections based on the predefined eligibility criteria. There were no discrepancies among the reviewers. The selected articles were extracted and presented in a table. The table consists of the name of the author, year of publication, subject, sex, speciment, type of exercise, and the effect. The diagram that describes the literature review process is shown in Figure 1.

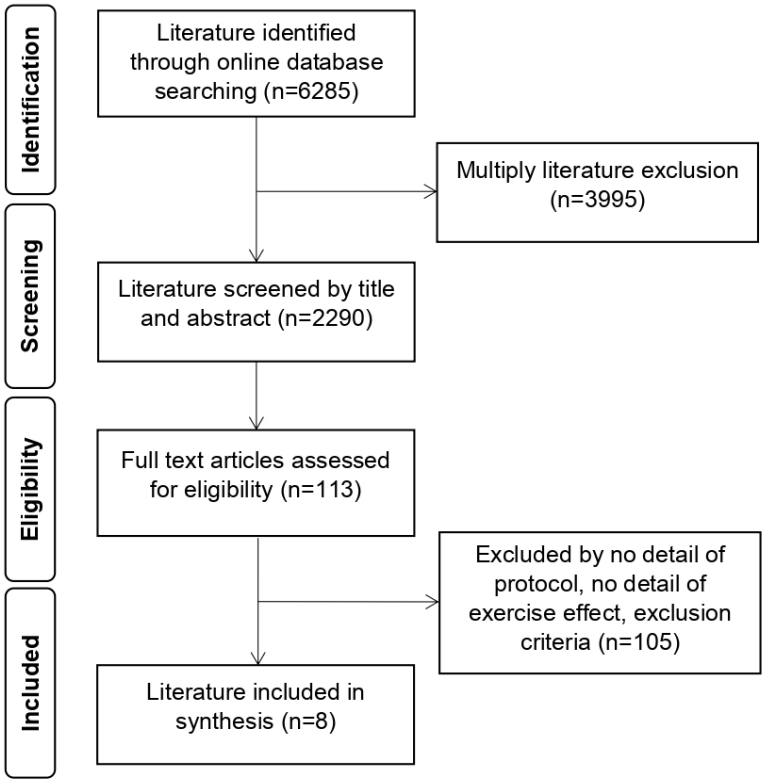


*Figure 1. Flow chart of literature search*

## Result and Discussion

The results of different miRNAs expression in regulation of CF after exercise induced, derived from several experimental studies, conducted in vitro, in vivo, and in clinical settings were shown in Table 1.

Table 1. Study characteristics.

| Author | Year | Subject (n) | Sex | Speciment | Type of exercise | Effect on miRNAs |
|---|---|---|---|---|---|---|
| **Pala M[38]** | 2023 | Rat (15) | M | Cardiac Tissue | Swimming, 60 min/day, 5days/week, 8weeks | Upregulated miR-132-3p Downregulated miR-290 |

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|---|---|---|---|---|---|---|
| **Stølen TO**[3] | 2020 | Rat (35) | F | Cardiac Tissue | Uphill running, 60 min/day, 5 days/week, 8 weeks | Upregulated miR-30a-5p<br>Downregulated miR-21-3p |
| **Lew JKS**[50] | 2020 | Mice (35) | M&F | Cardiac Tissue | Treadmill running, 50 min/day, 5days/week, 8weeks | Upregulated miR-15b<br>Upregulated miR-133 |
| **Yin X**[51] | 2020 | Man (18) | M | Blood Plasma | 8km race marathon run | Upregulated miR-133a-3p<br>Upregulated miR-1-3p |
| **Fernández-Sanjurjo**[54] | 2020 | Man (9) | M | Blood Plasma | 10km race marathon run | Upregulated miR-1-3p |
| **Li Y**[56] | 2018 | Man (10) | M | Blood Plasma | Basketball | Downregulated miR-21 |
| **Ramos**[53] | 2018 | Man (12) | M | Blood Plasma | Treadmill running | Upregulated miR-133a-3p<br>Upregulated miR-1-3p |
| | | Mice (6) | M | Blood Plasma | Treadmill running 60 min/day, 5 days/week, 4 weeks | Upregulated miR-133a-3p |
| **de Gonzalo**[37] | 2018 | Man (9) | M&F | Blood Plasma | 10km race marathon run | Upregulated miR-132-3p, miR-21-5p, miR-29a-3p, miR-30a-5p<br>Downregulated miR-29b-3p, miR-30b-5p |

miRNAs are involved in numerous of biological processes in normal and pathological setting (Condrat et al., 2020) that including cell metabolism (Wang et al., 2016), proliferation (Zhang et al., 2013), differentiation (Kim et al., 2009), and apoptosis (Tang et al., 2015). Cardiac fibrosis (CF) is a major type of pathological remodeling, predisposing the disease progression to ultimate heart failure. miRNAs dysregulation has been identified as one of the key regulators in fibrosis development. Many studies have shown that exercise induces physiological cardiac remodeling through miRNAs' regulatory network. Understanding the mechanism of CF requires a thorough exploration of the determined pathways in which miRNAs are involved. The ability of single miRNA to regulate multiple targets may complicate the analysis and interpretation of the data.[36] Exercise training stimulates physiological adaptive process through various adaptation mechanisms. These conditions lead to the release of neurotransmitters, growth hormones and growth factors, and activating sympathetic activity. Exercise training is known to induce physiological cardiac remodelling without developing fibrosis and alleviate cardiac fibrosis (Creemers & Van Rooij, 2016).

In a study, reseachers found a significant increase of miR-132-3p expression in human blood sample immediately after a 10km race and returned to baseline levels within 24 hours (de Gonzalo-Calvo et al., 2018). Another study reported a downregulated of miR-290 expression and increase expression of miR-132-3p in cardiac hypertrophy swimming induce rat model. The target of miR-290 is Kruppel-like factor 15 (Klf15). Klf15 overexpression decreases the expression of connective tissue growth factor (CTGF), which plays a role in the pathogenesis of fibrotic diseases. Studies have demonstrated that Klf15-null mice exhibit fibrosis and accumulate abnormal collagen production in the cardiac muscle (Pala et al., 2023; B. Wang et al., 2008). Pala et al revealed an upregulated expression of miR-132, which targets the Matrix Metalloproteinase 9 (MMP9). Elevated MMP9 expression leads to a rise in collagen levels. Thus, miR-132-3p upregulation can inhibits the progression of pathological cardiac remodeling process (Pala et al., 2023).

Some miRNAs had been known to regulate CF via TGF β pathway. A study stated that swimming training plays a role in collagen expression reduction through upregulation of miR-29. A decrease in COL1α1 and COL3α1 protein gene expression was found after training was done (Soci et al., 2011). An increase in miR-29a expression induced by physical exercise through mediated suppression of the TGF β1/Smad2/3 signaling pathway promotes cardiac fibrosis prevention (Xiao et al., 2017). Chaturvedi et al also stated that treadmill training

increased miR-29b and miR-455 expression. These changes stimulate the supression of MM9 expression, consequently inducing fibrosis and disrupting myocyte coupling (Chaturvedi et al., 2015). miR-29a works by binding to the 3'-UTR target site of TGF β1 and miR-101a to the 3'-UTR target site of fos. Fos regulation can increase TGF β1 transcription and activation of the TGFβ1/Smad2/3 signaling pathway. Activated TGFβR phosphorylates Smad2/3, which then combine with Smad4 to form a complex that controls the expression of fibrotic genes in the nucleus, which in turn regulates particular transcription factors for fibroblast differentiation (Hu et al., 2018; Ikeda et al., 2007; Van Rooij et al., 2008; Xiao et al., 2017).

In heart failure rat model, collagen content was increased five-fold after myocardial infarction (MI). TGF β1, collagen 1α1, and CTGF gene expression were also upregulated in MI hearts. In this study, they found an increase of miR-30a that has been suggested to play antifibrotic role after eight weeks of training. Both moderate and high intensity training mode reduced collagen content and gene expression close to Sham-sed levels (Stølen et al., 2020). Yang et al also revealed that upregulation of miR-30a-5p may decrease Smad2 levels and supressed collagen production in diabetes mellitus rat model (Yang & Zhao, 2022). Interestingly, a study reported an upregulated circulating level of miR-29a-3p and miR-30a-5p with downregulated of miR-29b-3p and miR-30b-5p after the marathon and returned to baseline levels by 24 hours post-race. In this study, different cardiac biomarkers serum levels also varied during the 72 hours post-race. In most cases, acute exercise increases cardiac biomarker level in a dose-dependent manner, followed by 72 hours of recovery period. It has been proposed that the elevation of cardiac injury parameters induced by exercise has little to no clinical relevance with myocardial damage. Exercise-induced reversible rise in biochemical indicators of stress and myocardial damage may be linked to the heart's physiological adaptations (Klinkenberg et al., 2016; Weippert et al., 2016).

Lew et al demonstrated downregulation of miR-15a/b and miR -133 in cardiac muscle of diabetic mice. These were correlated with significant increase of pro-fibrotic CTGF and TGF β1 gene expression, which describe myocardial fibrosis progression in diabetic heart disease. Moderate intensity training was able to increase the miR-15b and miR-133 expression (Lew et al., 2020). miR-133 has been identified to direct targeted the 3′ untranslated region of CTGF. Overexpression of miR-133 and miR-30c decreased the CTGF levels, followed by supression of collagen production (Duisters et al., 2009). Another human subject studies reported upregulation of miR-133a-3p and miR-1-3p levels in plasma after endurance run.[51,52] Both miRNAs are highly enriched in cardiac and skeletal muscle, thus could be a potential mediator of physiological stress (Ramos et al., 2018; Yin et al., 2020). Ramos et al stated that miR-133a and miR-1 were responsive to training with increasing intensity or duration. High intensity aerobic training was found to upregulate the human c-miR-133a (Ramos et al., 2018). Meanwhile, Fernandez et al stated that they only found an increase of miR-1-3p expression after marathon run and didn't find a significant change in the expression of miR-133a in their study (Fernández-Sanjurjo et al., 2020).

miR-21 were identified to modulate the activation of the AKT/mTOR pathway by targeting the phosphatase and tensin homolog (Pten), resulting in hypertrophy and fibrosis (Adam et al., 2012). Thum et al demonstrated that miR-21 targeting the extracellular regulated kinase inhibitor sprouty homolog 1 (Spry1), thereby stimulating MAPK signaling in cardiac fibroblasts and promoting cardiac fibrosis (Thum et al., 2008). Notably, many studies reported varied result. A study found a downregulation of miR-21 in heart failure rats after treadmill running for eight weeks (Stølen et al., 2020). In accordance with the result, Li et al showed a decrease of c-miR-21 levels after acute exercise (Li et al., 2018). Nielsen et al found a downregulation in miR-21 following a bound of training in cycle ergometer for twelve weeks (Nielsen et al., 2014). Contrariwise, Xu et al and Baggish et al reported an overexpression of miR-21 in response to acute exercise (Baggish et al., 2014; Xu et al., 2016). Meanwhile, Ramos

et al and Mooren et al identified that miR-21 exhibited no response to any of the tested intensities and durations (Mooren et al., 2014; Xu et al., 2016).

## Conclusion

Numerous studies have shown that exercise training has positive effects on the heart and is considered a lifestyle approach for managing cardiovascular disease. Different physical training protocols can differentially alter the pathways of miRNAs. These results imply that several miRNAs may protect the heart from fibrosis formation and excess collagen accumulation through the assistance of other miRNAs. The understanding of the relationship between the effect of exercise and the miRNAs expression were still quite restrictive due to biases found in the signaling of well-established molecules. To address this, future studies should investigate the mechanism of action, identify potential tissue and circulating biomarkers, and assess the impact of exercise training on clinical outcomes.

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