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Review

MicroRNAs in type 2 diabetes mellitus: potential role of physical exercise

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Abstract

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disease, and its prevalence has grown worldwide. Several pathophysiological processes contribute to the development, progression and aggravating of the disease, for example, decreased insulin synthesis and secretion, insulin resistance, inflammation, and apoptosis, all these processes are regulated by various epigenetic factors, including microRNAs (miRNAs). MiRNAs are small non-coding RNAs, which are around 20 nucleotides in length and are regulators of gene expression at the post-transcriptional level, have a specific function of inhibiting or degrading a messenger RNA target. Thus, miRNAs modulate the expression of many associated genes with the pathophysiological processes in T2DM. On the other hand, miRNAs are also modulated through physical exercise (PE), which induces a change in their expression pattern during and after exercise. Some scientific evidence shows that PE modulates miRNAs beneficially and improves the signaling pathway of insulin resistance, however, little is known about the function of PE modulating miRNAs associated with the processes of insulin secretion, inflammation, and apoptosis. Thus, the objective of this review is to identify the miRNAs expression pattern in T2DM and compare it with the exercise-induced miRNAs expression pattern, identifying the signaling pathways that these miRNAs are regulating in the processes of insulin secretion, insulin resistance, inflammation, and apoptosis in T2DM, and how PE may have a potential role in modulating these signal transduction pathways, promoting benefits for patients with T2DM.

Keywords: Type 2 diabetes; MicroRNAs; Physical exercise

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disease that is associated with genetic and environmental factors, such as, genes that predispose defects in insulin synthesis, consumption of hypercaloric foods, physical inactivity, excessive consumption of alcohol and obesity, generating a defect in insulin secretion and signaling [1], leading to hyperglycemia, insulin resistance and hyperinsulinemia [2].

Insulin resistance occurs when target tissues are unable to respond normally to the action of insulin [3]. Under physiological conditions, insulin binds to the insulin receptor, that is a type of tyrosine kinase receptor, starting autophosphorylation of the tyrosine residues, and the addition of phosphate groups generates a binding site for the insulin receptor substrate-1 (IRS-1). The activated IRS-1 initiates the signal transduction pathway activating phosphatidylinositol 3-kinase (PI3K) and consequently phosphorylates protein kinase B (PKB) also called (AKT), which activates the translocation of the glucose transporter 4 (GLUT4) from the cytoplasm to the cell surface [4], however, in insulin resistance, phosphorylation of the serine residue in IRS-1 occurs, decreasing the phosphorylation of PI3K, inhibiting activation of its pathway, impairing glucose uptake [5].

Other molecular mechanisms at the epigenetic level are associated with this defect in insulin signaling and insulin resistance, such as the regulation performed by microRNAs (miRNAs) [6]. MiRNAs are small ribonucleic acids (RNA), do not encode proteins, are around 18 to 25 nucleotides in length, with the function of inhibiting or degrading one or more messenger ribonucleic acids (mRNA) target [7].

Several miRNAs are modulating the insulin signaling pathway and the proteins associated, as well as miR-

128a, miR-96, miR-126 regulating the expression of the IRS-1; miR-29, miR-384-5p, miR-1 modulating PI3K expression; miR-143, miR-145, miR-29, miR-383, miR-33a, miR-33b, miR-21 regulating AKT expression and miR-133a, miR-133b, miR-223, miR-143 modulating the expression of GLUT4 [6], and dysregulation of these miRNAs can result in inhibition of the insulin signaling pathway, insulin resistance and T2DM.

On the other hand, evidence shows that physical exercise (PE) modulates the expression of miRNAs [8–10] and can induce a beneficial modification in signaling pathways in T2DM [11], increasing insulin sensitivity [12], reducing insulin resistance [13], in addition, to being an excellent non-pharmacological strategy to combat T2DM [14]. Thus, the objective of this review is to analyze the expression pattern of miRNAs in T2DM and compare with the expression pattern induced by PE, analyzing the signaling pathways associated with these miRNAs in the pathophysiological processes in T2DM.

2. Type 2 diabetes mellitus

The prevalence of T2DM continues to grow worldwide and represents 95% of all diabetes cases, increasing the incidence of disease-related morbidity and mortality. Genetic factors associated with hypercaloric diet, smoking, excessive alcohol intake and sedentary behavior are essential aspects for the development of insulin resistance and T2DM [15].

Constant hyperglycemia in the body causes increased insulin secretion, leading to chronic hyperinsulinemia associated with hyperglycemia and subsequently beta cell failure in pancreatic islets [16]. All of these factors associated promote impaired insulin signaling, suppressing glucose uptake by cells, decreasing the production of adenosine triphosphate (ATP) by glycolytic pathway, inducing a substrate switch with the predominance of fatty acid metabolism for production of ATP.

Increased lipolysis and elevated free fatty acid levels contributes to further increase glucose output, interfering with insulin signaling. An excess supply of fatty acids causes phosphorylation of the peroxisome proliferator-activated alpha (PPARα), resulting in intramyocardial triglyceride accumulation and increased reactive oxygen species (ROS) generation, which subsequently enhances inflammation, apoptosis, and contractile dysfunction, features characteristic of lipotoxicity [2,17].

PPARα has been reported to reduce the mitochondrial uncoupling protein 3 (UCP3) expression in myocytes through activation of the lipogenic factor sterol regulatory element-binding protein (SREBP)-1 and in response to fatty acids, involved with the development of selective insulin resistance in the heart [18]. Accordingly, mice with cardiac specific PPARα over-expression exhibited a similar phenotype of diabetic cardiomyopathy [19].

Further, study showed krüppel-like factor-5 (KLF5) is as a direct activator of the PPARα promoter in mice with streptozotocin-induced type-1 diabetes, indicating it is involved in diabetic cardiomyopathy either via stimulation of PPARα expression or independently via forkhead box protein O1 (FOXO1) activation. In agreement, diabetic mice with FOXO1 deletion had lower cardiac KLF5 expression and were protected from diabetic cardiomyopathy [20].

Other transcription factors have been described to regulate glucose uptake. The myocyte enhancer factor 2 (MEF2) appear to regulate the GLUT4 promoter [21]. In fact, MEF2 binding activity was substantially reduced in both heart and skeletal muscle of diabetic mice, which correlated with decreased transcription rate of the GLUT4 gene. These observations have raised the possibility that these transcriptional factors can drive pathophysiology in T2DM.

All of these mechanisms contribute to the progression of insulin resistance and damage to specific cells in T2DM, such as cardiomyocytes, endothelial cells, vascular smooth muscle cells, pancreatic beta cells, among others, generating inflammation, apoptosis, fibroblast activation, fibrosis and cell dysfunction [22], impressively, these mechanisms are regulated by miRNAs at the post-transcriptional level in T2DM [23].

2.1 MicroRNAs and insulin resistance in T2DM

Insulin resistance is a pathophysiological process in T2DM in which the target cells do not normally respond to the action of insulin, impairing the signaling of this protein [3]. MiRNAs as regulators of gene expression and consequently, regulators of protein expression [24], modulate the synthesis, secretion of insulin and the expression of proteins in its signaling pathway in T2DM (Table 1, Ref. [25–45]), such as PI3K, AKT and GLUT4 [46].

Evidence shows that miR-375 regulates the process of insulin secretion [47] and glucose homeostasis [48]. MiR-96 also participates in this process, reducing the expression of nucleolar complex protein 2 (NOC2) in pancreatic beta cells by decreasing insulin secretion [49]. Other miRNAs that regulate insulin secretion and are associated with the development of pancreatic beta cells are miR-15a [50] and miR-7 [51]. MiR-7 is overexpressed in the serum of T2DM patients [52] and regulates the expression of the IRS-2 gene, reduces the expression of this gene and impairs insulin signaling, inducing insulin resistance [53].

MiR-33a and miR-33b are also highly expressed in T2DM and inhibit the expression of IRS-2, in addition, miR-126 and miR-145 suppress the expression of IRS-1, all of these mechanisms contribute to impact the pathway of insulin signal transduction and promote insulin resistance [54]. Following the insulin signaling pathway, the miRNAs that regulate the PI3K-p85 αsubunit are miR-29 [55] and miR-320 [56], while miR-126 controls the expression of p85 βsubunit [57]. These deregulated miRNAs impact insulin signaling in T2DM.

Table 1. MiRNAs dysregulated in T2DM (Clinical Studies).

MicroRNA	Samples	Outcomes	Targets	References
↓ miR-130a	Diabetic Patients (n = 72) Peripheral blood samples	MiR-130 regulated glucose metabolism	PPARy	Jiao *et al*., 2015 [30]
↑ miR-128, miR-130b-3p, miR-374a-5p	Diabetic Patients – South Asians (n = 145) Serum samples	Differentially expressed miRNAs comparing prediabetes and T2DM patients with control subjects were: miR-128, miR-130b-3p, miR-374a-5p	IRS-1, PI3KR1, SOCS4; insulin signaling (e.g., insulin receptor, insulin receptor substrate-1 and phosphatidylinositol 3-kinases regulatory 1)	Prabu *et al*., 2015 [31]
↑ miR-572 ↓ miR-1249, miR-320b	Prediabetic and newly-diagnosed Diabetic Patients (n = 150) Plasma samples	MiR-1249, miR-320b, and miR-572 in plasma samples were all significantly different among T2D patients, prediabetes, and controls	FOXO1, EIF2AK3	Yan *et al*., 2016 [32]
↑ miR-29a, miR-34a, miR-375	Prediabetic and newly-diagnosed Diabetic Patients (n = 56) Serum samples	Serum analysis of seven miRNAs revealed altered expression levels; miR-34a showed the most significant differences		Kong *et al*., 2011 [33]
↓ let-7	Diabetic Patients (n = 4) Carotid endarterectomy specimens samples Diabetic mice (n = 6) Aortic samples	Proliferation, migration, inflammation	NF-kB	Brennan *et al*., 2017 [34]
↓ miR-503	Patients with T2DM, obesity or both (n = 56) Serum samples	MiRNAs (miR-138, miR376a and miR-15b) are potential biomarkers to distinguish obesity patients from obesity-T2D and T2D patients; the combination of miR-503 and miR-138can distinguish diabetic from obese diabetic patients	Insulin	Pescador *et al*., 2013 [35]
↑ miR-140-5p; miR-142-3p; miR-222 ↓ miR-423-5p; miR-125b; miR-192; miR-195; miR-130b; miR-532-5p; miR-126	Diabetic Patients (n = 150) Plasma samples	Levels of four miRNAs (miR-140-5p, miR-423-5p, miR-195, and miR-126) was specific for T2D	INS, IRS-1 PI3KR2, CXCL2, NFKBIZ	Ortega *et al*., 2014 [29]
↑ miR-144	Diabetic Patients (n = 50) Serum samples	miR-144 expression was upregulated in whole blood of T2D patients, concordant with the down-regulation of IRS1;miR-144 exhibited a relationship with increasing glycaemic status	IRS-1	Karolina *et al*., 2011 [26]
↑ miR-455-5p; miR-454-3p; miR-144-3p; miR-96-5p ↓ miR-409-3p; miR-665; miR-766-3p	Diabetic Patients (n = 15) Serum samples	The expression levels of miR-455-5p, miR-454-3p, miR-144-3p and miR-96-5p were higher in patients with T2DM, compared with those of healthy subjects, however, the levels of miR-409-3p, miR-665 and miR-766-3p were lower	SOCS3, RPS6KB1; TNF, TNFRSF1B, PRKAA2, SLC2A1 PRKAA1; PPARA, PDE3B, FOXO1, MAP2K; AKT1, IRS1, IRS2	Yang *et al*., 2017 [28]

Table 1. Continued.

MicroRNA	Samples	Outcomes	Targets	References
↑ miR-101, miR-375, miR-802	Diabetic Patients (n = 204) Serum samples	MiR-101, miR-375 and miR-802 are significantly increased in T2D patients versus NGT subjects	INS, Mtpn, EZH2, Hnf1b	Higuchi *et al*., 2015 [36]
↓ miR-23a, miR-186, miR-191, miR-146a, let-7i	Diabetic Patients (n = 60) Serum samples	Revealed low levels of miR-23a, let-7i, miR-486, miR-186, miR-191, miR-192, and miR-146a in T2D	NF-kB	Yang *et al*., 2014 [37]
↑ miR-1, miR-133a	Diabetic Patients (n = 86) Serum samples	MiR-133a levels were increased in type 2 diabetes patients as compared with healthy subjects; miR-1 and miR-133a levels were robustly associated with myocardial steatosis in type 2 diabetes patients	MEF2a	Gonzalo-Calvo *et al*., 2017 [38]
↓ miR-126	Diabetic Patients (n = 822) Plasma samples	Lower levels of miR-20b, miR-21, miR-24, miR-15a, miR-126, miR-191, miR-197, miR-223, miR-320, and miR-486 in prevalent DM, but a modest increase of miR-28-3p	PI3KR2, SPRAD1	Zampetaki *et al*., 2010 [39]
↓ miR-126	Diabetic Patients (n = 40) Plasma samples	MiR-126 expression was decreased before the manifestation of T2DM. MiR-126 level was inversely associated with the onset of DM	PI3KR2, SPRAD1	Zhang *et al*., 2015 [40]
↓ miR-126	Diabetic Patients (n = 455) Serum samples	MiR-126 was reduced in T2DM patients.	PI3KR2, SPRAD1	Liu *et al*., 2014 [41]
↓ miR-126	Diabetic Patients (n = 300) Plasma samples	MiR-126-3p and miR-21-5p levels declined significantly from CTR to T2DM non complicated and T2DM complicated patients	PI3KR2, SPRAD1	Olivieri *et al*., 2015 [42]
↑ miR-30a-5p, miR-150 ↓ miR-15a, miR-375	Diabetic Patients (n = 462) Plasma samples	It was identified that miRNAs are dysregulated before the development of type 2 diabetes and confirmed the expression profile after the disease is established in individuals, demonstrating the potential predictor of these genes		Jiménez-Lucena *et al*., 2018 [27]
↑ miR-424	Diabetic Patients (n = 122) Serum samples	MiR-424 expression increased after Actinidia chinensis juice consumption promoting anti-inflammatory and anti-oxidative effects	KEAP1, NRF2	Sun *et al*., 2017 [43]
↓ miR-146a	Diabetic Patients (n = 56) Serum samples	Reduction of miR-146a expression is associated with a proinflammatory state and increased expression of cytokines such as IL-8, TNF-α, IL-6 and IL-1β		Baldeón *et al*., 2014 [25]
↑ miR-21, miR-24, miR-34a, miR-148	Diabetic Patients (n = 58) Blood samples	MicroRNAs associated with pancreatic islet β cell function and glycemic control, as well as the development and progression of type 2 diabetes	SFRP4	Nunez Lopez *et al*., 2016 [44]
↑ miR-21, miR-30d, miR-34a, miR-148a	Diabetic Patients (n = 92) Plasma samples	MicroRNAs associated with insulin resistance, pancreatic islet β cell function and glycemic control, inflammation, apoptosis, as well as progression of type 2 diabetes	Insulin	Seyhan *et al*., 2016 [45]

MiRNAs such as miR-29a, miR-29b, miR-29c [58], miR-33a, miR-33b [59] and miR-153 [60] act by inhibiting AKT phosphorylation. Finishing the insulin signaling cascade, GLUT4 is regulated by several miRNAs, such as miR-21a, miR-29a, miR-29c, miR-93, miR-106b, miR-133a, miR-133b, miR-222, and miR-223, these inhibit GLUT4 expression and contribute to insulin resistance process in T2DM [61], and this process favors inflammation in various organs and systems in patients with T2DM, who are also mediated by miRNAs.

2.2 MicroRNAs and inflammation in T2DM

The inflammatory process is a very important within the pathophysiology of T2DM that affects organs and systems, miRNAs also regulate this process. Some miRNAs are associated with increased pro-inflammatory, such as miR-146a which is downregulated in the serum of T2DM patients [25]. Conversely, the miR-147 has been identified overexpressed in the serum of diabetic and obese rats with periodontitis, activating macrophages and increasing the expression of pro-inflammatory markers such as tumor necrosis factor-α (TNF-α), nitric oxide synthase-2 (NOS2) and interleukin-12 (IL-12) [62].

The increased levels of TNF-α, for example, leads to peripheral inflammation that affects central nervous system functioning and plays an important role in memory loss and cognitive decline, which are seen in T2DM and Alzheimer's disease [63], including, various miRNAs regulate inflammatory processes in both T2DM [11] and Alzheimer's disease [64].

Another miRNA associated to the inflammatory process in T2DM is miR-29c, which is overexpressed by regulating the tristetraprolin (TTP) gene. TTP is recognized for its anti-inflammatory function, but when serum and urinary levels of this protein are decreased an inflammatory response increases the expression of interleukin-6 (IL-6) and interleukin-18 (IL-18) in diabetic nephropathy by a miR-29c-regulated molecular mechanism that induces systemic and tissue inflammation in T2DM [65].

A recent meta-analysis revealed that increasing IL-6 levels in the blood might be associated with cognitive decline [66] an increase prevalence of dementia and Alzheimer's disease [67]. Inflammation and insulin resistance that happens in T2DM affects not only periphery, but also central nervous system and a link between T2DM and the increased risk of developing neurological disorders, such as Alzheimer's disease, has been reported [68].

Several evidences show that PE is an important non-pharmacological tool for the prevention and treatment of T2DM [69], improving the function of cells of the innate and adaptive immune system [70], reducing inflammation in T2DM [71], including, various training protocols are beneficial for individuals with Alzheimer's disease [72]. Both, aerobic or resistance PE can reduce insulin resistance and inflammatory profile in individuals with T2DM [73] or Alzheimer's disease, potentially modulating the expression of miRNAs and signaling pathways [64].

3. Type 2 diabetes mellitus and physical exercise

T2DM comprises up to 95% of diabetes cases worldwide [74]. PE can prevent and fight insulin resistance that occurs in T2DM [75]. PE protocols include mainly aerobic and resistance sessions and/or training, which should be prescribed based on scientific variables, such as volume, frequency, intensity, and duration [76].

Aerobic PE protocols lasting 30–60 minutes, 5 days/week revealed to enhance insulin sensitivity and cardiovascular functioning, reducing the risk for developing T2DM [77]. Resistance training protocols have also showed to reduce hyperglycemia in T2DM [78].

In general, PE training enhances peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) levels inducing the remodeling of skeletal muscle fiber composition, by leading to the browning of the adipose tissue and facilitating conversion of muscle fibers from oxidative to glycolytic and vice-versa, depending on if it is adopted an aerobic or resistance training, respectively [79]. PE leads to the production of irisin through the PGC-1α pathway having a role in T2DM [75].

Irisin is a myokine identified for its ability to induce the physiological changes contribute to prevent and avoid the development of insulin resistance and inflammation in T2DM [80]. Irisin is an important mediator of the beneficial effects of PE on metabolic and neurological profiles [81,82]. Thus, PE is an important non-pharmacological approach to reduce the risk of developing or worsening T2DM pathology.

3.1 MicroRNAs in T2DM and physical exercise

Homeostasis at the cellular level is affected by a single session of PE and also in response to chronic exercise inducing alterations in the circulating and cellular miRNA profile (Table 2, Ref. [83–109]) [11]. In both healthy and diabetic individuals, different types of PE modulate the expression of miRNAs [83,110]. Resistance and aerobic training promote changes in the expression of circulating microRNAs, specifically, miR-423-3p, miR-451a and miR-766-3p were upregulated in the plasma of diabetic patients after both training, and changes in miR-423-3p and miR-451a were correlated with body fat loss and with changes in fatty acid metabolism [111].

Aerobic exercise (cycling or exercising on an elliptical crosstrainer) induced a decrease in the expression of miR-29b-3p, miR-29c-3p and miR-135a-5p post-training in the skeletal muscle of diabetic individuals, including the reduction of miR-29c-3p was correlated with improvement in cardiorespiratory fitness [112]. Swimming training, another type of aerobic exercise, also induced a change in the expression of another miRNA, miR-382 was overexpressed

Table 2. MiRNAs in PE (Clinical Studies). PE modulating miRNAs in both the acute and chronic phases.

MicroRNAs	Targets	Source	Exercise Protocols	Reference
↑ miR-125a, miR-145, miR-181b, miR-193a, miR-197, miR-212, miR-223, miR-340, miR-365, miR-485, miR-505, miR-520d, miR-629, miR-638, miR-939, miR-940, miR-1225, miR-1238 ↓ miR-let-7i, miR-16, miR-17, miR-18a, miR-18b, miR-20a, miR-20b, miR-22, miR-93, miR-96, miR-106a, miR-107, miR-126, miR-130a, miR-130b, miR-151, miR-185, miR-194, miR-363, miR-660		Healthy men (n = 11) Serum samples	Acute Response Cycle ergometer exercise (10 × 2 min bouts, 1 min rest interval between each bout, 76% VO2peak)	Radom-Aizik *et al*., 2010 [85]
↑ miR-21, miR-146a, miR-221, miR-222, miR-20a	PTEN PDCD4 p27/KIP1 p21/WAF 1	Healthy men (n = 10) Plasma samples	Acute Response Cardiopulmonary exercise test Chronic Adaptation (90 days) Rowing training, 5 Km, 1–3 h per session, 20–24 strokes/min	Baggish *et al*., 2011 [88]
↑ miR-7, miR-15a, miR-21, miR-26b, miR-132, miR-140, miR-181a, miR-181b, miR-181c, miR-338, miR-363, miR-939, miR-940, miR-1225 ↓ let-7e, miR-23b, miR-31, miR-99a, miR-125a, miR-125b, miR-126, miR-130a, miR-145, miR-151, miR-199a, miR-199b, miR-221, miR-320, miR-451, miR-486, miR-584, miR-652		Healthy men (n = 12) Serum samples	Acute Response Cycle ergometer exercise (10 × 2 min bouts, 1 min rest interval between each bout, 76% VO2peak)	Radom-Aizik *et al*., 2012 [84]
↑ miR-149 ↓ miR-146a, miR-221		Healthy men (n = 12) Serum samples	Acute Response Resistance exercise (bench press and leg press) 3 days after exercise	Sawada *et al*., 2013 [89]
↓ miR-486	PTEN	Healthy men (n = 11) Serum samples	Acute Response Cycle ergometry 60 min at 70% VO2max Chronic Adaptation (4 weeks total) Systematic—cycling at 70% VO2max (3 × 30 min/ week)	Aoi *et al*., 2013 [90]
↑ miR-7, miR-29a, miR-29b, miR-29c, miR-30e, miR-142, miR-192, miR-338, miR-363, miR-590 ↓ let-7e, miR-126, miR-130a, miR-151, miR-199a, miR-221, miR-223, miR-326, miR-328, miR-652		Healthy men (n = 13) Serum samples	Acute Response Cycle ergometer exercise (10 × 2 min bouts, 1 min rest interval between each bout, 77% VO2peak)	Radom-Aizik *et al*., 2013 [86]
↑ miR-181b, miR-214, miR-1, miR-133a, miR-133b, miR-208b		Healthy men (n = 9) Plasma samples	Acute Response Uphill treadmill test (concentric) Immediately after Downhill treadmill test (eccentric) 2–6 h after exercise	Banzet *et al*., 2013 [91]
↑ miR-126, miR-133	CPK	Healthy men (n = 58) Plasma samples	Acute Response Single symptom-limited spiroergometry test Cycling 4 h at 70% of anaerobic threshold Marathon run Eccentric resistance exercise	Uhlemann *et al*., 2014 [92]

Table 2. Continued.

MicroRNAs	Targets	Source	Exercise Protocols	Reference
↑ miR-1, miR-126, miR-133a, miR-134, miR-146a, miR-208a, miR-499	CPK NT-proBNP hsCRP	Healthy men (n = 21) Plasma samples	Acute Response Marathon run Immediately after run (decreased after 24 h)	Baggish *et al*., 2014 [93]
↑ miR-1, miR-133a, miR-206, miR-208b, miR-499		Healthy men (n = 14) Plasma samples	Acute Response Marathon run Immediately after run	Mooren *et al*., 2014 [94]
↑ miR-1, miR-133a, miR-206		Healthy men (n = 5) Plasma samples	Acute Response Marathon run Immediately after run	Gomes *et al*., 2014 [95]
↑ miR-15a, miR-29b, miR-29c, miR-30e, miR-140, miR-324, miR-338, miR-362, miR-532, miR-660 ↓ miR-23b, miR-130a, miR-151, miR-199a, miR-221		Healthy men (n = 12) Serum samples	Acute Response Cycle ergometer exercise (10 × 2 min bouts, 1 min rest interval between each bout, 82% VO2max)	Radom-Aizik *et al*., 2014 [87]
↑ miR-1, miR-133a, miR-133b, miR-139-5p, miR-143, miR-145, miR-223, miR-330-3p, miR-338-3p, miR-424 ↓ miR-30b, miR-106a, miR-146, miR-151-3p, miR-151-5p, miR-221, miR-652, let-7i ↑ miR-103, miR-107, ↓ miR-21, miR-25, miR-29b, miR-92a, miR-133a, miR-148a, miR-148b, miR-185, miR-342-3p, miR-766, let-7d		Healthy men (n = 32) Plasma samples	Acute Response cycle ergometry test at 65% Pmax 1–3 h after exercise Immediately after exercise Adaptation (12 weeks total) Systematic endurance cycle ergometry training, 3–5 days after training	Nielsen *et al*., 2014 [83]
↑ miR-1, miR-133a, miR-133b, miR-206, miR-208b, miR-499		Healthy adults (n = 7) Plasma samples	Adaptation (5 months total) Systematic resistance training 36–72 h after training	Zhang *et al*., 2015 [96]
↑ let-7f, miR-21, miR-29c, miR-223 ↓ let-7f, miR-21, miR-29c, miR-223		Healthy adults (n = 13) PBMCs samples	Adaptation (18 weeks) Running exercise (3×/week, 60 min)	Dias *et al*., 2015 [97]
↑ miR-222	HIPK1	Heart failure patients (n = 28) Blood samples	Acute Response Heart failure patients Bicycle Ergometry Test	Liu *et al*., 2015 [98]
↑ let-7d-3p, let-7f-3p,miR-29a-3p, miR-34a-5p, miR-125b-5p,miR-132-3p, miR-143-3p, miR-148a-3p, miR-223-3p, miR-223-5p,miR-424-3p, miR-424-5p		Healthy men (n = 9) Serum samples	Acute Response Marathon run Immediately after run (decreased after 24 h)	De Gonzalo-Calvo *et al*., 2015 [99]

Table 2. Continued.

MicroRNAs	Targets	Source	Exercise Protocols	Reference
↑ miR-1, miR-30a, miR-133a ↓ miR-26a, miR-29b		Healthy adults (n = 30) Plasma samples	Acute Response Marathon run Immediately after run (decreased after 24 h) Immediately after run	Clauss *et al*., 2016 [100]
↑ miR-1, miR-133a, miR-206		Statin and nonstatin-using runners (n = 56) Plasma samples	Acute Response Marathon run Immediately after run (decreased after 24 h)	Min *et al*., 2016 [101]
↑ miR-1, miR-133a, miR-133b, miR-206, miR-485-5p, miR-509-5p, miR-517a, miR-518f, miR-520f, miR-522, miR-553, miR-888	NF-κB	Healthy men (n= 26) Plasma samples	Acute Response High intensity interval exercise 85–95% of HRmax Immediately after Vigorous intensity continuous exercise Immediately after	Cui *et al*., 2016 [102]
↑ miR-1, miR-486, miR-494	HDAC4 PAX7 PTEN FOXO1A	Healthy men (n = 128) Blood samples	Acute Response Aerobic exercise VO2max test (Endurance athletes, runners, cyclists and triathletes)	Denham *et al*., 2016 [103]
↑ miR-376a ↓ miR-16, miR-27a, miR-28		Obese older adults (n = 33) Plasma samples	Adaptation (5 months total) Aerobic run exercise training 30 min, 65–70% heart rate res. (4 days/week)	Zhang *et al*., 2017 [104]
↑ miR-21, miR-16, miR-93, miR-222 ↓ miR-222, miR-16		Healthy men (n = 30) Plasma samples	Adaptation 8 weeks of: Explosive strength training, Hypertrophic strength training, High-intensity interval training	Horak *et al*., 2018 [105]
↑ miR-221 ↓ miR-208b, miR-221, miR-21, miR-146a, miR-210		Healthy men (n = 10) Serum samples	Acute Response and Adaptation Basketball Exercise (3-months)	Li *et al*., 2018 [106]
↑ miR-21-5p, miR-27a-3p, miR-29a-3p, miR-30a-5p, miR-34a-5p, miR-126-3p, miR-132-3p, miR-142-5p, miR-143-3p, miR-150-5p, miR-195-5p, miR-199a-3p ↓ miR-16-5p, miR-29b-3p, miR-30b-5p, miR-103a-3p, miR-106b-5p, miR-107, miR-139-3p, miR-375, miR-497-5p, miR-590-5p		Healthy men (n = 9) Serum samples	Acute Response 10 Km race, half-marathon, marathon	De Gonzalo-Calvo *et al*., 2018 [107]
↓ miR-21-5p, miR-150-5p		Myasthenia Gravis patients (n = 10) Serum samples	Adaptation Aerobic and resistance training twice weekly for 12 weeks	Westerberg *et al*., 2017 [108]
↓ miR-1-3p, miR-26a-5p, miR-29a-3p, miR-133b, miR-206, and miR-378-5p		Healthy men (n = 17) Skeletal muscle samples	Acute Response Treadmill exercise, 40% VO2pico	Margolis *et al*., 2018 [109]

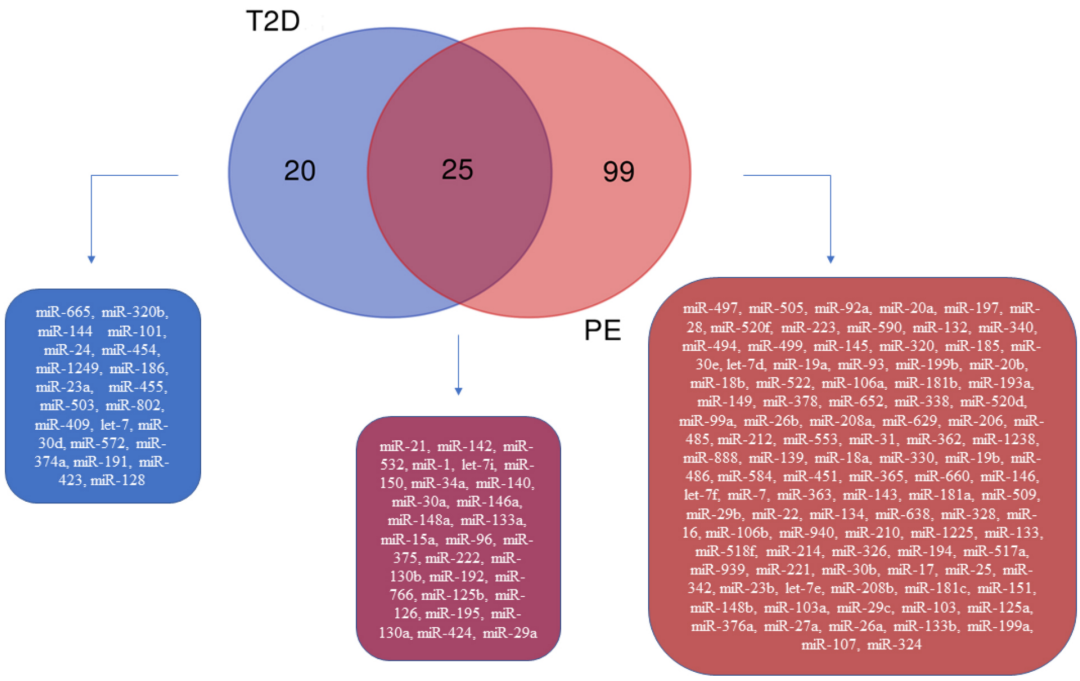

Fig. 1. Overlapping between miRNAs in T2DM and PE. In this Venn Diagram, deregulated miRNAs in T2DM (in blue), miRNAs modulated by PE (in pink) and miRNAs that were modulated in both T2DM and PE (in purple) were identified.

in the serum of diabetic mice after 12 weeks of training. The elevation of miR-382 reduced the expression of the resistin gene, attenuating insulin resistance in these animals [13].

In another study, however with Wistar rats, aerobic training on a treadmill generated overexpression of miR-27a and miR-27b in cardiac tissue after ten weeks of training [113]. On the other hand, it has already been shown that miR-27a and miR-27b are downregulated during adipocyte differentiation and synthesis [114]. It may be a molecular mechanism by which PE attenuates the differentiation into adipocytes, favoring the reduction of adipose tissue and improvement of insulin resistance.

The enhancement in the expression of miR-27a and miR-27b is probably involved in the control of body mass [115]. Thus, the production of irisin by PE practice may be possibly influencing the regulation of these miRNAs and vice-versa. There are yet many unknown mechanisms linking physiological changes to miRNAs up or down regulation, such as irisin release and its relation to miR-27a and miR-27b. Elucidating these linking mechanisms can contribute significantly to the development of new therapies towards T2DM.

Furthermore, some miRNAs are overexpressed in T2DM and after chronic PE they have the opposite expression. For example, miR-144 is overexpressed in T2DM regulating IRS-1 and IRS-2 expression in PI3K pathway [26]. The disturbance of IRS-1 and IRS-2 functioning is the main molecular mechanism in PI3K pathway that leads to insulin resistance in T2DM [75]. Conversely, it has been reported down-regulation of miR-144 when under PE stress [113]. There are also data that some miRNAs are down-regulated in T2DM whereas after PE these same miRNAs are up-regulated.

Different PE protocols should test different approaches on the volume, frequency, intensity, and duration of the training to evaluate what would be the miRNAs behavior. It is important to emphasize that different behaviors in the expression of miRNAs vary not only with the different PE protocols used, but also with the type of tissue analyzed. Elucidating all of these factors in the future, may guide researchers in choosing the best PE protocols to be used in patients with T2DM.

3.2 Overlapping between microRNA profile in T2DM and physical exercise

For a better understanding of the impact of PE on microRNAs in T2DM, a Venn diagram was made (Fig. 1). Of all miRNAs analyzed, 20 miRNAs were identified only in T2DM and 99 miRNAs were regulated by PE alone.

Interestingly, 25 miRNAs have been identified in both T2DM and PE, they are: miR-21, miR-142, miR-532, miR-1, let-7i, miR-150, miR-34a, miR-140, miR-30a, miR-146a, miR-148a, miR-133a, miR-15a, miR-96, miR-375, miR-222, miR-130b, miR-192, miR-766, miR-125b, miR-126, miR-195, miR-130a, miR-424 and miR-29a. Of these 25 miRNAs, we identified 4 miRNAs with different expression pattern in T2DM compared to PE, they are: miR-15a, miR-96, miR-192, miR-532 (Fig. 2), which may be potential beneficial molecular mechanisms regulated by PE in T2DM.

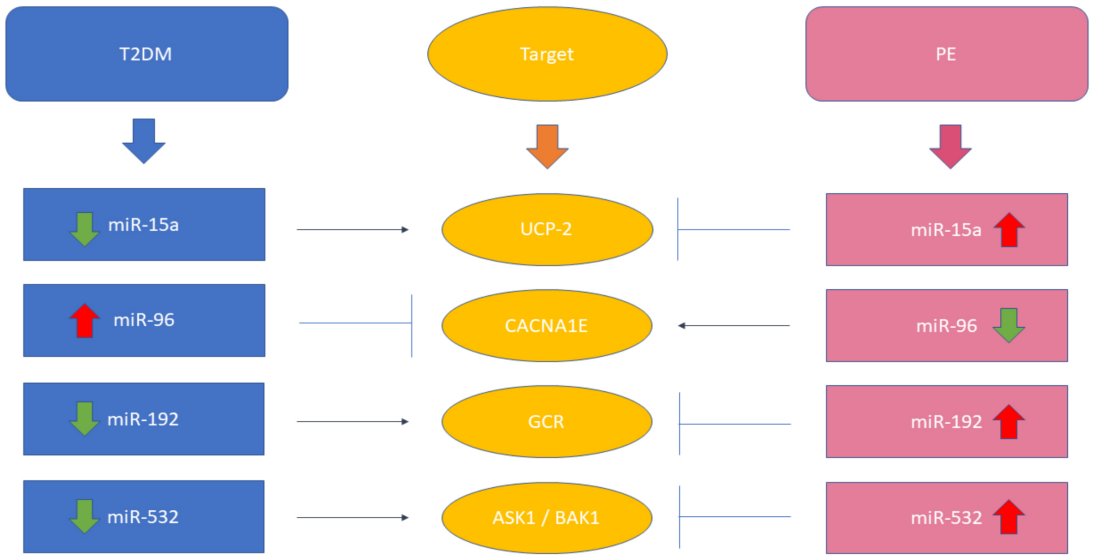

Fig. 2. MiRNAs with different expression patterns between T2DM and PE regulating specific genes. MiRNAs with modified expression in T2DM (in blue), which had opposite expression induced by PE (in pink), regulating target genes (in yellow).

MiR-15a expression is reduced in the plasma of individuals with T2DM and is associated with the development of the disease [27]. MiR-15a regulates the uncoupling protein-2 (UCP-2) gene that impairs insulin synthesis and secretion [116]. Thus, with reduced miR-15a expression and increased UCP-2 in beta cells, insulin secretion is impaired [117], favoring insulin resistance. In contrast, PE on an ergometer cycle induced increased miR-15a expression [84], demonstrating a potential molecular mechanism induced by PE to reduce UCP-2 expression and improve insulin secretion.

In this context, miR-96 also participates in the regulation of the insulin secretion process, this miRNA is overexpressed in the serum of patients with T2DM, inhibits the calcium voltage-gated channel subunit α1 E (CACNA1E) gene, a voltage-dependent calcium channel [28], impairing insulin secretion. On the other hand, PE reduced the expression of miR-96 [85], suggesting that in this way, PE can increase CACNA1E expression and improve insulin secretion.

MiR-192 is downregulated in the plasma of patients with T2DM [29], promoting increased expression of the glucocorticoid receptor (GCR) that favors insulin resistance, lipid accumulation, lipogenesis and hepatic microvesicular steatosis [118]. In contrast, PE induces overexpression of miR-192 [86], which can minimize GCR expression by attenuating insulin resistance, reducing lipid accumulation and lipogenesis.

Likewise, miR-532 also has reduced expression in patients with T2DM and is associated with insulin resistance [29] and inflammation [119]. Downregulation of miR-532 results in overexpression of your targets, apoptosis signal-regulating kinase 1 (ASK1) and pro-apoptotic gene homologous Bcl-2 Antagonist/Killer 1 (BAK1), that induce apoptosis [120]. ASK1 is an inflammation-derived kinase that activates other kinases as well as p38 mitogen-activated protein kinases (p38 MAPKs) that control several inflammatory [121], apoptotic and fibrotic processes in T2DM [122].

On the other hand, cycle ergometer PE increased the expression of miR-532 [87], which can be an excellent strategy for reducing ASK1, BAK1, and p38 MAPKs, and inducing the inhibition of the inflammatory, fibrotic and apoptotic process in T2DM, in addition, it may be a new beneficial molecular mechanism induced by PE in T2DM and new therapeutic target.

4. Conclusions

In this review, it was identified that many miRNAs have their expression pattern modified during and after PE and sometimes different from the expression pattern in T2DM. These finds suggest that PE beneficially modulates the expression of the miRNAs and signaling pathways of the processes of secretion and insulin resistance, lipogenesis, apoptosis, inflammation and fibrosis, promoting beneficial changes in the clinical parameters of individuals with T2DM.

Abbreviations

T2DM, Type 2 Diabetes Mellitus; MiRNAs, MicroRNAs; PE, Physical Exercise; IRS-1, insulin receptor substrate-1; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B; GLUT4, glucose transporter 4; RNA, ribonucleic acids; mRNA, messenger ribonucleic acids; ATP, adenosine triphosphate; PPARα, peroxisome proliferator-activated alpha; ROS, reactive oxygen species; NOC2, nucleolar complex protein 2; TNF-α, tumor necrosis factor-

α; NOS2, nitric oxide synthase-2; IL-12, interleukin-12; TTP, tristetrapolin; IL-6, interleukin-6; IL-18, interleukin-18; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; UCP-2, uncoupling protein-2; CACNA1E, calcium voltage-gated channel subunit α1 E; GCR, glucocorticoid receptor; ASK1, apoptosis signal-regulating kinase 1; BAK1, pro-apoptotic gene homologous Bcl-2 Antagonist/Killer 1; p38 MAPKs, p38 mitogen-activated protein kinases.

Author contributions

ACI-C, RALDS and TF wrote the manuscript; ACI-C, RALDS and TF performed the literature research; ACI-C, RALDS, TF and EMO analyzed and critically discussed the data; ACI-C, LR, BSFS, RAJ, TF and EMO performed formal analysis and supervision; ACI-C, TF and EMO performed review and final editing.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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