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Effect of Exercise and Non-exercise Interventions on Cardiac Angiogenesis in Diabetes Mellitus Patients: A Review

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Abstract: Background: It has been shown that about 80% of deaths in diabetic patients are due to cardiovascular disorders, which are called Diabetic Heart Disease or DHD, the most important of which are dysfunction and vascular damage, and consequently the stopping of coronary angiogenesis. Despite the many advances made in the field of medical research and the long-standing clinical history of diabetes mellitus, the risk of cardiovascular disease associated with diabetes has not been reduced. Method: Our search was performed by typing the words HIIT, MICT, Diabetic Heart Disease, MicroRNA, Cardiac Angiogenesis in pubmed. We reviewed the literature using articles that were relevant to our field of work. conclusion: Researchers have proposed different exercise programs to improve cardiovascular complications in diabetic patient, and their prominent role in improving the complications associated with microangiopathy compared to non-exercise interventions (hormone, complementary therapies, pharmaceutical methods, etc.) in these proven patients. but so far no study has been done to compare the effectiveness of exercise or non-exercise interventions on the improvement of microvascular complications in DHD patients. Therefore, this review article compares the types of interventions that affect the angiogenesis of patients with a history of DHD.

Keywords: HIIT, MICT, Diabetic Heart Disease, MicroRNA, Cardiac Angiogenesis

1. Introduction

Type 2 diabetes mellitus is one of the most complex diseases that virtually affects all tissues and systems of the body and is closely associated with diseases such as obesity and metabolic syndrome, and many scientists consider it an epidemic [1]. Epidemiological data of 1980 showed that 108 million diabetic patients have reported that the population has increased to 422 million young people with diabetes (normalized by age) by 2014 Which has increased the incidence of diabetes in the youth population from 4.7 to 8.5 percent this year [2]. An increase in the prevalence of diabetes in the continent and in different countries between 2010 and 2030 is estimated at 72% worldwide [3]. It is estimated that this number will rise to 642 million in 2040 and is recognized as one of the major causes of total or partial mortality and disability in the 21st Century [3]. This increase will lead to a high level of health spending, with its ever-increasing growth, leading to a 7 per cent increase and a cost of $ 776 billion by 2045 in the population aged 20-79 And if the age range is 18-99 years, the total cost will be $ 958 billion in 2045 [4]. Heart disease and eventual death occur in 80% of diabetics definitely and unequivocally, and scientists have found that the link between diabetes mellitus and cardiovascular disease is linear [5]. Due to increased obesity, mild lifestyle, lack of exercise and population aging, DHD is significantly increased relative to epidemic. Despite all the efforts made to address this global challenge, the onset of heart disease in people with diabetes remains a challenge for doctors. Therefore, recognizing modifiers of this disease not only leads to new and The most effective therapeutic interventions, but also the latest methods for early diagnosis of the disease before it occurs [6]. " Diabetic heart disease (DHD) is a type of heart disease that occurs in type 1 and type 2 diabetic populations and occurs with structural changes in the heart and blood vessels, molecular and functional, and includes coronary heart disease

(CHD) or Coronary artery disease (CAD), cardiomyopathy (CAN) or diabetic cardiomyopathy (DCM) and heart failure (HF). [7]. Molecular changes affecting diabetes activates a network of signaling pathways for the associated myocardial stress, which, with the activation of multiple transcription factors, brings about alignment of regulators and Micro-Ribonucleic Acids (miRs), leading to changes in gene expression At the heart of diabetes [8, 9]. MicroRNAs are small protein molecules They play an important regulatory role in translation or post-transcription processes. It has been estimated that more than 1000 miR is coded by the human genome [10]. The most important of them, expressed in the heart tissue, are miR-126 and miR-503. Because they play the most important role in controlling angiogenesis and vascular integration [11]. True attitude in cardiac events is incomplete, and it seems that processes that occur in the heart muscle are much more complicated than skeletal muscle [12]. Diabetes mellitus from a vascular perspective and angiogenesis is a paradox of the disease, due to the increase in angiogenesis in tissue such as the kidneys and eye and on the other hand leads to angiogenesis in the cardiovascular tissue [13]. The decrease in the incidence of angiogenesis is associated with fetal abnormalities in diabetic mothers, an increased risk of transplantation rejection, wound healing, and decreased lateral vessel formation in diabetic patients [14, 15]. many studies, Reduction of lateral vascular formation process and vascular angiogenesis in the People's hearts and animal models of type 2 diabetes mellitus have proven [16] Which subsequently reduces perfusion and hemorrhage to the myocardium and increases mortality [17]. MiR-126 and miR-503 play an important role in the angiogenesis in diabetic patients, such that miR-126 regulates the genes VEGF, IGF2 and miR-503 regulate cd25, cyclinA and CCNE1 genes [18]. Exercise can dramatically accelerate and enhance the process of cardiac angiogenesis in the diabetic population by stimulating the expression of MiR-126 and VEGF proteins. In support of this applied theory, a dramatic increase in the number and density of rat myocardial capillaries using a rat-specific swimming program consisting of 5 days per week was found to be due to changes in the two signaling pathways include VEGF/ Raf-1/ ERK and VEGF/P13K/AKT [11]. Exercise is also able to block SPRED1 and PIK3R2 proteinsby overregulating MiR-126 expression [11]. Therefore, it can be said that Structured and targeted exercise can be a valuable low-complication drug that dramatically over-regulates angiogenesis, accelerates and improves coronary blood flow, and ultimately improves the function of DHD patients. [11]. The prominent High-intensity interval training effect has been proven on the development of exercise aerobic capacity and cardiovascular function on healthy subjects and cardiovascular patients in comparison to moderate-intensity continuous training (MICT) [19, 20].

Sabzevari Rad et al (2020) in a study on diabetic rats proved that a period (6 weeks) of HIIT led to a significant increase in the miR-126 expression of cardiac gene and an increase in serum concentrations of VEGF and Raf-1 proteins and a decrease in Serum concentration of Spred-1 as well as angiogenesis mechanisms established by HIIT and signaling cascade (miR-126/Spred-1/Raf-1/VEGF) have proven that high intensity interval training is a potential and inexpensive therapeutic agent in the treatment of complications of diabetic heart disease and enhance the angiogenic process [21]. Many studies have also examined the effects of non-exercise interventions, including the use of pharmaceutical methods and therapies, and the use of different types of supplements in the development of angiogenesis in the heart of diabetic patients, but so far no study has been done to compare the effectiveness of exercise or non-exercise interventions on the improvement of microvascular complications in DHD patients. Therefore, this review article compares the types of interventions that affect the angiogenesis of patients with a history of DHD.

2. Methods

A google search was conducted in English by typing in the words HIIT, MICT, Diabetic heart disease, MicroRNA, Cardiac angiogenesis in pubmed. A literature review was done going through relevant articles.

3. Angiogenesis

Angiogenesis is the biological process of budding new vessels from the vessels in the tissue. This process is evident in embryonic, postnatal, and even adult life, which can be classified in two physiological and pathophysiological forms [22]. Physiological angiogenesis is essential for the growth of normal tissue, regeneration and production of new vessels. Generally, the angiogenesis process involves the steps of Ecs stimulation, capillary laminar destruction, EC migration, capillary formation, and vascular maturation [23]. Smooth muscle contractions and cells can maintain stability and perfusion (fluid transfer through the circulatory or lymphatic system to a tissue) during angiogenesis [24]. Angiogenesis is not only effective in the regeneration and growth of the tissue but also involved in malignant diseases [25]. For example, abnormal vascular growth or changes can lead to complications of diabetes, arthritis, psoriasis, endometriosis, cancer, inflammatory disorders, high blood pressure, eye diseases, etc [25, 26]. Reducing angiogenesis has also been proven in many diseases such as stroke, myocardial infarction, wounds, diabetic ulcers and neurological disorders, preeclampsia, coronary artery disease, amyotrophic sclerosis, Crohn's disease, lupus etc [25, 26]. It is important to note that the signaling pathways that initiate vasculogenesis and angiogenesis are: fibroblast growth factor pathway (FGFs) and platelet-derived growth factor (PDGF) pathway, mTOR pathway, hypoxic pathway, VEGF/VEGFR pathway, angiopin pathway (Ang) or specific receptor for tyrosine kinase, nitric oxide pathway [27, 28]. Several cytokines play a essential role in the process of angiogenesis. These angiogenesis enhancer factors include VEGF, FGF-2, IL-8, pairing growth factor, TGF-β, PDGF, Angs [29], While the angiogenesis inhibitors are endostatin, angiostatin and thromosponidine [30].

3.1. Relationship Between Diabetes and Angiogenesis

Diabetes affects pro-angiogenic and anti-angiogenic agents that alter the balance between angiogenesis stimulant and angiogenesis inhibitors and thus, with altering angiogenesis, cardiovascular disease increases [31, 32]. On the other hand, pathological angiogenesis and its increase is connected to diabetic retinopathy and bleeding in atherosclerotic plaques and their instability. Despite the increasing awareness of the anti-diabetic effects of angiogenesis, The effective molecular mechanisms involved in the angiogenesis phenomenon are not precisely known [33]. Inhibition of angiogenesis in diabetes is probably due to poor Base membrane decomposition, changes in the balance of growth factors, vascular stabilization cytokines, or pathway signal transmission problems. On the other hand, angiogenesis in diabetes is associated with an increase in the level of VEGF, FGF, incremental regulation of integrin (which is responsible for the migration and triggers essential growth factors in the process of angiogenesis), motility disorders and non-enzymatic glycosylation [33]. Endothelial dysfunction and abnormal angiogenesis are the main attributes of diabetes. Responsible factors in endothelial dysfunction are impaired lipid metabolism and vascular inflammation, so that the decrease in TNF-α activity improves insulin sensitivity and also improves endothelial function [33]. Dyslipidemia also affects the endothelium in T2DM patient, although LDL levels in these patients do not increase in particular, but these molecules easily penetrate the damaged endothelium and are prone to peroxidation, But on the other hand, the HDL value in these patients has decreased. HDL has anti-oxidant activity and eNOS activation, and decreases the expression of adhesive molecules that exhibit protective effects on the vessels [33].

3.2. Diabetic Heart Disease (DHD) and Its Pathogenesis

The first in the 1980s was a combination of microangiopathies, cardiomyopathy, coronary atheroma and auto-corneal neuropathy [7]. The definition of the National Health Association (NIH) of DHD is as follows: "DHD is a collection of cardiovascular diseases that includes coronary autonomic neuropathy (CAN), diabetic cardiomyopathy (DCM), coronary artery disease (CAD) or coronary heart disease (CHD) and heart failure (HF) ". These diseases can lead to structural, functional, and molecular changes in the cardiovascular system [7]. Therefore, the disease does not mean coronary disease because the increased incidence of coronary risk factors in diabetes is not able to predict the deaths from cardiovascular causes [7]. Mechanisms of DHD have been poorly investigated and as a myocardial disorder, individuals with type 2 diabetes can not express the individual effects of unknown heart disease, hypertension and coronary artery disease [34]. The DHD etiology remains mysterious due to the multiplicity of its contributing factors. In the development of DHD, two factors hyperglycemic and insulin resistance are more prominent [35, 36]. Other factors, such as microvascular disease and cardiac neuropathy, coronary artery disease, and risk factors such as obesity, HTN, hypercholesterolaemia, also play a role in the prevalence of this disease [37].

3.3. Drug Interventions in the Treatment of DHD

Diabetic patients to reduce the risk of microvascular diseases (neuropathy, retinopathy and nephropathy) Use of blood glucose lowering drugs, anti-HTN and anticholesterol, aspirin. An effective and specific drug has not yet been identified for diabetic patients (due to the multifactorial and lack of clarity of the mechanisms associated with this disease) [38]. In a Fallow up study for more than 10 years in T2DM subjects, progressive glucose control (with fasting blood sugar less than 6mmol/L) significantly reduced microvascular complications compared with deaths associated with diabetes complications (such as angina pectoris and heart failure) [38].

3.4. miR-126 as a Special Cardiac Angiomir

miR-126 is known as the specific angiomiR of the heart, expressed only in endothelial cells, and enhances vascular survival (by enhancing the expression of angiogenic factors such as VEGF, FGF). And through direct suppression of intracellular anti-angiogenic signals such as PI3KR2/P85-b/ Spred-1 performs its angiogenic actions [39] and through pro- angiogenic features of endothelial growth factor-enhancing (VEGF) and fibroblastic growth factor (FGF), maintain the integrity of the vessels [40, 41]. The vasculoprptective mir-126 role in several studies has been proven [42-46]. miR-126 is necessary in regulating post-MI cardiac rehabilitation, apoptosis myositis and vascular inflammation [47]. Significantly found that Mir-126 is released into the circulation and linked to blood lipoproteins as microvasicol, and this is the place where we can keep the concentration constant or change or manipulate. From this, Mir-126 is used to diagnose and predict cardiovascular disease biomarkers and their treatment before it occurs [42, 48]. Low levels of miR-126 expression have been reported in plasma samples of type 2 diabetic patients and have been used as a new diagnostic marker for type 2 diabetic patients with heart failure [49]. Interestingly, miR-126 is also reduced in atherosclerosis (One of the most important cardiovascular complications) in diabetic patients [50]. Exercise with major changes in stimulating the expression of MiR-126 gene and VEGF protein has a potentially important role in increasing cardiac angiogenesis. In line with this important finding, 10 weeks of swimming training with a frequency of 5 sessions per week significantly increased the myocardial capillary density in mice. This effect was due to the signaling cascade of two important angiogenesis pathways including VEGF/ Raf-1/ERK and VEGF/P13K/AKT [11].

3.5. Exercise Interventions in the Treatment of DHD

Regular exercise in type 2 diabetic patients improves glycemic control and reduces the risk of cardiovascular disease and death [51]. American Diabetes Association (ADA) and diabetes prevention programs (DPP), Have suggested exercise activity as An effective pharmacotherapy agent in the prevention and treatment of diabetes mellitus, but its molecular

mechanisms have not yet been determined [52]. Both high and moderate exercise can improveVO2max in diabetic patients. Considering that the heart tissue has a high metabolic demand and this function correlates with the proper coronary flow, and the impairment of coronary artery disease is strongly influenced by myocardial infarction, so Low intensity exercise (less than 50% VO_2max) may not be suitable for improving cardiac respiratory endurance [53]. Many studies have proved (field and laboratory) that if volume and intensity factors are used properly, with an increase in VO_2max, the E/A ratio, LVEF. EDV, ESV, CO and the ventilation ratewill improve the myocardial dysfunction. The summary of this research is presented in Table 2. 14 months of moderate intensity resistance trainning on young with T2DM resulted in improved flow-dependent and independent dilatation in sodium nitroprusside and acetylcholine responses, although performance evaluation in these studies was more based on brachial artery (not coronary endothelial). It was also proved that there is a high correlation between coronary peripheral endothelial function [54], as well as improvement of endothelial function in Brachial artery (the indicator of flow-dependent dilatation improvement), with the implementation of an 8-week moderate-intensity resistance program It has been proven [55].

3.6. HIIT's Prominent Effects on Diabetes

Researchers have been suggesting moderate to severe exercise in type 2 diabetes management. Approximately 30% of patients with T2DM perform exercise activities based on this suggestions, which One of the main reasons for their lack of participation in sports programs is lack of time [51]. Recently, the effectiveness of HIIT and interval walking in T2DM has been proven that HIIT are easier and more effective in controlling glycemic control of type 2 diabetic patients, leading to improvements in body composition, oxidative stress, aerobic capacity, insulin sensitivity and They are more effective than MICT. Therefore, it plays an important role in the management of T2DM patients [19, 51, 56]. Researchers have shown that HIIT can effectively control blood glucose and improve diabetes in T2DM patients by reducing the postprandial glucose response as well as improving hyperglycemia in these individuals [19, 51, 56]. 16 weeks of HIIT compared with MICT in reducing abdominal mass in T2DM postmenopausal women [57]. It has also been reported that HIIT is a good option for improving glycemic control, aerobic fitness, body composition, blood pressure, and lipid measurements in people with T2DM. It is more cost effective than MICT, so good treatment for this Patients are considered [58]. Several studies have shown that PGC-1α elevation and consequently increased mitochondria biogenesis of skeletal muscle through HIIT, as well as have shown a significant increase of 73-50% in increasing the re-uptake of calcium into the sarcoplasmic network [19, 53, 59]. It has been proven that interval exercises, with low and high intensity and with one session, can improve endothelial function and reduce 24-hour glycemic levels in T2DM patients [60]. Also, the implementation of a session of HIIT (90-95% HRmax) Compared with MICT (60-75% HRmax) for improving glycemic levels has similar effects [61]. Other studies have shown that both exercises (HIIT and MICT), despite different characteristics and modalities and different effects, can improve body composition, muscle strength, blood pressure, insulin sensitivity, glycemic control and aerobic capacity [62]. Some other studies have also reported that HIIT leads to an acute increase in the elimination of non-oxidative glucose and a Chronic reduction of visceral fat (visceral fat may possibly play a role in increasing insulin sensitivity in T2DM individuals) [63]. However, so far there is no evidence of chronic physiological adaptation in this population by HIIT. and that the effects of different interventions (in terms of intensity and duration) are different. Both safety and efficacy Such exercises have not yet been fully understood in T2DM patients with a history of cardiovascular disease and the elderly [51, 64]. The summary of the significant effects of HIIT in comparison with MICT in the DHD patient is depicted in the Table 1.

Table 1. *Paramount effect of HIIT compared with MICT in Diabetic Heart Disease (DHD) [84]*

↑Quality of life	
↑Enjoyment of exercise	
↑Vo2peak	
↑Myocardial function	↓ Energy costs
↑Cardiorespiratory fitness	↓ Femoral intima media thickness
↑Mesenteric arteries Dilation	↓ Arterial stiffnes
↑Vascular health	↓ HRrest
↑Cardiac reserve	↓ MiR-195
↑Recovery kinetic oxygen demand	↓ SIRT -1
↑Left ventricular mass	↓ BCL-2
↑Diastolic filling	↓Spred-1
↑SV	↓PI3KR2
↑LVEF%	More time efficient
↑FS%	Attractive option
↑PGC-1α	Gain in less time
↑MiR-126/VEGF/Raf-1	
↑PI3K/AKT/eNos	

SIRT1: Sirtuin 1BCL-2, LVEF: left ventricular ejection fraction, FS: fractional shortening, SV: stroke volume, Spred-1: Sprouty-related, EVH1 domain-containing protein 1, VEGF: vascular endothelial growth factor, Bcl-2: B-cell CLL/lymphoma 2.

The researches associated with effect of exercise and non- exercise interventions on cardiac angiogenesis in diabetes mellitus patients is summarized in Table 2.

Table 2. *Summary of the research on the effect of exercise and non- exercise interventions on cardiac angiogenesis in diabetes mellitus patients.*

Researchers	Subjects	Intervention with and without exercise	Protocols
Sabzevari rad et al (2020) [21]	40maleWistar rats with type 2 diabetes	High-intensity interval training for 6 weeks	HIIT was utilized for 6 weeks, 6 D/ week (95–100% VO2max) with the principle of overload
Zhang et al (2008) [65]	Diabetic Cardiomyopathy rats	Mesenchymal stem cells (MSCs) injection	Exogenous MSCs were injected 8 weeks after STZ injection into the femoral vein of the rats
Dariushnejad et al (2018) [66]	Male Wistar rats with type 2 diabetes	treatments with crocin and voluntary exercise for 8 weeks	Crocin supplementation was taken orally (50 mg/kg), exercises were performed alone or with crocin. Mice that could not run more than 2,000 meters per day were eliminated.
Wang et al (2015) [67]	diabetic rats	Ghrelin and [D-Lys3]-GHRP-6 for 4 weeks	The rats suffered from myocardial infarction 12 weeks after STZ injection through ligationleft anterior descending artery (LAD) and treatment Perform with intraperitoneal injection of ghrelin (200 mcg/kg) and [D-Lys3] -GHRP-6 (50 mg/kg).
Samuel et al (2010) [68]	Type 1 Diabetic Rats with Infarcted Myocardium	Coadministration of Angiopoietin-1 and Adenoviral Vascular Endothelial Growth Factor	Angiopoietin-1 and Adenoviral Vascular Endothelial Growth Factor were intramyocardially administered in combination immediately after myocardial infarction (in nondiabetic and diabetic rats). The myocardial function was measured by echocardiography (30 days after the intervention).
Erekat et al (2014) [69]	Type I Diabetic Rats	Treadmill Exercise Training for 8 weeks	rats were running 40 min/day with 18 m/min for 5 days/week.
Thirunavukkarasu et al (2013) [70]	Diabetic rats subjected to MI	Simvastatin treatment for 15 days	Simvastatin (1mg/kg) was collected for 15 days (2 weeks after STZ/saline injection). MI was induced 30 days after treatment (by permanent LAD ligation)
Shekarchizadeh (2012) [71]	type 1 diabetic rats	Resistance training for 4 weeks	rats performed 6 rep of ascending the ladder with 1-min rest intervals. A second set of 6 rep (1min rest intervals after 3-minute rest). first day (load: 30% weight, (2 sets with 6 rep). second day, load was increased to 50% of weight. From the third day onwards, the training load gradually increased until the seventh day, when the training load increased to 100% weight. In the flat load phase (load: 100% weight, 6 rep/set, 3 sets /D and 3 D/ Wk) until the end of the fourth week
Cassidy et al (2019) [72]	22men with T2DM	high intensity interval training for 12 weeks	Maximal graded cardiopulmonary exercise was performed on a semi-recumbent ergometer (workload: increasing by 10Watts/min) 3 D/Wk.
Yardley et al (2017) [73]	14 patients with heart transplant (HTx) (mean age of 53±13 years) (time since HTx, 3±2 years)	A session of HIIT and MICT	HIIT: warm-up (RPE equal 11–12). grade or speed was increased every 2 minutes to create complete disability of the subjects (exhaustion), exhaustion defined as RPE equal 18–19 and (RER) >1.10. test duration (8-12min) MICT with 60-70%max effort for 30min
Naderi et al (2019) [74]	Male Wistar rats rats with type 1 diabetes	garlic and voluntary exercise for 6 weeks	Mice were supplemented using freshly homogenized garlic (250 mg /kg) and were divided into two groups: voluntary training. (stainless-steel running wheels distance: 2000 m/day) and combined garlic + voluntary exercise
Ghaffari-Nasab et al (2018) [75]	Forty male Wistar rats with type 1 diabetes	8 weeks of treatment with IMOD™	IMOD ™, setarud brand, is made as a natural immune modulator of extracts enriched with Tanacetum vulgare and Rosa canina Utricia diocia and selenium with a dose of 20mg / kg / day.
Chodari et al (2019) [76]	Sixty-three castrated diabetic rats	Testosterone Therapy and voluntary exercise for 6 weeks	The rats were recived testosterone (with doase 2 mg/kg/day) or voluntary exercise alone or voluntary exercise + testosterone for 6Wk
Kandemir et al (2018) [77]	40 male Wistar rats With diabetes mellitus	Melatonin Therapy for 56 Days	Melatonin was injected to rats intraperitoneally (with dose of 50 mg/kg/day)
Da Silva et al (2012) [11]	Female Wistar rats with 3 group: Sedentary (s) Training 1 (T1) Training 2 (T2)	Swimming training for 10 week	(Tl): swimming with moderate workload, 60-min, 5 day/week for 10 week, workload: 5% caudal body weight. (T2): swimming with the same swimming training protocol as in Tl until the end of the 8 week. In the ninth week, 2 session per days, and in the 10th week, 3 session per days.
Zampetaki et al (2010) [78]	Patients with type 2 diabetes (DM)	miRNAs extraction	Total extracted RNA was obtained from plasma samples using a Bruneck population-based prospective study
Fan Yi et al (2017) [79]	old Wistar Rats and Type-2 diabetic cardiomyopathy	MicroRNA-193-5p modulates angiogenesis through IGF2	
Dai et al (2018) [80]	Diabetic angiopathy Wistar rats	MicroRNA-216b is able to actively regulate diabetic angiopathy	

Researchers	Subjects	Intervention with and without exercise	Protocols
Gui et al (2018) [81]	Rat Model of Diabetic Cardiomyopathy	Neuregulin-1 Promotes Myocardial Angiogenesis	12 weeks after induction of diabetes, NRG-1 was injected at a dose of 10 μg/kg / day into the tail vein of mice to treat them for 10 consecutive days.
Khakdan et al (2018) [82]	diabetic rats	Continuous endurance training and High-intensity interval training for 8 weeks	Continuous endurance training: Every session: (warm up: 5min running at 30–40% of VO_2max, 30 min running at 60–65% of VO_2max, cool down: 3min running at 30–40% of VO_2max). High-intensity interval training: (warm up: 5min running with 30–40% of VO2max with 2 min intervals at 85-90% of VO_2max, cool down: 3min running at 30–40% of VO_2max), The number of repetitions in intense intermittent training consisted of 2 repetitions in the first week, 3 repetitions in the second and third week, 4 repetitions from the fourth week to the end of the eighth week.
Francois et al (2018) [83]	53 adults with T2D	combined interval training and post-exercise milk for12 weeks	HIIT: (4-10 sets ×1 min at 90% HRmax) + post-exercise milk, milk-protein (20 g of milk-protein after HIIT).

Table 2. *Continued.*

Researchers	Measuring level	Indicator	Result
Sabzevari rad et al (2020) [21]	Cardiac tissue and plasma	miR-126 expression Spred-1, Raf-1, VEGF plasma	HIIT caused a significant increase in the miR-126 expression, VEGF and Raf-1 serum proteins and decreased the serum concentration of Spred-1 protein in the exercise group compared to the control group.
Zhang et al (2008) [65]	cardiomyocytes and vascular endothelial cells	matrix metalloproteinase (MMP)	The MSCs transplantation resulted in significant increased heart cell density, MMP-2 activity and reduced the amount of diabetic myocardial collagen, MMP-9 transcriptional levels and improved cardiac function. MSCs transplant leads to increase in cardiac function and angiogenesis in diabetic cardiomyopathy rats
Dariushnejad et al (2018) [66]	Cardiac tissue	Akt and ERK1/2 levels	Significant increase in the levels of Akt and ERK1/ 2 proteins in exercise groups and crocin compared to diabetic groups. Significant increase in the levels of ERK1/2 and Akt proteins and CD31 immunostaining in the crocin-voluntary exercise group compared to other groups. Treatment with crocin and voluntary exercise in synergist leads to angiogenesis progression through the protective effects of signaling pathways Akt and ERK1/2 in the heart of diabetic rats.
Wang et al (2015) [67]	cardiac microvascular endothelial cells (CMECs)	Left ventricular function, microvascular density (MVD), myocardial infarct size, HIF1, VEGF, Flk-1, Flt-1, AMPK, eNOS	ghrelin promoted the Flk-1, Flt-1 expression HIF1 -a, VEGF, AMPK and eNOS phosphorylation (in diabetic rats). MVD, LVEF, fractional shortening (FS) were increased. in DM + ghrelin group: decreased remarkably in myocardial infarct size. Ghrelin leads to increase in angiogenesis in diabetic rats with myocardial infarction, and these benefits are mediated by the regulation of AMPK/eNOS HIF1, VEGF, and its Flk-1 (Flt-1) and Flt-1 receptors.
Samuel et al (2010) [68]	Infarcted Myocardium	Adenoviral VEGF and Angiopoietin-1	increased capillary/arteriolar density and reduced ventricular remodeling, in the treated diabetic animals (as assessed by echocardiography). increased (activated protein kinase-2), phosphorylated mitogen-activated protein kinase (2 days post treatment) and increased expression of Ang-1, Tie-2, and surviving, VEGF, Flk-1 (4 days post treatment in the diabetic group). coadministration of Ang-1 and adenoviral VEGF lead to ventricular remodeling reduced and increase in angiogenesis in the infarcted diabetic myocardium.
Erekat et al (2014) [69]	Cardiac tissue	VEGF expression	exercise training significantly increased VEGF expression in the cardiac tissue, exercise improved diabetes-induced down-regulation in the cardiac VEGF expression in diabetic rats.
Thirunavukkarasu et al (2013) [70]	Cardiac tissue	factor 1-alpha-(HIF-1alpha)-prolyl-4-hydroxylase3 (PHD-3)	increased in arteriolar and VEGF expression in after 4 days post-MIand decreased PHD-3. 4 weeks after post-MI showed significant improvement in EF and FS in both statin-treated MI groups in diabetic status. statin therapy amilorate impairment of myocardial dysfunction and angiogenesis following MI in the diabetic rat (via PHD3 inhibition)
Shekarchizadeh (2012) [71]	Plasma	nitric oxide (NO), (VEGF) and soluble form of VEGF receptor-1 (sFlt-1)	After 4 weeks of resistance training, plasma NO concentration increased. Significant increase in plasma sFlt-1 concentration in diabetic rats compared with the control group. The result was that resistance exercise was not able to change the plasma VEGF, sFlt-1 and VEGF / sFlt-1 ratios and only increased the plasma NO concentration in diabetic animals. Therefore, the effects of resistance exercise on the angiogenesis process are negligible.
Cassidy et al (2019) [72]	Plasma	HbA1c (%)	Significant decrease was observed in HIAT group HbA1c (%) compared to control group, but changes in cardiovascular autonatomic performance indices were not significant. HIIT exercises in type 2 diabetic patients lead to improvement of glasmic control, but the effects of this exercise on cardiopulmonary cardiovascular autonuclear function is.
Yardley et al (2017) [73]		Inflammatory markers associated with vascular inflammation,	1. Exercise, regardless of severity, resulted in a rapid, meaningful reaction in several angiogenetic, vascular and in inflammatory mediators in HTX receptors. 2. HIT resulted in an increase in responses in the von Willebrand, (VEGF) and angiopoietin-2 and decreased

Researchers	Measuring level	Indicator	Result
		blood platelet activation and angiogenesis modulation	responses in the growth-differentiating factor of 15 compared to the MICT, and concluded that the angiogenetic mediator response rate, could Helpful HIT effects on HTX recipients
Naderi et al (2019) [74]	Cardiac tissue	miR-126 and miR-210 expressions, serum lipid profile	Diabetes reduces the expression of miR-126 in the heart, increases the expression of miR-210 and impairs angiogenesis. Treatment of diabetic mice using a combination of garlic + voluntary exercise led to an effective improvement in the expression of miR-126 and miR-210, a combination of garlic + Combined voluntary exercise significantly improves the serum lipid profile of diabetic rats.
Ghaffari-Nasab et al (2018) [75]	Cardiac tissue	miR-503 and CDC25 expression	The use of IMOD™ method in the treatment of diabetes leads to increased angiogenesis in the heart tissue of diabetic rats by decreasing the expression of miR-503 and increasing the expression of CDC25.
Chodari et al (2019) [76]	Cardiac tissue	miR-132 levels and CD31	The combination of testosterone + exercise increased miR-132 and CD31 levels in the hearts of castrated diabetic mice.
Kandemir et al (2018) [77]	coronary vessels	expression and phosphorylation of the VEGF-A	after melatonin treatment, The lower constitutive phosphorylation of VEGF-A was increased in coronary vessels. Cardio-protective effect of melatonin lead to decresed of damages of diabetes mellitus on heart muscle fibers and coronary vessels via phosphorylation of VEGF-A. Melatonin treatment in coronary and cardiac angiogenesis associated with the pathological cardiac hypertrophy.
Da Silva et al (2012) [11]	Cardiac tissue	mir126, VEGF expression	Increased in Cardiopulmonary capillary in T1 (58%) and T2 (101%) relative to (s), increased in The expression of VEGF protein in T1 (42%) and T2 (108%) relative to (s), increased in mir126 Heart tissue in T1 (26%) and T2 (42%) than (sdecreased in SPRED-1 protein in T1 (41%) and T2 (39%) relative to (s), decreased in expression of PI3KR2 gene in T1 (39%) and T2 (78%) relative to (s), increased in expression of PI3K / Akt / eNOS messenger path components in training groups.
Zampetaki et al (2010) [78]	Plasma	miRNA profiles	Reduced expression (mir 24, 21, 20b, 15a, 191, 197, 223, 320, 126, 150, 28-3p), Mir126 was identified as a predictor of diabetes mellitus
Fan Yi et al (2017) [79]	myocardial microvascular endothelial cells (MMECs)	MiR-193-5p expression	MiR-193-5p is overexpressed in myocardial microvascular endothelial cells and has vital angiogenic effect in MMEC of diabetic rats (via inducing proliferation and migration). IGF2 was directly regulated by miR-193-5p in MMEC. MiR-193-5p acts as an angiogenic activator through reverse regulation of the downstream IGF2 gene in diabetic cardiomyopathy.
Dai et al (2018) [80]	myocardial microvascular endothelial cells (MMECs)	MiR-216b expression	MiR-216b was dramatically overexpressed in MMECs of diabetic rats. MiR-216b downregulation significantly promote angiogenesis via promoting proliferation and invasion in MMECs of diabetic rats. frizzled class receptor 5 FZD5 was inversely upregulated in miR-216b-downregulated in MMECs of diabetic rats and, FZD5 downregulation leads to angiogenesis suppressing (via block proliferation and invasion in miR-216b-downregulated in MMECs of diabetic rats.
Gui et al (2018) [81]	coronary artery smooth muscle cells	The expression of Ang-1 and VEGF and the phosphorylation of Tie-1 andFlk1	Decresed in capillary density in Diabetic Cardiomyopathy (DCM) rats. A significant increase in capillary number and density was observed in the NRG-1 treatment group and a significant decrease in VEGF and Ang-1 expression and Flk1 and Tie-1 phosphorylation were observed in the DCM group. NRG-1 may potentiate DCM myocardial angiogenesis by increasing VEGF and Ang-1 expression.
Khakdan et al (2018) [82]	Cardiac tissue	miR-195 expression and myocardial function	HIIT effectively decreases miR-195 expression and increases Sirt1 and BCL-2 expression, increases left ventricular ejection fraction (LVEF٪) and increases fractional shortening (FS ٪) in diabetic rats. HIIT in particular is an excellent strategy to dramatically reduce miR-195 gene expression and improve myocardial function in diabetic rats.
Francois et al (2018) [83]		resting heart rate, arterial stiffness and femoral artery intima media thickness (IMT)	HIIT can leads to decresed in arterial stiffness, femoral intima media thickness, and resting heart rate in adults with T2D. post-exercise milk or protein to HIIT did not have Significant impact in cardiovascular improvement achievement. HIIT alone may be has an Diminutive effect in cardiovascular complications in T2D.

4. Discussion

Various studies using exercise and non- exercise (pharmaceutical) interventions have been able to accelerate the improvement process in diabetic patients by affecting cardiac angiogenesis. The common denominator of all these studies (whether based on exercise, medication, and other methods) is that they enhance and increase cardiac angiogenesis through various signaling cascades and ultimately improve the diabetes. Of course, it is important to note that HIIT has a more pronounced effect on cardiac angiogenesis compared with (MICT) for the reasons listed in Table 1. There are several possible mechanisms for increasing cardiac angiogenesis by HIIT training compared to MICT, which are described below:

1. Volume and intensity of exercise: HIIT leads to an increase in intracellular calcium and energy charge through Calmodulin and calcineurin, which with an increase in PGC-1a leads to an increase in cardiac angiogenesis, HIIT also increased HIF-1a and subsequently produced NO after these exercises and increased angiogenesis by increasing coronary blood flow [85].

2. Release Ca from SR: HIIT leads to increased ca release of SR through CAMCII and Movement of GLUT4 to the surface of the muscle cell membrane and by activating MAPK-p38 will increase angiogenesis, HIIT will also increase ATP consumption and increase cardiovascular capacity to receive oxygen by earobic pathway (so, cs), which will increase angiogenesis by increasing coronary blood flow [86].
3. Muscle adaptations: HIIT will decrease pcr destruction and increase muscle glycogenesis by increasing GH, IGF-I (PI3K/AKT/ mTOR), adenosine, which will increase NO production and eventually VEGF expression and angiogenesis [87].
4. Immediate shear stress: HIIT will increase the activation of ion channels, especially potassium and activate PI3K/AKT/eNOS through p38 phosphorylation and ultimately enhance angiogenesis [88].
5. Improving glucose profile: HIIT will lead to Improving glucose profile and Inhibition of anti-angiogenic agents and up-regulation of VEGF, VEGF-R2, which will eventually lead to increased angiogenesis [89].
6. Dephosphorylation of AMP: HIIT will lead to Dephosphorylation of AMP via Enzyme ecto 5-nucleotidase and increase in Adenosine levels, which by increasing the production of NO and VEGF expression will eventually increase the phenomenon of angiogenesis [90].
7. Hypoxia: HIIT leads to increased secretion and migration of HIF-a to the nucleus and activation of HRE, which is associated with increased binding of HIF-1a to HRE by increasing induction of angiogenic factors will and lead to enhanced angiogenesis, HIIT will also lead to an increase in the release of cytokines and entry into ECs and vascular chains via NO and an increase in VEGF expression, which will eventually lead to an increase in the process of angiogenesis, HIIT will also lead to an increase in Flt-1 in Ecs, which will increase the binding of Flt-1 to VEGF and, with an increase in VEGF expression, will lead to an increase in angiogenesis [91, 92].
8. Muscle blood flow: HIIT will increase muscle blood flow (10-20 fold) and consequently increase sher stress through PI3K/AKT/eNOS activation which will lead to increased NO production and with an increase in VEGF expression Will increase the process of angiogenesis [93].
9. Muscle stretch: HIIT will increase Muscle length relative to rest and consequently increase MMPs in Ecs which will eventually lead to angiogenesis by increasing Decomposition of the basement membrane via ca [94, 95].

5. Conclusion

Therefore, it can be concluded that exercise interventions as a valuable non-pharmacological agent compared to non-exercise interventions potentially causes angiogenesis up-regulation and also improves coronary blood flow and improves the function of DHD patients. Also, among all variant of exercise, HIIT, compared to MICT and RT, due to its attractiveness, More time efficient, Gain in less time, Enjoyment of exercise, leads to increased motivation and continuity of participation in exercise, and ultimately will lead to quality of life in DHD patients. Of course, it should be noted that when using HIIT, protocols and standard exercises should be used. Otherwise, exhaustive exercise will lead to increased oxidative stress and ultimately damage to the cardiovascular system.

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