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The effect of exercise to cardiac fibrosis in mice with non-communicable diseases, especially myocardial infarction and diabetes mellitus: A literature review

Rifqi Alamsyah Putra [1,*], Sundari Indah Wiyasihati [2], Hayuris Kinandita Setiawan [2], Kusuma Eko Purwantari [3] and Sakina [3]

[1] *Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[2] *Department of Medical Physiology and biochemistry, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[3] *Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*

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Abstract

Non-communicable diseases (NCDs) are chronic disease caused by multifactor mainly unhealthy lifestyle and are still have one of the highest mortality rate in the world. Cardiovascular manifestations are commonly found in several type of NCDs such as heart disease and diabetes Mellitus (DM). One of that cardiovascular manifestation is cardiac remodeling especially cardiac fibrosis. Regular exercise has been considered as the effective method to improve cardiovascular function in NCD patients especially heart disease and DM, it also can reduce cardiac fibrosis in mice with NCD. This review aims summarize the effect of various exercise to cardiac fibrosis in mice with NCD especially myocardial infarction and diabetes mellitus. From six studies that reviewed in this article, five of them found that exercise can reduce cardiac fibrosis in mice with myocardial infarction or diabetic mice. Further study is required to determine the effect of various exercise type, intensity, and intervention period to cardiac remodeling, especially cardiac fibrosis, in mice with other NCDs.

Keywords: Exercise; Non-communicable disease; Cardiac fibrosis; Mice; Myocardial infarction; Diabetes mellitus

1. Introduction

Non-communicable disease (NCDs) are chronic diseases caused by multifactor such as genetics, environment and lifestyle. The modifiable risk factors for NCDs include inactivity, smoking habits, and obesity. NCDs continue to represent a significant global health challenge, contributing to a substantial burden of morbidity and mortality. That mortality rate is highest in the age group 35-69 years and mostly occur in developing countries with lower middle income (1).

One of the diseases included in NCD is heart disease. There are many types of heart disease such as heart failure, coronary heart disease, cardiomyopathy and many others (2). In most heart disease pathophysiology always involves a cardiac remodeling process, one of the common is cardiac fibrosis. It can be defined as an excess of extracellular matrix deposition by cardiac fibroblast (CFs) within the myocardium leading to structural and functional change of the heart (3). Not only heart disease, other NCDs such as diabetes mellitus (DM) can also cause cardiac fibrosis. One of the cardiovascular complications of DM is diabetic cardiomyopathy. Cardiac fibrosis is a hallmark of diabetic cardiomyopathy occurrence (4).

Exercise regularly has been considered as one of the effective interventions to improve cardiovascular function and reduce mortality rate of cardiovascular disease (5). Not only that, exercise also potentially reduce cardiac risk factor for diabetic cardiomyopathy. Several mechanism such as lowering fasting blood glucose, improving oxidative stress, and inhibiting inflammation in cardiac tissue might attenuates cardiac damage in diabetic mice (6). Exercise also was proven

* Corresponding author: Rifqi Alamsyah Putra

to attenuates cardiac fibrosis by effecting some signaling pathways (7). Despite all of that, the studies that focused the relation between various exercise types and intensities to cardiac fibrosis is still limited. This review article aims to summarize the effect of various exercise to cardiac fibrosis in mice with NCD especially myocardial infarction and diabetes mellitus.

2. Material and methods

The literature exploration for this literature review was conducted by utilizing ScienceDirect and PubMed. Some Keywords such as 'Exercise', ' 'Cardiac fibrosis', and 'mice' were used to find related studies. After that, the results of the literature exploration were manually screened and selected either that study used animal sample with NCDs or not.

3. Results and discussion

3.1. Exercise and its classification

Exercise is type of physical activity that is planned, measurable, structured, and focuses on improving certain aspects of physical fitness (8). There are many benefits that can be obtained from exercise depending on the frequency, duration, intensity and type of exercise. In general, intensity is defined as the level of metabolic energy requirements during exercise (9).

Based on the intensity, exercise can be categorized into several types, such as low intensity (<40% VO_2 max), Moderate intensity (40—69% VO_2 max), High intensity (70—85% VO_2 max), and very high intensity (> 85% VO_2 max) training (10). Besides that, exercise also can be categorized into continuous *or* interval training. Continuous training is exercise that is done continuously without any rest time. Meanwhile, interval training is training at a certain intensity with rest intervals (11).

3.2. Cardiac remodeling, especially cardiac fibrosis

Cardiomyocyte in mammals, including humans, are fully differentiated after birth. However, cardiac muscle tissue can undergo remodeling to respond to environmental stimuli (12). Cardiac remodeling is defined as molecular and cellular changes in heart muscle cells that cause changes in the size, shape, weight, and even function of the heart after an injury or other stimulus (13).

Cardiac fibrosis is defined as the excessive deposition of extracellular matrix (ECM) proteins, mainly type-I and type-III collagen, in cardiac muscle tissue (14). This condition accompanies several cardiac pathology conditions such as myocardial infarction (MI) and hypertension. During MI a huge number cardiomyocytes undergo sudden death and caused inflammation and activate reparative myofibroblast leading to formation of fibrosis, this type of fibrosis called reparative fibrosis. Another type of fibrosis is called reactive fibrosis that happen in perivascular and interstitial part of cardiac muscle. This type caused by prolonged activation of fibrogenic stimuli (15). Hypertension, obesity and diabetes are associated with reactive fibrosis and caused reduced ventricular compliance and increased myocardial stiffness potentially leading to heart failure (14).

There are several methods that can used to observed cardiac fibrosis. Several histological staining such as Masson's trichrome staining (stained blue) and picrosirius red staining can (stained red) be used to observe cardiac fibrosis (16,17). Besides that, immunohistochemistry staining for collagen-I, collagen-III, TGF-b, and Smad3 in cardiac tissue also can be used to observe cardiac fibrosis (18).

3.3. Effect of Exercise to Cardiac Fibrosis in Mice

After literature exploration was conducted, three studies that discussed the effect of exercise on cardiac fibrosis in mice induced with myocardial infarction were found. One of them is the study by kim, et al (2021). Eight-week-old male C57BL6 mice were used as sample in this study. The method used to induce myocardial infarct (MI) is by weekly intraperitoneal injection of doxorubicin hydrochloride (DOX) 8 mg/kg for a total of 4 week. That sample were divided into 3 study group consist of sedentary control (CON), DOX-treated sedentary (DOX), and DOX-treated endurance ET (ET-DOX) groups (17).

Before randomization, all mice were acclimatized by light treadmill exercise (10 m/min for 30 min a day for five days). After the acclimatization, ET-DOX group undergo progressive treadmill running up to 18 m/min for 45 min, 5 days a week for 8 weeks. Exercise intervention was conducted between 09:00 and 12:00. All mice were sacrificed after all the

experiment concluded. Masson's trichrome staining was used to evaluated cardiac fibrosis in all mice. Perivascular fibrosis was found in DOX and ET-DOX group but not in control group. There were no significant quantitative differences of cardiac fibrosis observed between the DOX group and ET-DOX group (17).

Another study also analyzed the effect of exercise on cardiac fibrosis in mice induced by myocardial infarction was conducted by Ma, et al (2021). This study used 3-months-old male C57BL/6J mice as study sample. That mice were raised until 10 months old to induce genetic modification for other variable in this study, but not effected the exercise variable. Generally, the sample were divided into four groups consist of control (CON), myocardial infarction sedentary (S-MI), myocardial infarction with aerobic training (AET-MI), and myocardial infarction with resistance training (RET-MI). Ligation of the left anterior descending (LAD) coronary artery was done in order to induce MI model one week before exercise intervention. The control group also undergo operation but without ligation (19).

The exercise regimen for AET-MI group was 10 m/min tread mill running for 60 min per day, for four weeks. Meanwhile for RET-MI group was given 9-step-leader steeping, 3 times per set, 9 sets a day, while carrying 75% of maximum load as training intervention. Between each set, there is one minutes rest time for the mice. That exercise also given for four weeks. Before the exercise intervention was given, both AET-MI and RET-MI group was acclimatized with each exercise method respectively but with lighter intensity. After four weeks training intervention finished, all mice were sacrificed. The degree of cardiac fibrosis was determined by calculated the percentage of collagen volume fraction (CVF). Masson trichrome and Sirius red staining were performed on myocardial tissue sections to observe the degree of myocardial fibrosis This study found that all of MI mice have significant higher CVF than the control group. Besides that, both AET-MI and RET-MI group have significant lower CVF than S-MI group (19).

A study by tan et al (2023) also analyzed the effect of exercise to cardiac fibrosis in mice with MI induced by LAD coronal artery ligation. Eight-week-old male mice were used as sample in this study. Besides that, this study used CTRP9 KO mice to analyze the role of those protein in cardiac fibrosis, but it doesn't affect the exercise variable on wild type mice. The wild-type mice were divided into 4 groups consist of one control (Sed), group and three group with different exercise doses consist of 15 mins (E_{15}) , 30 mins (E_{30}) , and 60 mins (E_{60}) of swimming training per day (20).

The exercise intervention was started four weeks after the surgery that inducing MI. During the first day of exercise intervention, all groups undergo 10 mins swimming session and then progressively increased to their target dose over a week. The mice exercised in the 60 cm × 90 cm water tanks filled with warm water (32 ◦ C–35 ◦ C) to a depth of 25 cm. These exercises were given for 5 days/week for 8 weeks (20).

After the exercise intervention was done, all mice were sacrificed and then histological preparations were made using Masson trichrome staining. Among three exercise groups, only the low-dose exercise (E_{15}) group that can significantly reduce the cardiac fibrosis. Not only that, (E_{15}) group also reduced heart weight to body weight ratio, the size of cardiomyocytes and improvement of cardiac function in general. Quite the opposite, high-dose exercise (E_{60}) slightly increased the cardiac fibrosis in mice post MI (20).

Studies that analyze the effect of exercise to cardiac fibrosis in mice with diabetes mellitus (DM) were also found during the study exploration. A study conducted by Veeranki et al (2016) analyzed the effect of MIIT to cardiac fibrosis in mice with diabetes mellitus (DM). Eight-weeks old male lean control (db/+) and diabetic obese (db/db) mice was used as this study sample. Both of those sample were also divides into two study groups (Sedentary and exercise). So, there are four groups analyzed in this study. Those groups are control mice sedentary (Con-Sed), control mice with exercise (Con-Ex), Diabetic mice sedentary (db/db-Sed), and Diabetic mice with exercise (db/db-Ex) groups. Both exercise groups undergo a MIIT training consist of a 330 meters daily tread mill running with the speed of 10 meters/min for the first two weeks and with the speed of 11 meters /min for the third until the fifth week (end of exercise intervention). The mice were rested for 10 mins after every 100 meters of running. That training regimen was given for five days a week for five consecutive weeks (21).

The mice in all study groups were sacrificed after all the training intervention was done completely. Subsequently, cardiac slide preparate was made with Masson's trichrome staining to observe cardiac fibrosis in mice heart. Perivascular and interstitial fibrosis in (db/db-Sed) mice were significantly higher than in other study groups. The fibrosis in (db/db-Ex) group also significantly lower than (db/db-Sed) mice, it indicates that exercise enhanced the heart function by reducing fibrosis in diabetic mice (21).

A study conducted by Lu, et al (2021) also analyzed the effect of exercise to cardiac fibrosis on mice with DM. Besides that, this study also analyzed the effect of metformin therapy and combination of metformin and exercise to cardiac fibrosis on mice with DM. Eight-week-old diabetic male mice were randomly assigned into four study groups. These

groups consist of control (Con), exercise (Ex), metformin (M), and exercise combined with metformin (Ex + M). Besides that, a wild type group (WT) also required to compare cardiac remodeling between wild type and diabetic sample. All groups were fed standard chow diet (22).

The (Ex) and (Ex + M) study groups both were undergo an aerobic exercise model consist of tread mill running 30—40 min/day at a speed of 7—12 m/min, 5 days/week, for 8 weeks. For the (Ex + M) group the training intervention was conducted 30 minutes after the metformin administered. After the exercise intervention completed, all the mice sample were sacrificed. Subsequently, cardiac Histological preparations were made using sirius red staining to observed the cardiac fibrosis (22).

The cardiac fibrosis was quantitatively analyzed using ImageJ software. The cardiac fibrosis area divided by total myocardial area were calculated to determine the collagen volume fraction of the myocardium (CVF). The result show that the CVF in diabetic mice (Con) was significantly increased compared with (WT) group. But, the CVF in (Con) group were significantly higher than the (Ex), (M), and (Ex + M) groups (22).

Another study with the aims to analyze the effect of HIIT and MICT to cardiac remodeling on mice with DM type 2-induced cardiac injury is also reviewed in this article. A study conducted by Pei et al (2023) was using 17-week-old male C57BL/6J mice as the study sample. That sample were divided into four groups, before the randomization, all sample acclimatize for one week in the new environment. That study groups are control (CON) group and experiment groups. The experiment groups consist of T2DM, T2DM + medium-intensity continuous training (T2DM+MICT), and T2DM + high-intensity interval training (T2DM+HIIT) groups. Streptozotocin with 50 mg/kg dose was injected to the mice in the experiment groups to induce T2DM. Besides that, the experimental group were also fed with a high-fat diet (fat 60%, protein 20%, carbohydrate 20%) for six weeks (18).

The T2DM+HIIT groups were given 9 sets of 1.5 min high-intensity running sessions [85% maximum velocity (Vmax)] with 1min of active rest time in between sets. Meanwhile the T2DM+MICT group were given moderate-intensity running session (60%Vmax). The same movement distance should be kept in HIIT and MICT, so the exercise duration for T2DM+MICT group are not constant. Both of those exercise groups undergo the training during afternoon, five days per week for 24 consecutive weeks (23).

After the 24 weeks exercise intervention have done all the mice were sacrificed and the heart organ was harvested. Immunohistochemistry testing was conducted using rabbit anti-TGF-b, rabbit anti-Smad3, rabbit anti-Co I and rabbit anti-Co III antibodies. The result of this study showed that all these antibodies were significantly increased in T2DM group compared to the control group. Both T2DM+HIIT and T2DM+MICT groups had lower antibodies for cardiac fibrosis that the T2DM group, but only T2DM+HIIT group had statistically significant impact on decreasing cardiac fibrosis in T2DM mice (23).

The summary of six studies reviewed in this review article can be seen in the table 1, below:

Table 1 Summary of effect of exercise on cardiac fibrosis in mice with NCDs from several studies

No.	Studies	Exercise			Sample Condition	Result
		Type & Intensity	Duration & Frequency	Period		
1.	Kim *et al.*, 2021(17)	Aerobic (tread mill running) endurance training	45-minute progressive training up to 18m/min Five days a week	8 weeks	8-week-old male mice with Dox-Induced Myocardial Injury	No significant difference in degree of perivascular fibrosis between the group treated with DOX and the group treated with ET-DOX.
2.	Ma *et al.*, 2021(19)	Aerobic Exercise Training (AET) by tread mill running)	60 minutes a day with 10m/mins speed. Five days a week	4 weeks	10-month-old male mice with myocardial infarct induced by the ligation of	AET and RET significantly reduce collagen volume fraction (cardiac fibrosis) in MI mice.

		Resistance Exercise Training (RET) by (leader stepping while carrying weight)	9-step-leader steeping 3X per set 9 sets a day, while carrying 75% of maximum load. There 1 min rest between set Five days a week		LAD coronal artery.	
3.	Tan et al., 2023 (20)	Different dose Swimming training	- (E_{15}): 15 mins a day / low-dose - (E_{30}): 30 mins a day / med-dose, and - (E_{60}): 60 mins a day/ high-dose Five days a week	8 weeks	8-week-old male mice with infarct myocardia induced by the ligation of LAD coronal artery.	Low-dose training (E_{15}) significantly reduce cardiac fibrosis. Meanwhile, High-dose training slightly increase cardiac fibrosis in MI mice.
4.	Veeranki et al., 2016 (21)	MIIT treadmill running	330 meters daily distance with 10 m/mins speed for first 2 weeks then 11 m/min speed of for the rest of the period (3 weeks). After every 100 m of tread mill run, the mice was rested for 10 minutes.	5 weeks	8-week-old obese and diabetic male mice	Percentage of collagen in heart (cardiac fibrosis) decrease significantly in diabetic mice received exercise intervention than sedentary diabetic mice.
5.	Lu, et al (2021) (22)	MICT treadmill running	30—40 min/day at a speed of 7—12 m/mins 5 Days a week.	8 weeks	8-week-old diabetic male mice	Percentage of cardiac fibrosis in diabetic mice (Con) was significantly higher compared with (WT) group. But, exercise (EX) group have significantly lower cardiac fibrosis.
6.	Pei et al., 2023 (18)	HIIT (85% Vmax) tread mill running	9 set of 1.5 mins with 1 min rest between set Five days a week	24 weeks	17-week-old male mice with Type-2 Diabetes Melitus	HIIT significantly decrease fibrosis in T2DM mice. MICT also decrease the fibrosis in T2DM mice. but not significant
		MICT (60% Vmax) tread mill running	Duration depend on distance, must kept same with HIIT Five days a week			

4. Conclusion

From this review article can be concluded that exercise mostly reduced the amount of cardiac fibrosis in mice with NCD significantly. Further study is required to investigate the effect of various exercise types and intensities on cardiac remodeling in NCD patients or animal models. Additionally, a further study that analyzes the effect of the exercise intervention period on heart remodeling is required to obtain information regarding the minimum period needed to get the cardioprotective effects from exercise.

Compliance with ethical standards

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Disclosure of Conflict of interest

There is no conflict of interest during the process of making this study.

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