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Effects of physical activity on cell-to-cell communication during type 2 diabetes: A focus on miRNA signaling

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Abstract

Type 2 diabetes (T2D) is a progressive disease characterized by hyperglycemia that results from alteration in insulin secretion, insulin resistance, or both. A number of alterations involving different tissues and organs have been reported to the development and the progression of T2D, and more relevantly, through cell-to-cell communication pathways. Recent studies demonstrated that miRNAs are considerably implicated to cell-to-cell communication during T2D. Physical activity (PA) is associated with decreasing risks of developing T2D and acts as insulin-like factor. Cumulative evidence suggest that this effect could be mediated in part through improving insulin sensitivity in T2D and obese patients and modulating miRNAs synthesis and release in healthy patients. Therefore, the practice of PA should ideally be established before the initiation of T2D. This review describes cell-to-cell communications involved in the pathophysiology of T2D during PA.

Keywords: Type 2 diabetes, physical activity, miRNA, extracellular vesicles, antidiabetic drugs.

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1. Introduction

Diabetes is one of the public health problems and commonly related to metabolic syndrome. It is characterized by hyperglycemia that results from alteration in insulin secretion, insulin resistance, or both [1]. The diagnosis of diabetes is based on a fasting blood glucose concentration above 7.0 mmol/L (126 mg/dL), a random blood glucose concentration above 11.1 mmol/L (200 mg/dL) with symptoms, or an abnormal result from an oral glucose tolerance test. Patients affected by this disease exhibit some symptoms such as fatigue, increased thirst, blurred vision, and frequent urination. The chronic hyperglycemia of diabetes is a major cause mortality resulting long-term failure of various organs and complications such as neuropathy, stroke, arteriopathy, heart attack and chronic kidney disease. Diabetes exists in several forms. The first is called type 1 diabetes (T1D) or insulin-dependent diabetes, usually occurs in childhood hence the name of juvenile diabetes. T1D is a chronic auto-immune disease characterized by insulin secretion deficiency due to pancreatic β -cell loss. More than 40 million people worldwide have T1D as it accounts for 5 – 10% of the total cases of diabetes [2]. The second is called type 2 diabetes (T2D), also known as non-insulin-dependent diabetes, which is the most common diabetes in the world with more than 462 million people affected by the pathology [3]. The global prevalence of T2D is currently estimated around 6000 cases per 100,000 and projected to increase to more than 7000 cases per 100,000 by 2030 [3]. T2D usually occurs after 40 years old and increases in frequency with age [1]. It is characterized by failure and dysfunction of pancreatic β -cells and insulin resistance. Another type is named gestational diabetes which develops commonly during the second or third trimester of pregnancy and usually disappears after delivery [3].

Although pharmacological treatment amelioration is still occurring, a

steady rise in the prevalence of diabetes and its related diseases have been observed during past decades [4]. Thus, prophylactic approaches such as weight loss, the practice of physical activity (PA), healthy diet, limitation of alcohol intake, quitting smoking and control of blood pressure are now considered as a major interest. Today, sport in general stands out as a slogan due to its association with health. It is well known that regular PA acts as insulin-like factor and associated to a decrease of T2D incidence [5]. Furthermore, physical inactivity is an essential factor which contributes to the development and the progression of T2D [5].

Due to high socio-economic costs, T2D and its related diseases are actually the subject of particular attention. Therefore, an early prevention based on the practice of PA should ideally be established before the initiation of T2D. This prevention requires more investigations of pathways and mediators involved in the pathophysiology of T2D, particularly those mediated through inter-organ and cell-to-cell communications such as hormones, bioactive lipids, non-coding RNA.

Non-coding RNAs are small RNAs that do not encode for a protein. They include microRNAs (miRNAs), small nucleolar RNAs, long non-coding RNAs, circular RNAs, PIWI-interacting RNAs and other species of regulatory non-coding RNAs [6]. Initially considered to be non-functional, mi-RNAs recently appear to regulate signaling pathways. They are synthesized from primary miRNAs (pri-miRNAs) by two RNase III-family proteins located in the nucleus (Drosha) and in the cytoplasm (Dicer) [6]. The mature miRNAs are then bound by Argonaute subfamily proteins and induce RNA silencing of genes and their post-transcriptional regulations leading to changes in some cellular activities such as the metabolism of their targeted cells, the expression of proteins and

figure 1 : miRNA synthesis : miRNAs are synthesized from primary miRNAs (pri-miRNA) by two RNase III-family proteins located in the nucleus (Drosha) and in the cytoplasm (Dicer). The mature miRNAs are then bound to specific mRNA and lead to gene silencing.

signaling pathways involved in the proliferation, the differentiation, and apoptosis (Figure 1) [6]. This effect is mediated through the activation of large ribonucleoprotein assemblies, known as RNA-induced silencing complexes [7]. To avoid any redundancies or mis-annotations, miRNAs are named using numerical identifier (miRNA-XX) and followed in some cases by -3p or -5p according to which end of the miRNA they are found on. The 3' miRNA would be miRNA-XX-3p and the 5' miRNA would be miRNA-XX-5p [6]. Additional nomenclatures are used to differentiate pri/pre-miRNAs from mature miRNAs. Some circulating miRNA such as miR-28-3p, miR-501, miR-199a are reported to be upregulated in the bloodstream of T2D patients and have been suggested as biomarkers for T2D [8–10].

Most miRNA are carried by a group of cell-derived lipid bound membranous structures called extracellular vesicles (EV) [11,12]. Three subtypes of EVs have been described. Small EVs with a diameter less than 150 nm are called exosomes and

released through multivesicular bodies using endosomal pathway in a similar manner to that of retroviruses. Microvesicles or ectosomes are small membrane-enclosed sacs ranging from 50 to 1000 nm in diameter that are thought to be shed from a variety of cell types. During apoptosis, cells release large EVs called apoptotic bodies with various sizes ranging from 0.5 to 10 μm in diameter that are hard to distinguish from other types of EVs. Circulating EV interact with specific target cells where they deliver their cargos including miRNA into the cytosol through ligand-receptor interaction, direct membrane fusion, phagocytosis, and clathrin-mediated endocytosis [11,12]. Proteomic and transcriptomic analysis revealed that EV contain specific proteins and nucleic acids derived from the parent cells and are used as biomarkers to evaluate physiological and pathophysiological responses related to cell and organs activities where they are generated [12,13]. For example, EVs have been suggested to be a biomarker of tumor progression and metastasis, early neurodegenerative

diseases or cardiovascular diseases [12,14,15]. The expression of some proteins such as tetraspanins (CD9, CD63, CD37, CD81, or CD82) are specially enriched in the membrane of exosomes, while β 1 integrin receptors and vesicle-associated membrane protein 3 are generally carried by microvesicles [11,16].

In this review, we will (i) describe roles of organs implicated in glycemic control and the physiopathology of T2D, (ii) review the PA-induced modulation of miRNA expression and (iii) discuss the mediators involved in the benefic effects of PA in T2D with a focus on miRNA.

2. Circulating organ-specific miRNAs during T2D

Hundreds of miRNA, bioactive lipids, peptides, and hormones are described to play major roles in the physiopathology of T2D through modulations of molecular targets function, and their activation such as receptors, enzymes, transporters, ion channels, and nucleic acids [17,18]. This section is focused on the most important organs implicated in the physiopathology of T2D: pancreas, skeletal muscle, adipose tissue and liver.

Pancreas

During normal situations, pancreas synthesizes and releases hormones such as insulin, glucagon, somatostatin, and pancreatic polypeptide. Insulin is released by β -cells clustered in the islets of Langerhans and stimulates the storage of glucose in fat, muscle, liver and other body tissues. A progressive decline of insulin synthesis by the pancreas and alteration of insulin cell signaling represent the most causes of the onset of T2D [19]. In addition to insulin, pancreas communicates with other organs through the release of glucagon. This hormone is produced by α -cells present in the islets of Langerhans. It has the opposite effect to insulin, by raising glycemic levels. Glucagon acts on the liver

and activates glycogen hydrolysis into glucose [19].

Exposure to some features of the T2D microenvironment was associated with dysregulation of miRNA synthesis in pancreatic β -cells. A part of these miRNA has been shown to act on other cells and organs. Zhang et al. showed that miRNA-29, miRNA-375, miRNA-223, miRNA-26, and miRNA-143 were two to three times increased in the medium of cultured pancreatic β -cells after high glucose stimulation [20]. Among these miRNAs, miRNA-223 secreted by pancreatic β -cells has been identified to stimulate GLUT-4 expression in skeletal muscles and liver tissues of ob/ob mice and consequently favored insulin sensitivity [20]. In addition, Werneck-de-Castro JP et al. recently showed that high glucose treatment up-regulates miRNA-199 expression in β -cells [21]. This miRNA has been shown to negatively impact β -cell function and regulate the myosin heavy chain protein levels in myoblasts [22]. These *in vitro* and *in vivo* data suggest that quantification of serum miRNA released by pancreatic β -cells could be used as biomarker to assess early diabetes-associated β -cell dysfunction before onset of disease[8].

Skeletal muscle

Skeletal muscle is one of the main predominant organ of insulin-mediated glucose uptake, and is thereby directly involved in the physiopathology of T2D. Skeletal muscle synthesizes a group of mediators called myokines [23] that allow to communicate with different organs such as adipose tissue, intestine, liver, and pancreas [24]. Among these myokines, interleukin-6 (IL-6) is produced in response to muscle contractions and regulates glucose intake and energy metabolism [25]. IL-6 has been shown to increase insulin-stimulated glucose disposal, fatty acid oxidation, glucose transport, and GLUT-4 translocation to the plasma membrane in myotubes [26]. Other studies showed a relationship between skeletal muscle and

gut through the release of IL-6. In a murine model, exercise-induced IL-6 has been shown to act on intestinal L cells and stimulated glucagon-like peptide-1 (GLP-1), a hormone inducing insulin secretion [27]. This effect was supported by a clinical study demonstrating that total GLP-1 plasma levels were significantly increased in patients presenting high plasma levels of IL-6 in comparison with healthy control subjects [28].

In addition, irisin hormone mainly released by skeletal muscle has been described to improve glucose homeostasis, lipid profile and metabolic parameters [29]. This observation suggest that the muscle communicates with insulin-sensitive cells such as adipocytes through this hormone. Rana SK et al reported on 79 T2D individuals an increased level of circulating irisin compared to healthy volunteers [30]. In this study, the level of irisin was positively correlated with body mass index, body fat percentage, HbA1c and soluble E-selectin and negatively correlated with visceral adiposity. In addition, they observed a significant increase of E-selectin on human primary endothelial cell treated for 4h with irisin. Overall, these data suggested that irisin was elevated during T2D and may be responsible for the T2D-induced endothelial disturbance. However, in another study, Xiang L et al observed a decrease level of circulating irisin in 188 newly diagnosed T2D Chinese patients compared to healthy subjects [31]. This contradictory effect may probably be due to the exclusion of patients with cardiovascular diseases (microangiopathy, macroangiopathy, neuropathy, retinopathy, cerebrovascular disease and peripheral vascular diseases) in this study while irisin is considered as a biomarker of cardiovascular diseases in T2D patients [30–32]. Some miRNAs, such as miRNA-19b and miRNA-140, have been suggested to downregulate irisin expression and thereby to promote weight loss through reduced energy expenditure [33,34].

Skeletal muscle is one of the tissues most affected during T2D as Andersen et al. showed a significant decrease in muscle strength in patients with 11-year T2D [35]. Volpato S. et al. reported that T2D is associated with lower muscle density, knee and ankle strength, and worse muscle quality [36]. This effect could be related to insulin synthesis since this hormone acts as a potent inhibitor of protein degradation in human skeletal muscle and stimulate muscle mitochondrial function [37]. A recent clinical study demonstrated that high-sensitivity C-reactive protein, an inflammation-related biomarker, is associated with the loss of the muscle strength during T2D [38]. However, the muscle could react to this situation during physical activity through the modulation of inflammatory and oxidative cytokines, and the synthesis of heat shock proteins [39,40].

In addition, it has been described that skeletal muscle synthesizes a group of miRNAs, called myomiRNA [41]. Increasing evidence suggest an involvement of myomiRNAs in the regulation of other organs. For example, myomiRNA-7, myomiRNA-96, and myomiRNA-124a have been recognized to alter pancreatic β -cell [42,43], while myomiRNA-26, myomiRNA-148, myomiRNA-182, and myomiRNA-483 stimulated insulin gene transcription [44,45]. Recently, a short report showed that circulating miRNAs with functions in skeletal muscle (miRNA-106b and miRNA-20b-5p) were associated with development of diabetes [46]. Those data are related to Japanese American cohort as epigenetic marker for diabetes development [46]. Changes in miRNA releases by the muscle could be implicated in pancreas dysfunction and the progression of T2D.

Adipose tissue

Adipose tissue is known as the main organ for energy storage. It is composed of adipocytes and many other cell types such as macrophages, lymphocytes, and fibroblasts embedded in a connective tissue.

Figure 2: Representative schema showing major communication pathways implicated in the pathophysiology of type 2 diabetes. FGF-21: fibroblast growth factor-21, GLP-1: glucagon-like peptide-1, IGF-1: insulin-like growth factor-1, IL: interleukin, miRNA: microRNA, myomiRNA: muscle-derived microRNA, TNF- α : tumor necrosis factor- α .

During normal situations, adipose tissue represents about 20% of the body mass in men and about 30% in women. In obese people, this tissue may reach 50% of the body mass. The increase of adipose tissue ratio, especially in obese individuals, gained tremendous scientific interest as a major risk factor for the development of T2D [18].

Additionally, adipose tissue acts as an endocrine organ through the release of several hormones and mediators called adipokines such as leptin and adiponectines. In a case-control study conducted in middle-aged women, it has been shown that high soluble leptin receptor levels were significantly associated with a lower risk of T2D [47]. Furthermore, TNF- α , a pro-inflammatory cytokine mainly derived from adipose tissue macrophages, is associated with insulin resistance. Indeed, TNF- α has been shown to inhibit insulin/Akt signaling

in high fat diet-fed mice and upregulate miRNA-494 in cultured skeletal muscle cells leading to insulin resistance [48,49]. Therefore, miRNA-494 could be a relevant target for insulin resistance therapy during T2D. In addition, injection of miRNA-containing exosomes isolated from macrophage associated adipose tissue of obese mice into control ones, induces glucose intolerance and insulin resistance in muscle, visceral adipose tissue and liver [50]. This effect has been identified to be mediated by increased miRNA-155 which then targeted peroxisomal proliferator-associated receptor δ (PPAR δ) and decreased insulin sensitivity [50]. These data suggest that miRNA released by adipose tissue could be implicated in the modulation of physiological activities in several organs, especially during T2D.

Liver

The liver synthesizes and releases into the bloodstream a subfamily of mediators called hepatokines such as insulin-like growth factor-1 (IGF-1), angiotensinogen, thrombopoietin, hepcidin, betatrophin, and fibroblast growth factor (FGF)-21.

Lee YS et al. showed that palmitic acid treatment enhanced the production and miRNA 122 and miRNA 192 contents of exosomes released by hepatocytes [51]. Moreover, these exosomes caused an increase in the expression levels of fibrotic genes in other hepatocyte cells. Recently, Wu J et al. showed that hepatic exosome-derived miRNA-130a-3p increased glucose uptake *via* GLUT4 signaling pathway in adipocyte [52]. Altogether, these works suggest that exosomes and miRNA derived from hepatocytes may have important roles in the cell-to-cell communication especially in the progression of T2D.

The **table 1** summarizes the most common miRNA released by T2D-related organs and the **figure 2** summarizes major communication pathways implicated in the physiopathology of T2D.

Organs	miRNA	Effects	Ref
Pancreas	miRNA-199	Muscle fiber type Conversion	[22]
	miRNA-223	↑ GLUT-4 expression	[20]
Skeletal muscle	miRNA-7	Pancreatic β -cell alteration	[42,43]
	miRNA-24	↑ insulin secretion	[44]
	miRNA-26	↑ insulin gene transcription	[44,45]
	miRNA-96	Pancreatic β -cell alteration	[42,43]
	miRNA-124a	Pancreatic β -cell alteration	[42,43]
	miRNA-148	↑ insulin gene transcription	[44,45]
	miRNA-182	↑ insulin gene transcription ↑	[44,45]
	miRNA-483	insulin secretion	[45]
	miRNA-494	Insulin resistance	[48,49]
Adipose tissue	miRNA-155	↓ insulin sensitivity	[50]
Bone	miRNA-106b-5p	↑ β -cell proliferation	[87]
Hepatocyte	miRNA 122	↑ expression of fibrotic genes	[51]
	miRNA 192	↑ expression of fibrotic genes	[51]

Table 1: Major miRNA released by type 2 diabetes-related organs.

3. Role of PA in patients with T2D

PA is defined as any corporal effort produced by skeletal muscles that involves energy expenditure such as walking, running, and cycling [53]. Three types of PA are generally described depending on the overall effect on the human body: (1) Flexibility exercises such as stretching improve the range of motion of muscles and joints, (2) aerobic exercises such as walking and running cause cardiovascular endurance, and (3) anaerobic exercises such as weight training, functional training or sprinting increase short-term muscle strength [54]. Physical performance is mostly evaluated by the maximal oxygen consumption (VO_{2max}), the minute ventilation/carbon dioxide production (VE/VCO_2) slope, and the blood lactate concentration. VO_{2max} is defined as the aptitude to transport and consume oxygen during exhausted work [55]. Cardiac output and the capacity of active muscle to extract oxygen from arterial blood are considered as main factors which could limit VO_{2max} [54]. Regular PA practice is known to improve VO_{2max} by increasing cardiac output, aerobic enzyme activity in the muscles, and intramuscular glycogen storage [54]. Whereas, VE/VCO_2 is negatively correlated to cardiac output. The decreased VE/VCO_2 slope could be a result of an enhancement of physical performance through the increase of both ventilation perfusion and diffusion of metabolic gases. While, low lactate concentrations exhibit an enhancement of aerobic metabolic capacity and thereby physical performance [56]. Patients with T2D exhibit a decreased VO_{2max} [57]. This effect is correlated with loss of insulin sensitivity; endothelial dysfunction, decreased myocardial perfusion, and slowed tissue hemoglobin oxygen saturation and mitochondrial function [57,58]. Impairments in VO_2 kinetics are considered as earliest indicators and important risk factors for T2D progression [57,58].

Several clinical studies demonstrated that PA significantly reduced the incidence of T2D [59,60]. Thus, the type and the intensity of PA could be taken into consideration for improved glycemic control. Recently, Dela et al. demonstrated that high-intensity interval training program (total of eight sessions, each comprised of 10 x 1 minutes ergometer bicycle exercise at > 80% of maximal heart rate, interspersed with one minute of rest) improves skeletal muscle insulin sensitivity in patients with T2D [61].

A clinical randomized trial including 251 adults age 39 to 70 years with T2D demonstrated that aerobic exercise training performed three times per week for 22 weeks significantly decreased hemoglobin A1c, a marker revealing the glycemic control for a long time [60]. Another study investigated the effects of an 8-week aerobic exercise (3 sessions per week, each session 60 to 75 minutes with 60-80% of maximum heart rate) on endogenous levels of GLP-1 and DPP4 on 48 patients with T2D [62]. In this study, aerobic exercises induced an increase in GLP-1 and a decrease in DPP4 blood levels in T2D patients [62]. Thus, glycemic control effects observed after exercise is related to an increase of incretin circulating levels and thereby to insulin secretion in human.

Another clinical study showed that low-intensity exercise (treadmill at 50% of VO_{2max}) is as effective as high-intensity exercise (treadmill at 75% of VO_{2max}) to reduce insulin resistance in patient with T2D [63]. This study showed no significant difference between groups, regarding inflammatory and blood lipid profiles, glycated hemoglobin, basal artery diameter, and flow mediated arterial dilation. Furthermore, a recent randomized controlled trial including 44 diabetic elderly patients has compared resistance training group (three times a week) to active control group (stretching workout once per week) after 12 weeks [64]. However, Chen ZP et al. showed that change from low (40% of

VO_{2max}) to medium (60% of VO_{2max}) intensity exercise increases skeletal muscle AMP-activated protein kinase (AMPK) signaling, whose activation elicits insulin-sensitizing effects [65]. This discrepancy could be related to differences in experimental protocols.

Based on these clinical data, the American Diabetes Association recommends to T2D patients to practice about 30 minutes of moderate-to-vigorous intensity aerobic exercise for 3 to 5 days a week without more than 2 days of inactivity [66,67]. In addition, French physicians can now prescribe PA to type 2 diabetic patients thus considering PA as a part of the treatment of T2D.

At a cellular level, several molecular mechanisms involved in insulin-like effects related to PA have been described. A recent study has shown that treatment with β -aminoisobutyric acid, a substance produced by skeletal muscles which is increased during exercise, attenuates insulin resistance in adipocytes through AMPK-mediated pathway [68]. Meanwhile, it has been demonstrated that repeated exercise bouts by obese patients induced an activation of AMPK and Rab-GTPase-activating proteins pathways in skeletal muscles after biopsy [69]. AMPK signaling have been shown to be involved in mitochondrial biogenesis during exercise through the modulation of peroxisome proliferator-activated receptor gamma coactivator-1 α (PGC-1 α), nitric oxide, and calcium/calmodulin-dependent protein kinase II (CaMKII) synthesis [70]. These molecular adaptations lead to the increase of GLUT-4 expression [71], and thereby to an improvement of insulin sensitivity, explaining the decreased insulin resistance induced by PA in patients suffer from metabolic disorders. However, further investigations are needed in order to clearly decipher the precise molecular mechanisms involved in the PA-induced insulin sensitivity in T2D.

4. PA as a modulator of miRNA expression

Several studies show that miRNA synthesis is modified in response to different exercise programs depending on type, duration and intensity and these miRNAs have been shown to play an important role in cell-to-cell communication through EV during T2D [72]. Recent studies have demonstrated that PA increases miRNA-126 containing EV release into bloodstream [73,74], suggesting that EV could participate in cell-to-cell communication during exercise-mediated adaptation by carrying miRNA to other organs and tissues. This hypothesis is supported by the fact that the majority of the previous reported miRNA, myokines, adipokines, and other mediators implicated in T2D progression, were found in EV. Recent results related to miRNA expression in cell-to-cell communication have arose novel pathways which can explain the PA antidiabetic effects (Figure 3).

Figure 3: Proposal of some mechanisms related to physical activity effects during type 2 diabetes through the modulation of miRNA synthesis and extracellular vesicle releases. Physical activity could modify AMPK: AMP-activated protein kinase, GLUT-4: glucose transporter-4, miRNA: microRNA, PGC-1α: peroxisome proliferator-activated receptor-γ coactivator-1α.

Several studies demonstrated that PA modifies miRNA expression in healthy humans. Radom-Aizik S et al. largely contributed to identify the modifications of

circulating miRNA expression after PA in human [75–78]. Tables 2 and 3 summarize the miRNA with up and down regulated expression after PA in healthy human. Whether ten miRNA or precursors (miRNA-15a, miRNA-30e, miRNA-130a, miRNA-151-5p, miRNA-181b, miRNA-223, miRNA-338-3p, miRNA-486, miRNA-499, miRNA-652) present a clear modified expression which is described by three different authors or more, some data remain divergent with a description of both down- and up-regulation of other miRNA (miRNA-1, miRNA-20a, miRNA-21, miRNA-27a-5p, miRNA-107, miRNA-125a-5p, miRNA-126, miRNA-133a, miRNA-133b, miRNA-143-3p, miRNA-145, miRNA-146a, miRNA-206, miRNA-221, miRNA-222, miRNA-363, miRNA-451).

These discrepancies can be explained by the type of PA. Sapp RM et al [79] effectively demonstrated that 30-minute high intensity interval cycling exercise bouts increased the expression of circulating miRNA-126-3p and miRNA-126-5p compared to 30-minute moderate continuous cycling exercise bouts in ten young and healthy men. Similarly, both Mooren FC et al. [80], Baggish AI et al. [81] and Clauss S et al. [82] observed an increased expression of miRNA-133a in the blood circulation of healthy subjects after a marathon while Cui SF et al. [83] observed a decreased expression of the same miRNA-133a after a 30-second intervals intensive sprint cycling in healthy young men. Following the type of PA (aerobic / nonaerobic, endurance training / high intensity training), an opposite effect on the expression of some miRNA can be observed.

In addition, by comparing miRNA expression in muscle of ten young (24.2 ± 0.9 years) and ten old (66.6 ± 1.1 years) males after acute bout of resistance exercise, Zacharewicz E et al. [84] observed

miRNA	Organ	References
miRNA-1	Blood circulation	[80–82, 88–92]
miRNA-7	PBMCs NK cells	[76,77,93]
miRNA-10a-5p	Blood circulation	[94,95]
miRNA-15a	Blood circulation	[96,97]
miRNA-20a	PBMCs	[77]
miRNA-21	Monocytes	[78]
miRNA-21-5p	Blood circulation	[98]
miRNA-22-3p	Blood circulation	[98,99]
miRNA-24	PBMCs	[100]
miRNA-24-2-5p		[101]
miRNA-26b	Blood circulation	[94,102]
miRNA-27-a		[61,103]
miRNA-27a-5p		[101]
miRNA-27b-3p	PBMCs	[77]
miRNA-29a		[104,105]
miRNA-29b	Blood circulation	[101]
miRNA-29c		[106,107]
miRNA-30a-5p	NK cells	[76,108]
miRNA-30d-5p	NK cells	[76,105]
miRNA-30e	NK cells	[78]
miRNA-96-5p	Monocytes	[104]
miRNA-98-3p	Blood circulation	[103]
miRNA-103		[111]
miRNA-107		[89,112]
miRNA-122		[89]
miRNA-125a-5p		[83,113]
miRNA-126	Blood circulation	[111]
miRNA-126-3p	Neutrophils	[75]
miRNA-126-5p		[114,115]
miRNA-128	Blood circulation	[116]
miRNA-132		[79,106]
miRNA-133		[79]
miRNA-133a		[94]
miRNA-133b	PBMCs	[77,117]
miRNA-134		[114]
miRNA-139-5p	Blood circulation	[114]
miRNA-140-5p		[80,81,85,88,90–92,118]
miRNA-142-3p	Blood circulation	[88,92, 118]
miRNA-142-5p		[81]
miRNA-143		[89,109, 119]
miRNA-143-3p	PBMCs	[77,78]
miRNA-145	Monocytes	[76]
miRNA-146a	NK cells	[106]
miRNA-146a-5p	Blood circulation	[76]
miRNA-149		[89,103, 120]
miRNA-150		[109]
miRNA-181a	Neutrophils	[75,121]
miRNA-181a-5p		[81,92,98,122]
miRNA-181a-2		[106]
miRNA-181b	Blood circulation	[123]
miRNA-181c		[104,124]
miRNA-186	PBMCs	[77,125]
miRNA-192	Blood circulation	[92,101]
miRNA-193a-3p	PBMCs	[77]
miRNA-195-5p	Neutrophils	[75]
miRNA-197		[88,96]
miRNA-197-3p	Blood circulation	[77]
miRNA-206	PBMCs	[77]
miRNA-208a	Neutrophils	[75]
miRNA-208b		[78]
miRNA-212	Monocyte	[77]
miRNA-214		[75]
miRNA-221	Blood circulation	[77]
miRNA-221-3p	PBMCs	[77]
miRNA-222	NK cells	[75]
miRNA-223		[75]
miRNA-324-3p	Neutrophils	[75]
miRNA-330-3p	Monocyte	[78]
miRNA-338-3p	Blood circulation	[89]
miRNA-339-3p	Blood circulation	[89]
miRNA-340	PBMCs	[77,129]
miRNA-362-3p	NK cells	[76]
miRNA-362-5p	Monocytes	[78]
miRNA-363		[77]
miRNA-365	PBMCs	[77]
miRNA-378a-3p	Neutrophils	[75]
miRNA-378a-5p		[75]
miRNA-378f		[75]
miRNA-378g		[75]
miRNA-378i		[75]
miRNA-422a		[75]
miRNA-451	Blood circulation	[94]
miRNA-485-3p	Muscle	[85,131]
miRNA-485-5p	Neutrophils	[75]
miRNA-494		[118]
miRNA-499		[104]
miRNA-499-5p	Blood circulation	[80,92]
miRNA-505		[81,88,91]
miRNA-509-5p	Neutrophils	[75]
miRNA-517a		[75]
miRNA-518f-3p	Blood circulation	[118]
miRNA-520d-3p		[118]
miRNA-520f	Neutrophils	[75]
miRNA-522		[75]
miRNA-532-3p	Blood circulation	[118]
miRNA-532-5p	Monocytes	[78]
miRNA-553	Monocytes	[78]
miRNA-629	Blood circulation	[94]
miRNA-638		[118]
miRNA-888	Blood circulation	[118]
miRNA-939		[118]
miRNA-940	PBMCs	[77]
miRNA-1202	Neutrophils	[77]
miRNA-1225-5p	Monocyte	[78]
miRNA-1238	PBMCs	[77]
miRNA-1260	Neutrophils	[75]
miRNA-1305	Blood circulation	[104]
	Monocyte	[78]

Table 2: Upregulated miRNAs in healthy human after physical activity. PBMCs: peripheral blood mononuclear cells; NK: natural killer. miRNAs involved in insulin pathway are in bold.

miRNA	Organ	Reference
miRNA-1	Muscle	[118]
	Blood circulation	[83]
	Muscle	[132]
miRNA-7-5p	Blood circulation	[106]
miRNA-16	Blood circulation Neutrophils	[83] [75]
miRNA-17	Neutrophils	[75]
miRNA-18a		
miRNA-18b		
miRNA-20a		
miRNA-20b		
miRNA-21	Blood circulation	[77,89,99,133]
miRNA-22	Neutrophils	[75,134]
miRNA-23b	PBMCs Monocytes	[77,135] [78]
miRNA-24-2p	Blood circulation	[101]
miRNA-25		[89]
miRNA-25-3p		[106]
miRNA-26a	Muscle	[85,108]
miRNA-27a-5p	Blood circulation	[101]
miRNA-29a	Muscle	[85,108]
miRNA-29b-3p	Blood circulation	[105,106]
miRNA-29c-3p		
miRNA-30a		
miRNA-30b	PBMCs	[82]
miRNA-30d-5p		[89]
miRNA-31		[136]
miRNA-92a-3p	PBMCs	[77]
miRNA-93	Blood circulation	[106]
miRNA-93-5p	Blood circulation	[106]
miRNA-96	Blood circulation Neutrophils	[96] [75]
miRNA-99	PBMCs	[77]
miRNA-106a	Blood circulation Neutrophils	[89] [75]
miRNA-107	Neutrophils	[75]
miRNA-125a-5p	PBMCs	[77]
miRNA-126	Neutrophils NK cells	[81,115] [75] [76,77]
miRNA-130a	PBMCs Neutrophils NK cells Monocytes	[77] [75] [76] [78]
miRNA-130b	Neutrophils	[75]
miRNA-133a	Blood circulation Muscle	[83] [132]
miRNA-133b	Blood circulation Muscle	[83] [132]

miRNA-143-3p	Blood circulation	[109]
miRNA-144		[104]
miRNA-145	PBMCs	[77,121]
miRNA-146a	Blood circulation	[123][89]
miRNA-148a		[89]
miRNA-148b		[89]
miRNA-151-5p	PBMCs Neutrophils NK cells Monocytes Muscle	[77] [75] [76] [78] [84]
miRNA-151-3p	Blood circulation PBMCs	[89] [77]
miRNA-151-5p	Blood circulation Neutrophils	[89] [75]
miRNA-181-5p	Blood circulation	[101]
miRNA-185	Blood circulation Neutrophils	[89] [75]
miRNA-194	Neutrophils	[75]
miRNA-199a-3p	NK cells Monocytes	[76] [78]
miRNA-199a-5p	PBMCs NK cells	[77] [76]
miRNA-199b-3p	PBMCs	[77]
miRNA-206	Muscle	[126,132]
miRNA-210	Blood circulation	[100,133]
miRNA-221	Neutrophils Monocytes	[76,77,127] [78]
miRNA-222	Blood circulation	[128] [133]
miRNA-320	PBMCs	[77,138]
miRNA-320b	Blood circulation	[104]
miRNA-320c		
miRNA-320d		
miRNA-320e		
miRNA-326		
miRNA-328	NK cells	[76]
miRNA-342-3p	Blood circulation	[89]
miRNA-363	Neutrophils NK cells	[75] [76]
miRNA-378	Muscle	[85,139]
miRNA-483-5p	Muscle	[84]
miRNA-486	Blood circulation PBMCs Muscle	[140] [77] [139]
miRNA-486-5p	Blood circulation	[106]
miRNA-574-3p	Muscle	[84]
miRNA-584	PBMCs	[77]
miRNA-592-5p	NK cells	[76]
miRNA-652	Blood circulation PBMCs NK cells	[89] [77] [76]
miRNA-660	Neutrophils Monocytes	[75] [78]
miRNA-766	Blood circulation	[89]
miRNA-935	Muscle	[84]
miRNA-3656	Blood circulation	[104]

Table 3 regulated miRNAs in healthy human after physical activity. PBMCs: peripheral blood mononuclear cells; NK: natural killer. miRNAs involved in insulin pathway are in bold.

variations of expression for seven miRNA (miRNA-146a-5p, miRNA-191-5p, miRNA-320a, miRNA-483-5p, miRNA-486-3p, miRNA-539-5p and miRNA-628-5p) with different effects for the two groups. The age should also be considered in the modified expression of miRNA after PA.

The long-term training has also been studied to evaluate whether it can modify the expression of miRNA after a PA. Nielsen S et al. [85] observed an increased expression of miRNA-1 and miRNA-133a after a 60-minute cycle ergometer exercise bout in muscle of ten healthy men while no modification of the expression was observed after 12 weeks of high intensity endurance training in the same subjects. Long term training of subjects has also to be considered suggesting that the physical exertion does not induce the same metabolism for trained subjects compared to non-trained subjects and lead to variations of miRNA expression in these two populations.

It is noteworthy that the majority of the studies reported in [tables 2 and 3](#) indicate miRNA expression in blood circulation or in cells from the blood circulation. Blood samples is easy to perform and in human, biopsies remain very invasive procedures and few data reported level expression of miRNA after PA in specific organs. Even if they are in the blood circulation, miRNA can originate from organs. Because miRNA can be carried by EV and that EV can express specific markers of the organ from which they come from, the organ origin of the circulating miRNA could be partly identified by a co-staining of specific markers of EV. Then, characterization of EV and identification of their organ origin would allow to precise the origin of circulating miRNA. Interestingly, recent studies have demonstrated that PA increased EV release into bloodstream [73,74], suggesting that EV could participate in cell-to-cell communication during exercise-mediated adaptation by

carrying miRNA to other organs and tissues. This hypothesis is supported by the fact that the majority of the previous reported miRNA, myokines, adipokines, and other mediators implicated in T2D progression, are found in EV.

More recently, some studies examined the effect of PA on miRNA-contained EV release in specific organs such as liver, muscle, kidney, and adipose tissue. De Mendonça M et al, showed that aerobic training induces a decrease of miRNA-122, miRNA-192, and miRNA-22 levels in the circulating EV of obese mice [86]. In addition, the aerobic exercise reduced adipocyte hypertrophy and increased the expression of adipogenesis markers in this animal model. Furthermore, the expression of adipogenesis and insulin sensitivity markers is negatively correlated with miRNA-22 levels. This study also showed that aerobic training reverted obesity-induced steatohepatitis and adipogenesis markers and were negatively correlated with miRNA-122 levels in the liver. These observations from a murine model suggest that miRNA-contained EV might be involved in communication between liver and adipose tissue during aerobic exercise but need to be confirmed in human.

Interestingly, among miRNAs mainly increased by T2D ([table 1](#)), miRNA-96 has also been described to be decreased after PA ([table 3](#)). This means that PA can counterbalance some T2D-induced skeletal miRNAs. However, further studies are needed to specifically evaluate if PA can decrease all the overexpressed miRNA in T2D conditions.

5. Conclusion

Regarding its health benefits, physicians generally prescribe PA as first-line therapy for T2D patients. PA causes adjustments in the releases of insulin, myokines, adipokines, hepatokines, and

other mediators, by which it improves cell-to-cell communication during T2D. Some of these mediators including miRNA are released within EV. Additional studies are now needed to determine and to characterize the roles miRNA in these conditions. Determination of miRNA cell origins especially those modified during PA in T2D conditions, is essential to shed the light on pathways implicated in antidiabetic effects of PA. Administration of isolated EV from athletes following exercise or bioengineered EV carrying miRNAs could also be a promising beneficial tool for T2D treatment.

6. References

- DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, et al. Type 2 diabetes mellitus. *Nat Rev Dis Primer*. 2015 Jul 23;1(1):1–22.
- Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. *Endocrinol Metab Clin North Am*. 2010 Sep;39(3):481–97.
- Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Kaabi JA. Epidemiology of Type 2 Diabetes – Global Burden of Disease and Forecasted Trends. *J Epidemiol Glob Health*. 2019 Nov;10(1):107–11.
- American Diabetes Association. 1. Improving Care and Promoting Health in Populations: Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018;41(Suppl 1):S7–12.
- Lee I-M, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet Lond Engl*. 2012 Jul 21;380(9838):219–29.
- Desvignes T, Batzel P, Berezikov E, Eilbeck K, Eppig JT, McAndrews MS, et al. microRNA nomenclature: A view incorporating genetic origins, biosynthetic pathways, and sequence variants. *Trends Genet TIG*. 2015 Nov;31(11):613–26.
- Treiber T, Treiber N, Meister G. Regulation of microRNA biogenesis and its crosstalk with other cellular pathways. *Nat Rev Mol Cell Biol*. 2019 Jan;20(1):5–20.
- Guay C, Regazzi R. Circulating microRNAs as novel biomarkers for diabetes mellitus. *Nat Rev Endocrinol*. 2013 Sep;9(9):513–21.
- Wong WKM, Sørensen AE, Joglekar MV, Hardikar AA, Dalgaard LT. Non-Coding RNA in Pancreas and β -Cell Development. *Non-Coding RNA*. 2018 Dec 13;4(4).
- Vasu S, Kumano K, Darden CM, Rahman I, Lawrence MC, Naziruddin B. MicroRNA Signatures as Future Biomarkers for Diagnosis of Diabetes States. *Cells* [Internet]. 2019 Nov 28 [cited 2020 Dec 7];8(12). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6953078/>
- Doyle LM, Wang MZ. Overview of Extracellular Vesicles, Their Origin, Composition, Purpose, and Methods for Exosome Isolation and Analysis. *Cells* [Internet]. 2019 Jul 15 [cited 2020 May 10];8(7). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6678302/>
- van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol*. 2018 Apr;19(4):213–28.
- Durcin M, Fleury A, Taillebois E, Hilaret G, Krupova Z, Henry C, et al. Characterisation of adipocyte-derived extracellular vesicle subtypes identifies distinct protein and lipid signatures for large and small extracellular vesicles. *J Extracell Vesicles* [Internet]. 2017 Apr 10 [cited 2020 May 10];6(1). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5405565/>
- Chong SY, Lee CK, Huang C, Ou YH, Charles CJ, Richards AM, et al. Extracellular Vesicles in Cardiovascular Diseases: Alternative Biomarker Sources, Therapeutic Agents, and Drug Delivery Carriers. *Int J Mol Sci*. 2019 Jan;20(13):3272.
- Fais S, O'Driscoll L, Borrás FE, Buzas E, Camussi G, Cappello F, et al. Evidence-Based Clinical Use of Nanoscale Extracellular Vesicles in Nanomedicine. *ACS Nano*. 2016 Apr 26;10(4):3886–99.
- McDaniel K, Correa R, Zhou T, Johnson C, Francis H, Glaser S, et al. Functional role of microvesicles in gastrointestinal malignancies. *Ann Transl Med* [Internet]. 2013 Apr [cited 2021 Feb 9];1(1). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3890379/>
- Chakraborty C, Doss CGP, Bandyopadhyay S, Agoramoorthy G. Influence of miRNA in insulin signaling pathway and insulin resistance: micro-molecules with a major role in type-2 diabetes. *WIREs RNA*. 2014;5(5):697–712.

18. Lee M-W, Lee M, Oh K-J. Adipose Tissue-Derived Signatures for Obesity and Type 2 Diabetes: Adipokines, Batokines and MicroRNAs. *J Clin Med*. 2019 Jun;8(6):854.
19. Fu Z, Gilbert ER, Liu D. Regulation of Insulin Synthesis and Secretion and Pancreatic Beta-Cell Dysfunction in Diabetes. *Curr Diabetes Rev*. 2013 Jan 1;9(1):25–53.
20. Zhang A, Li D, Liu Y, Li J, Zhang Y, Zhang C-Y. Islet β cell: An endocrine cell secreting miRNAs. *Biochem Biophys Res Commun*. 2018 08;495(2):1648–54.
21. Werneck-de-Castro JP, Blandino-Rosano M, Hilfiker-Kleiner D, Bernal-Mizrachi E. Glucose stimulates microRNA-199 expression in murine pancreatic β -cells. *J Biol Chem*. 2020 Jan 31;295(5):1261–70.
22. Zhang Y, Yang M, Zhou P, Yan H, Zhang Z, Zhang H, et al. β -Hydroxy- β -methylbutyrate-Induced Upregulation of miR-199a-3p Contributes to Slow-To-Fast Muscle Fiber Type Conversion in Mice and C2C12 Cells. *J Agric Food Chem*. 2020 Jan 15;68(2):530–40.
23. Lee JH, Jun H-S. Role of Myokines in Regulating Skeletal Muscle Mass and Function. *Front Physiol* [Internet]. 2019 Jan 30 [cited 2020 Apr 26];10. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6363662/>
24. Pedersen L, Hojman P. Muscle-to-organ cross talk mediated by myokines. *Adipocyte*. 2012 Jul 1;1(3):164–7.
25. Carson BP. The Potential Role of Contraction-Induced Myokines in the Regulation of Metabolic Function for the Prevention and Treatment of Type 2 Diabetes. *Front Endocrinol* [Internet]. 2017 May 2 [cited 2020 Apr 26];8. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5411437/>
26. Carey AL, Steinberg GR, Macaulay SL, Thomas WG, Holmes AG, Ramm G, et al. Interleukin-6 increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in vitro via AMP-activated protein kinase. *Diabetes*. 2006 Oct;55(10):2688–97.
27. Ellingsgaard H, Hauselmann I, Schuler B, Habib AM, Baggio LL, Meier DT, et al. Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. *Nat Med*. 2011 Oct 30;17(11):1481–9.
28. Kahles F, Meyer C, Möllmann J, Diebold S, Findeisen HM, Lebherz C, et al. GLP-1 secretion is increased by inflammatory stimuli in an IL-6-dependent manner, leading to hyperinsulinemia and blood glucose lowering. *Diabetes*. 2014 Oct;63(10):3221–9.
29. Perakakis N, Triantafyllou GA, Fernández-Real JM, Huh JY, Park KH, Seufert J, et al. Physiology and role of irisin in glucose homeostasis. *Nat Rev Endocrinol*. 2017 Jun;13(6):324–37.
30. Rana KS, Pararasa C, Afzal I, Nagel DA, Hill EJ, Bailey CJ, et al. Plasma irisin is elevated in type 2 diabetes and is associated with increased E-selectin levels. *Cardiovasc Diabetol*. 2017 09;16(1):147.
31. Xiang L, Xiang G, Yue L, Zhang J, Zhao L. Circulating irisin levels are positively associated with endothelium-dependent vasodilation in newly diagnosed type 2 diabetic patients without clinical angiopathy. *Atherosclerosis*. 2014 Aug;235(2):328–33.
32. El-Lebedy DH, Ibrahim AA, Ashmawy IO. Novel adipokines vaspin and irisin as risk biomarkers for cardiovascular diseases in type 2 diabetes mellitus. *Diabetes Metab Syndr*. 2018 Sep;12(5):643–8.
33. Peng Q, Wang X, Wu K, Liu K, Wang S, Chen X. Irisin attenuates H2O2-induced apoptosis in cardiomyocytes via microRNA-19b/AKT/mTOR signaling pathway. *Int J Clin Exp Pathol*. 2017 Jul 1;10(7):7707–17.
34. Parr EB, Camera DM, Burke LM, Phillips SM, Coffey VG, Hawley JA. Circulating MicroRNA Responses between ‘High’ and ‘Low’ Responders to a 16-Wk Diet and Exercise Weight Loss Intervention. *PLoS ONE* [Internet]. 2016 Apr 21 [cited 2021 Feb 10];11(4). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4839646/>
35. Andersen H, Nielsen S, Mogensen CE, Jakobsen J. Muscle strength in type 2 diabetes. *Diabetes*. 2004 Jun;53(6):1543–8.
36. Volpato S, Bianchi L, Lauretani F, Lauretani F, Bandinelli S, Guralnik JM, et al. Role of Muscle Mass and Muscle Quality in the Association Between Diabetes and Gait Speed. *Diabetes Care*. 2012 Aug 1;35(8):1672–9.
37. Barazzoni R, Short KR, Asmann Y, Coenen-Schimke JM, Robinson MM, Sreekumaran Nair K. Insulin fails to enhance mTOR phosphorylation, mitochondrial protein synthesis, and ATP production in human skeletal muscle without amino acid replacement. *Am J Physiol-Endocrinol Metab*. 2012 Sep 11;303(9):E1117–25.
38. Lee M-R, Jung SM, Bang H, Kim HS, Kim YB. Association between muscle strength and type 2 diabetes mellitus in adults in Korea. *Medicine (Baltimore)* [Internet]. 2018 Jun 18 [cited 2020 Dec 7];97(23).

- Available from:
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5999476/>
39. Sun Z, Liu L, Liu N, Liu Y. Muscular response and adaptation to diabetes mellitus. *Front Biosci J Virtual Libr.* 2008 May 1;13:4765–94.
  40. Gan Z, Fu T, Kelly DP, Vega RB. Skeletal muscle mitochondrial remodeling in exercise and diseases. *Cell Res.* 2018;28(10):969–80.
  41. Kirby TJ, McCarthy JJ. MicroRNAs in skeletal muscle biology and exercise adaptation. *Free Radic Biol Med.* 2013 Sep;64:95–105.
  42. Nieto M, Hevia P, Garcia E, Klein D, Alvarez-Cubela S, Bravo-Egana V, et al. Antisense miR-7 impairs insulin expression in developing pancreas and in cultured pancreatic buds. *Cell Transplant.* 2012;21(8):1761–74.
  43. Lovis P, Gattesco S, Regazzi R. Regulation of the expression of components of the exocytotic machinery of insulin-secreting cells by microRNAs. *Biol Chem.* 2008 Mar;389(3):305–12.
  44. Melkman-Zehavi T, Oren R, Kredo-Russo S, Shapira T, Mandelbaum AD, Rivkin N, et al. miRNAs control insulin content in pancreatic β -cells via downregulation of transcriptional repressors. *EMBO J.* 2011 Mar 2;30(5):835–45.
  45. Mohan R, Mao Y, Zhang S, Zhang Y-W, Xu C-R, Gradwohl G, et al. Differentially Expressed MicroRNA-483 Confers Distinct Functions in Pancreatic β - and α -Cells. *J Biol Chem.* 2015 Aug 7;290(32):19955–66.
  46. Wander PL, Enquobahrie DA, Bammler TK, Srinouanprachanh S, MacDonald J, Kahn SE, et al. Short Report: Circulating microRNAs are associated with incident diabetes over 10 years in Japanese Americans. *Sci Rep.* 2020 Apr 16;10(1):6509.
  47. Sun Q, van Dam RM, Meigs JB, Franco OH, Mantzoros CS, Hu FB. Leptin and Soluble Leptin Receptor Levels in Plasma and Risk of Type 2 Diabetes in U.S. Women. *Diabetes.* 2010 Mar;59(3):611–8.
  48. Lee H, Jee Y, Hong K, Hwang GS, Chun K-H. MicroRNA-494, Upregulated by Tumor Necrosis Factor- α , Desensitizes Insulin Effect in C2C12 Muscle Cells. *PLoS ONE* [Internet]. 2013 Dec 11 [cited 2019 Jan 15];8(12). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3859653/>
  49. da Costa RM, Neves KB, Mestriner FL, Louzada-Junior P, Bruder-Nascimento T, Tostes RC. TNF- α induces vascular insulin resistance via positive modulation of PTEN and decreased Akt/eNOS/NO signaling in high fat diet-fed mice. *Cardiovasc Diabetol* [Internet]. 2016 Aug 25 [cited 2019 Jan 15];15(1). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5000486/>
  50. Ying W, Riopel M, Bandyopadhyay G, Dong Y, Birmingham A, Seo JB, et al. Adipose Tissue Macrophage-Derived Exosomal miRNAs Can Modulate In Vivo and In Vitro Insulin Sensitivity. *Cell.* 2017 Oct 5;171(2):372–384.e12.
  51. Lee Y-S, Kim SY, Ko E, Lee J-H, Yi H-S, Yoo YJ, et al. Exosomes derived from palmitic acid-treated hepatocytes induce fibrotic activation of hepatic stellate cells. *Sci Rep.* 2017 16;7(1):3710.
  52. Wu J, Dong T, Chen T, Sun J, Luo J, He J, et al. Hepatic exosome-derived miR-130a-3p attenuates glucose intolerance via suppressing PHLPP2 gene in adipocyte. *Metabolism.* 2020;103:154006.
  53. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep.* 1985;100(2):126–31.
  54. Rivera-Brown AM, Frontera WR. Principles of Exercise Physiology: Responses to Acute Exercise and Long-term Adaptations to Training. *PM&R.* 2012 Nov 1;4(11):797–804.
  55. Vilaça-Alves J, Freitas NM, Saavedra FJ, Scott CB, dos Reis VM, Simão R, et al. Comparison of oxygen uptake during and after the execution of resistance exercises and exercises performed on ergometers, matched for intensity. *J Hum Kinet.* 2016 Oct 15;53:179–87.
  56. Goodwin ML, Harris JE, Hernández A, Gladden LB. Blood Lactate Measurements and Analysis during Exercise: A Guide for Clinicians. *J Diabetes Sci Technol Online.* 2007 Jul;1(4):558–69.
  57. Leite SA, Monk AM, Upham PA, Chacra AR, Bergenstal RM. Low cardiorespiratory fitness in people at risk for type 2 diabetes: early marker for insulin resistance. *Diabetol Metab Syndr.* 2009 Sep 21;1:8.
  58. Reusch JEB, Bridenstine M, Regensteiner JG. Type 2 diabetes mellitus and exercise impairment. *Rev Endocr Metab Disord.* 2013 Mar;14(1):77–86.
  59. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of Exercise on Glycemic Control and Body Mass in Type 2 Diabetes Mellitus: A Meta-analysis of Controlled Clinical Trials. *JAMA.* 2001 Sep 12;286(10):1218–27.

60. Sigal RJ, Kenny GP, Boulé NG, Wells GA, Prud'homme D, Fortier M, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. *Ann Intern Med.* 2007 Sep 18;147(6):357–69.
61. Dela F, Ingersen A, Andersen NB, Nielsen MB, Petersen HHH, Hansen CN, et al. Effects of one-legged High-intensity Interval Training on insulin-mediated skeletal muscle glucose homeostasis in patients with type 2 diabetes. *Acta Physiol Oxf Engl.* 2018 Dec 26;e13245.
62. Rahimi N, Samavati Sharif MA, Goharian AR, Pour AH. The Effects of Aerobic Exercises and 25(OH) D Supplementation on GLP1 and DPP4 Level in Type II Diabetic Patients. *Int J Prev Med.* 2017;8:56.
63. Braun B, Zimmermann MB, Kretchmer N. Effects of exercise intensity on insulin sensitivity in women with non-insulin-dependent diabetes mellitus. *J Appl Physiol Bethesda Md 1985.* 1995 Jan;78(1):300–6.
64. Rech A, Botton CE, Lopez P, Quincozes-Santos A, Umpierre D, Pinto RS. Effects of short-term resistance training on endothelial function and inflammation markers in elderly patients with type 2 diabetes: A randomized controlled trial. *Exp Gerontol.* 2019 Jan 3;118:19–25.
65. Chen Z-P, Stephens TJ, Murthy S, Canny BJ, Hargreaves M, Witters LA, et al. Effect of exercise intensity on skeletal muscle AMPK signaling in humans. *Diabetes.* 2003 Sep;52(9):2205–12.
66. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. *Diabetes Care.* 2016 Nov;39(11):2065–79.
67. Drive ADA 2451 C, Arlington S 900, Va 22202 1-800-Diabetes. American Diabetes Association Releases 2018 Standards of Medical Care in Diabetes, with Notable New Recommendations for People with Cardiovascular Disease and Diabetes [Internet]. American Diabetes Association. 2018 [cited 2018 Dec 13]. Available from: <http://www.diabetes.org/newsroom/press-releases/2017/american-diabetes-association-2018-release-standards-of-medical-care-in-diabetes.html>
68. Jung TW, Park HS, Choi GH, Kim D, Lee T. β -aminoisobutyric acid attenuates LPS-induced inflammation and insulin resistance in adipocytes through AMPK-mediated pathway. *J Biomed Sci.* 2018 Mar 28;25(1):27.
69. Jessen N, An D, Lihn AS, Nygren J, Hirshman MF, Thorell A, et al. Exercise increases TBC1D1 phosphorylation in human skeletal muscle. *Am J Physiol - Endocrinol Metab.* 2011 Jul;301(1):E164–71.
70. Lira VA, Benton CR, Yan Z, Bonen A. PGC-1 α regulation by exercise training and its influences on muscle function and insulin sensitivity. *Am J Physiol - Endocrinol Metab.* 2010 Aug;299(2):E145–61.
71. Leick L, Fentz J, Biensø RS, Knudsen JG, Jeppesen J, Kiens B, et al. PGC-1 α is required for AICAR-induced expression of GLUT4 and mitochondrial proteins in mouse skeletal muscle. *Am J Physiol-Endocrinol Metab.* 2010 Jul 13;299(3):E456–65.
72. La Marca V, Fierabracci A. Insights into the Diagnostic Potential of Extracellular Vesicles and Their miRNA Signature from Liquid Biopsy as Early Biomarkers of Diabetic Micro/Macrovascular Complications. *Int J Mol Sci [Internet].* 2017 Sep 14 [cited 2020 Apr 27];18(9). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5618623/>
73. Ma C, Wang J, Liu H, Chen Y, Ma X, Chen S, et al. Moderate Exercise Enhances Endothelial Progenitor Cell Exosomes Release and Function. *Med Sci Sports Exerc.* 2018 Oct;50(10):2024–32.
74. Whitham M, Parker BL, Friedrichsen M, Hingst JR, Hjorth M, Hughes WE, et al. Extracellular Vesicles Provide a Means for Tissue Crosstalk during Exercise. *Cell Metab.* 2018 Jan 9;27(1):237–251.e4.
75. Radom-Aizik S, Zaldivar F, Oliver S, Galassetti P, Cooper DM. Evidence for microRNA involvement in exercise-associated neutrophil gene expression changes. *J Appl Physiol Bethesda Md 1985.* 2010 Jul;109(1):252–61.
76. Radom-Aizik S, Zaldivar F, Haddad F, Cooper DM. Impact of brief exercise on peripheral blood NK cell gene and microRNA expression in young adults. *J Appl Physiol.* 2013 Jan 3;114(5):628–36.
77. Radom-Aizik S, Zaldivar F, Leu S-Y, Adams GR, Oliver S, Cooper DM. Effects of Exercise on microRNA Expression in Young Males Peripheral Blood Mononuclear Cells. *Clin Transl Sci.* 2012;5(1):32–8.
78. Radom-Aizik S, Zaldivar FP, Haddad F, Cooper DM. Impact of brief exercise on circulating monocyte gene and microRNA expression: implications for atherosclerotic vascular disease. *Brain Behav Immun.* 2014 Jul;39:121–9.

79. Sapp RM, Evans WS, Eagan LE, Chesney CA, Zietowski EM, Prior SJ, et al. The effects of moderate and high-intensity exercise on circulating markers of endothelial integrity and activation in young, healthy men. *J Appl Physiol*. 2019 Sep 5;127(5):1245–56.
80. Mooren FC, Viereck J, Krüger K, Thum T. Circulating micrnas as potential biomarkers of aerobic exercise capacity. *Am J Physiol-Heart Circ Physiol*. 2013 Dec 20;306(4):H557–63.
81. Baggish AL, Park J, Min P-K, Isaacs S, Parker BA, Thompson PD, et al. Rapid upregulation and clearance of distinct circulating microRNAs after prolonged aerobic exercise. *J Appl Physiol*. 2014 Jan 16;116(5):522–31.
82. Clauss S, Wakili R, Hildebrand B, Käab S, Hoster E, Klier I, et al. MicroRNAs as Biomarkers for Acute Atrial Remodeling in Marathon Runners (The miRathon Study--A Sub-Study of the Munich Marathon Study). *PloS One*. 2016;11(2):e0148599.
83. Cui SF, Li W, Niu J, Zhang CY, Chen X, Ma JZ. Acute responses of circulating microRNAs to low-volume sprint interval cycling. *Front Physiol [Internet]*. 2015 [cited 2020 Apr 27];6. Available from: <https://www.frontiersin.org/articles/10.3389/fphys.2015.00311/full>
84. Zacharewicz E, Gatta PD, Reynolds J, Garnham A, Crowley T, Russell AP, et al. Identification of MicroRNAs Linked to Regulators of Muscle Protein Synthesis and Regeneration in Young and Old Skeletal Muscle. *PLOS ONE*. 2014 Dec 2;9(12):e114009.
85. Davidsen PK, Gallagher IJ, Hartman JW, Tarnopolsky MA, Dela F, Helge JW, et al. High responders to resistance exercise training demonstrate differential regulation of skeletal muscle microRNA expression. *J Appl Physiol Bethesda Md 1985*. 2011 Feb;110(2):309–17.
86. de Mendonça M, Rocha KC, de Sousa É, Pereira BMV, Oyama LM, Rodrigues AC. Aerobic exercise training regulates serum extracellular vesicle miRNAs linked to obesity to promote their beneficial effects in mice. *Am J Physiol Endocrinol Metab*. 2020 01;319(3):E579–91.
87. Tsukita S, Yamada T, Takahashi K, Munakata Y, Hosaka S, Takahashi H, et al. MicroRNAs 106b and 222 Improve Hyperglycemia in a Mouse Model of Insulin-Deficient Diabetes via Pancreatic β -Cell Proliferation. *EBioMedicine*. 2017 Feb;15:163–72.
88. Banzet S, Chennaoui M, Girard O, Racinais S, Drogou C, Chalabi H, et al. Changes in circulating microRNAs levels with exercise modality. *J Appl Physiol*. 2013 Aug 15;115(9):1237–44.
89. Nielsen S, Åkerström T, Rinnov A, Yfanti C, Scheele C, Pedersen BK, et al. The miRNA Plasma Signature in Response to Acute Aerobic Exercise and Endurance Training. *PLOS ONE*. 2014 Feb 19;9(2):e87308.
90. Gomes CPC, Oliveira-Jr GP, Madrid B, Almeida JA, Franco OL, Pereira RW. Circulating miR-1, miR-133a, and miR-206 levels are increased after a half-marathon run. *Biomarkers*. 2014 Nov 1;19(7):585–9.
91. Min P-K, Park J, Isaacs S, Taylor BA, Thompson PD, Troyanos C, et al. Influence of statins on distinct circulating microRNAs during prolonged aerobic exercise. *J Appl Physiol*. 2015 Oct 15;120(6):711–20.
92. Guescini M, Canonico B, Lucertini F, Maggio S, Annibalini G, Barbieri E, et al. Muscle Releases Alpha-Sarcoglycan Positive Extracellular Vesicles Carrying miRNAs in the Bloodstream. *PLOS ONE*. 2015 May 8;10(5):e0125094.
93. Matarese A, Gambardella J, Lombardi A, Wang X, Santulli G. miR-7 Regulates GLP-1-Mediated Insulin Release by Targeting β -Arrestin 1. *Cells*. 2020 Jul;9(7):1621.
94. McLean CS, Mielke C, Cordova JM, Langlais PR, Bowen B, Miranda D, et al. Gene and MicroRNA Expression Responses to Exercise; Relationship with Insulin Sensitivity. *PLOS ONE*. 2015 May 18;10(5):e0127089.
95. Guo Y, Zhu X, Zeng S, He M, Xing X, Wang C. miRNA-10a-5p Alleviates Insulin Resistance and Maintains Diurnal Patterns of Triglycerides and Gut Microbiota in High-Fat Diet-Fed Mice [Internet]. Vol. 2020, *Mediators of Inflammation*. Hindawi; 2020 [cited 2021 Feb 12]. p. e8192187. Available from: <https://www.hindawi.com/journals/mi/2020/8192187/>
96. Chilton WL, Marques FZ, West J, Kannourakis G, Berzins SP, O'Brien BJ, et al. Acute Exercise Leads to Regulation of Telomere-Associated Genes and MicroRNA Expression in Immune Cells. *PLOS ONE*. 2014 Apr 21;9(4):e92088.
97. Lee IS, Park KC, Yang K-J, Choi H, Jang YS, Lee JM, et al. Exenatide reverses dysregulated microRNAs in high-fat diet-induced obese mice. *Obes Res Clin Pract*. 2016 May 1;10(3):315–26.
98. Baggish AL, Hale A, Weiner RB, Lewis GD, Systrom D, Wang F, et al. Dynamic regulation of circulating microRNA during

- acute exhaustive exercise and sustained aerobic exercise training. *J Physiol*. 2011;589(16):3983–94.
99. Zhang B, Shen C, Zhu B, An H, Zheng B, Xu S, et al. Insight into miRNAs related with glucometabolic disorder. *Biomed Pharmacother*. 2019 Mar 1;111:657–65.
100. Denham J, O'Brien BJ, Marques FZ, Charchar FJ. Changes in the leukocyte methylome and its effect on cardiovascular-related genes after exercise. *J Appl Physiol Bethesda Md* 1985. 2015 Feb 15;118(4):475–88.
101. Tonevitsky AG, Maltseva DV, Abbasi A, Samatov TR, Sakharov DA, Shkurnikov MU, et al. Dynamically regulated miRNA-mRNA networks revealed by exercise. *BMC Physiol*. 2013 Jun 7;13(1):9.
102. Thibonnier M, Esau C. Metabolic Benefits of MicroRNA-22 Inhibition. *Nucleic Acid Ther*. 2020 Apr;30(2):104–16.
103. Schmitz B, Niehues H, Lenders M, Thorwesten L, Klose A, Krüger M, et al. Effects of high-intensity interval training on microvascular glycocalyx and associated microRNAs. *Am J Physiol-Heart Circ Physiol*. 2019 Apr 12;316(6):H1538–51.
104. Backes C, Leidinger P, Keller A, Hart M, Meyer T, Meese E, et al. Blood Born miRNAs Signatures that Can Serve as Disease Specific Biomarkers Are Not Significantly Affected by Overall Fitness and Exercise. *PLOS ONE*. 2014 Jul 10;9(7):e102183.
105. Simaitis S, Schulte-Körne B, Schiffer T, Bloch W, Predel H-G, Brixius K, et al. Evidence for Training-Induced Changes in miRNA Levels in the Skeletal Muscle of Patients With Type 2 Diabetes Mellitus. *Front Physiol [Internet]*. 2020 [cited 2021 Feb 12];11. Available from: <https://www.frontiersin.org/articles/10.3389/fphys.2020.599651/full>
106. Barber JL, Zellars KN, Barringhaus KG, Bouchard C, Spinale FG, Sarzynski MA. The Effects of Regular Exercise on Circulating Cardiovascular-related MicroRNAs. *Sci Rep*. 2019 May 17;9(1):1–8.
107. Kostyniuk DJ, Marandel L, Jubouri M, Dias K, de Souza RF, Zhang D, et al. Profiling the rainbow trout hepatic miRNAome under diet-induced hyperglycemia. *Physiol Genomics*. 2019 Sep 1;51(9):411–31.
108. Deng N, Guo R, Zheng B, Li T, Liu RH. IRS-1/PI3K/Akt pathway and miRNAs are involved in whole grain highland barley (*Hordeum vulgare* L.) ameliorating hyperglycemia of db/db mice. *Food Funct*. 2020 Nov 19;11(11):9535–46.
109. Vogel J, Niederer D, Engeroff T, Vogt L, Troidl C, Schmitz-Rixen T, et al. Effects on the Profile of Circulating miRNAs after Single Bouts of Resistance Training with and without Blood Flow Restriction—A Three-Arm, Randomized Crossover Trial. *Int J Mol Sci*. 2019 Jan;20(13):3249.
110. Kim J-W, You Y-H, Jung S, Suh-Kim H, Lee I-K, Cho J-H, et al. miRNA-30a-5p-mediated silencing of Beta2/NeuroD expression is an important initial event of glucotoxicity-induced beta cell dysfunction in rodent models. *Diabetologia*. 2013 Apr;56(4):847–55.
111. Schmitz B, Breulmann FL, Jubran B, Rolfes F, Thorwesten L, Krüger M, et al. A three-step approach identifies novel shear stress-sensitive endothelial microRNAs involved in vasculoprotective effects of high-intensity interval training (HIIT). *Oncotarget*. 2019 Jun 4;10(38):3625–40.
112. Xu Q, Li Y, Shang Y-F, Wang H-L, Yao M-X. miRNA-103: molecular link between insulin resistance and nonalcoholic fatty liver disease. *World J Gastroenterol*. 2015 Jan 14;21(2):511–6.
113. Benatti RO, Melo AM, Borges FO, Ignacio-Souza LM, Simino L a. P, Milanski M, et al. Maternal high-fat diet consumption modulates hepatic lipid metabolism and microRNA-122 (miR-122) and microRNA-370 (miR-370) expression in offspring. *Br J Nutr*. 2014 Jun 28;111(12):2112–22.
114. Uhlemann M, Möbius-Winkler S, Fikenzer S, Adam J, Redlich M, Möhlenkamp S, et al. Circulating microRNA-126 increases after different forms of endurance exercise in healthy adults. *Eur J Prev Cardiol*. 2014 Apr;21(4):484–91.
115. Nie H, Zhang K, Xu J, Liao K, Zhou W, Fu Z. Combining Bioinformatics Techniques to Study Diabetes Biomarkers and Related Molecular Mechanisms. *Front Genet [Internet]*. 2020 [cited 2021 Feb 12];11. Available from: <https://www.frontiersin.org/articles/10.3389/fgene.2020.00367/full>
116. da Silva ND, Roseguini BT, Chehuen M, Fernandes T, Mota GF, Martin PKM, et al. Effects of oral N-acetylcysteine on walking capacity, leg reactive hyperemia, and inflammatory and angiogenic mediators in patients with intermittent claudication. *Am J Physiol Heart Circ Physiol*. 2015 Sep;309(5):H897-905.
117. Capuani B, Pacifici F, Della-Morte D, Lauro D. Glucagon Like Peptide 1 and MicroRNA in Metabolic Diseases: Focusing on GLP1 Action on miRNAs. *Front Endocrinol*. 2018;9:719.

118. Cui SF, Wang C, Yin X, Tian D, Lu QJ, Zhang CY, et al. Similar Responses of Circulating MicroRNAs to Acute High-Intensity Interval Exercise and Vigorous-Intensity Continuous Exercise. *Front Physiol* [Internet]. 2016 [cited 2020 Apr 27];7. Available from: <https://www.frontiersin.org/articles/10.3389/fphys.2016.00102/full>
119. Li J, Su L, Gong Y-Y, Ding M-L, Hong S-B, Yu S, et al. Downregulation of miR-139-5p contributes to the antiapoptotic effect of liraglutide on the diabetic rat pancreas and INS-1 cells by targeting IRS1. *PloS One*. 2017;12(3):e0173576.
120. Jordan SD, Krüger M, Willmes DM, Redemann N, Wunderlich FT, Brönneke HS, et al. Obesity-induced overexpression of miRNA-143 inhibits insulin-stimulated AKT activation and impairs glucose metabolism. *Nat Cell Biol*. 2011 Apr;13(4):434–46.
121. Wen F, Yang Y, Jin D, Sun J, Yu X, Yang Z. MiRNA-145 is involved in the development of resistin-induced insulin resistance in HepG2 cells. *Biochem Biophys Res Commun*. 2014 Mar 7;445(2):517–23.
122. Liu H, Ren G, Zhu L, Liu X, He X. The upregulation of miRNA-146a inhibited biological behaviors of ESCC through inhibition of IRS2. *Tumour Biol J Int Soc Oncodevelopmental Biol Med*. 2016 Apr;37(4):4641–7.
123. Sawada S, Kon M, Wada S, Ushida T, Suzuki K, Akimoto T. Profiling of Circulating MicroRNAs after a Bout of Acute Resistance Exercise in Humans. *PLOS ONE*. 2013 Jul 29;8(7):e70823.
124. Van Craenenbroeck AH, Ledeganck KJ, Van Ackeren K, Jürgens A, Hoymans VY, Fransen E, et al. Plasma levels of microRNA in chronic kidney disease: patterns in acute and chronic exercise. *Am J Physiol Heart Circ Physiol*. 2015 Dec 15;309(12):H2008–2016.
125. Shukla U, Tumma N, Gratsch T, Dombkowski A, Novak RF. Insights into Insulin-Mediated Regulation of CYP2E1: miR-132/-212 Targeting of CYP2E1 and Role of Phosphatidylinositol 3-Kinase, Akt (Protein Kinase B), Mammalian Target of Rapamycin Signaling in Regulating miR-132/-212 and miR-122/-181a Expression in Primary Cultured Rat Hepatocytes. *Drug Metab Dispos*. 2013 Oct 1;41(10):1769–77.
126. Shree N, Venkategowda S, Venkatranganna MV, Datta I, Bhonde RR. Human adipose tissue mesenchymal stem cells as a novel treatment modality for correcting obesity induced metabolic dysregulation. *Int J Obes*. 2019 Oct;43(10):2107–18.
127. Zhao H, Tao S. MiRNA-221 protects islet β cell function in gestational diabetes mellitus by targeting PAK1. *Biochem Biophys Res Commun*. 2019 Nov 26;520(1):218–24.
128. Wardle SL, Bailey MES, Kilikevicius A, Malkova D, Wilson RH, Venckunas T, et al. Plasma MicroRNA Levels Differ between Endurance and Strength Athletes. *PLOS ONE*. 2015 Apr 16;10(4):e0122107.
129. Dou L, Wang S, Sun L, Huang X, Zhang Y, Shen T, et al. Mir-338-3p Mediates Tnf- α -Induced Hepatic Insulin Resistance by Targeting PP4r1 to Regulate PP4 Expression. *Cell Physiol Biochem*. 2017;41(6):2419–31.
130. Stirn L, Huypens P, Sass S, Batra R, Fritsche L, Brucker S, et al. Maternal whole blood cell miRNA-340 is elevated in gestational diabetes and inversely regulated by glucose and insulin. *Sci Rep*. 2018 Jan 22;8(1):1366.
131. Zhuo S, Yang M, Zhao Y, Chen X, Zhang F, Li N, et al. MicroRNA-451 Negatively Regulates Hepatic Glucose Production and Glucose Homeostasis by Targeting Glycerol Kinase-Mediated Gluconeogenesis. *Diabetes*. 2016 Nov 1;65(11):3276–88.
132. Nielsen S, Scheele C, Yfanti C, Åkerström T, Nielsen AR, Pedersen BK, et al. Muscle specific microRNAs are regulated by endurance exercise in human skeletal muscle. *J Physiol*. 2010;588(20):4029–37.
133. Bye A, Røsjø H, Aspenes ST, Condorelli G, Omland T, Wisløff U. Circulating MicroRNAs and Aerobic Fitness – The HUNT-Study. *PLOS ONE*. 2013 Feb 28;8(2):e57496.
134. Diniz GP, Huang Z-P, Liu J, Chen J, Ding J, Fonseca RI, et al. Loss of microRNA-22 prevents high-fat diet induced dyslipidemia and increases energy expenditure without affecting cardiac hypertrophy. *Clin Sci*. 2017 Dec 4;131(24):2885–900.
135. Motiño O, Francés DE, Mayoral R, Castro-Sánchez L, Fernández-Velasco M, Boscá L, et al. Regulation of MicroRNA 183 by Cyclooxygenase 2 in Liver Is DEAD-Box Helicase p68 (DDX5) Dependent: Role in Insulin Signaling. *Mol Cell Biol*. 2015 Jul;35(14):2554–67.
136. Kranjc T, Milojevic M, Kocjan T, Jensterle M, Marc J, Ostanek B. Plasma levels of miR-30d-5p are decreased in regularly exercising postmenopausal women. *Menopause*. 2020 Mar;27(3):319–25.
137. Chen Y-H, Heneidi S, Lee J-M, Layman LC, Stepp DW, Gamboa GM, et al. miRNA-93 Inhibits GLUT4 and Is Overexpressed in

- Adipose Tissue of Polycystic Ovary Syndrome Patients and Women With Insulin Resistance. *Diabetes*. 2013 Jul 1;62(7):2278–86.
138. Ling H-Y, Ou H-S, Feng S-D, Zhang X-Y, Tuo Q-H, Chen L-X, et al. CHANGES IN microRNA (miR) PROFILE AND EFFECTS OF miR-320 IN INSULIN-RESISTANT 3T3-L1 ADIPOCYTES. *Clin Exp Pharmacol Physiol*. 2009;36(9):e32–9.
  139. Fyfe JJ, Bishop DJ, Zacharewicz E, Russell AP, Stepto NK. Concurrent exercise incorporating high-intensity interval or continuous training modulates mTORC1 signaling and microRNA expression in human skeletal muscle. *Am J Physiol-Regul Integr Comp Physiol*. 2016 Apr 13;310(11):R1297–311.
  140. Aoi W, Ichikawa H, Mune K, Tanimura Y, Mizushima K, Naito Y, et al. Muscle-enriched microRNA miR-486 decreases in circulation in response to exercise in young men. *Front Physiol* [Internet]. 2013 [cited 2020 Apr 27];4. Available from: <https://www.frontiersin.org/articles/10.3389/fphys.2013.00080/full>