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REVIEW ARTICLE

Regulation of microRNAs in Alzheimer´s disease, type 2 diabetes, and aerobic exercise training

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Abstract

Alzheimer's disease (AD) is the most common type of dementia. The evolution and aggregation of amyloid beta (β) oligomers is linked to insulin resistance in AD, which is also the major characteristic of type 2 diabetes (T2D). Being physically inactive can contribute to the development of AD and/or T2D. Aerobic exercise training (AET), a type of physical exercise, can be useful in preventing or treating the negative outcomes of AD and T2D. AD, T2D and AET can regulate the expression of microRNAs (miRNAs). Here, we review some of the changes in miRNAs expression regulated by AET, AD and T2D. MiRNAs play an important role in the gene regulation of key signaling pathways in both pathologies, AD and T2D. MiRNA dysregulation is evident in AD and has been associated with several neuropathological alterations, such as the development of a reactive gliosis. Expression of miRNAs are associated with many pathophysiological mechanisms involved in T2D like insulin synthesis, insulin resistance, glucose intolerance, hyperglycemia, intracellular signaling, and lipid profile. AET regulates miRNAs levels. We identified 5 miRNAs (miR-21, miR-29a/b, miR-103, miR-107, and miR-195) that regulate gene expression and are modulated by AET on AD and T2D. The identified miRNAs are potential targets to treat the symptoms of AD and T2D. Thus, AET is a non-pharmacological tool that can be used to prevent and fight the negative outcomes in AD and T2D.

Keywords Alzheimer · Diabetes · Physical exercise · Physical activity · Insulin resistance

Introduction

Alzheimer´s disease (AD) is the most common neurodegenerative disease (EMA 2018). Six million Americans were living with AD in 2020 and it is expected that in 2050 we will have approximately 13.8 million people living with AD worldwide (Physicians 2020). AD is also a type of dementia where patients usually present difficulty forming new memories. The dementia has been clinically attributed to the cell death that results from a large number of insoluble amyloid fibrils. These amyloid fibrils may be present in a vast number of tissues (muscle, bones, etc.) and can cause damage to peripheral tissues and the brain (Gong et al. 2003). Aggregations of amyloid beta (Aβ) oligomers, strong central nervous system (CNS) neurotoxins, are thought to be responsible for cellular damage, and has been associated with the development of insulin resistance and cognitive decline in AD (Dias et al. 2020).

The main feature of type 2 diabetes (T2D) is also insulin resistance (De Sousa et al. 2021b). This chronic metabolic disorder affects over 200 million individuals globally, and it is projected that this may rise to 400 million individuals with diabetes by 2030 (IDF 2015). T2D is characterized by the presence of hyperglycemia and insulin resistance, with or without insulin deficiency (De Sousa et al. 2021b). The presence of cognitive decline in T2D is supported by a higher risk of developing neurodegenerative diseases (De Sousa et al. 2021e), especially AD (Wang et al. 2018a). Physical inactivity can contribute to the development of AD and/or T2D (Snel et al. 2012). For this reason, physical exercise is a non-pharmacological recommendation for patients

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with diabetes (De Sousa 2018; Ranasinghe et al. 2018), AD (Alkadhi and Dao 2018; De Sousa et al. 2021d), and many others pathological conditions (Pedersen and Saltin 2015; De Sousa et al. 2020b, 2021a; Eskandari et al. 2020; Cavalcante et al. 2021).

Aerobic exercise training (AET), a type of physical exercise, can induce marked physiological adaptations, such as increased production of Irisin (De Sousa et al. 2021c). AET can also regulate microRNAs (miRNAs), which play an important role in the regulation of signaling pathways that will interfere in different pathologies (Caria et al. 2018). Examining the effects of AET in AD and T2D may help to explain mechanisms of insulin resistance, inflammation and metabolic dysregulation in neurodegenerative disorders. A recent systematic review suggested that large-scale, robust controlled randomized clinical trials should be performed to evaluate if physical exercise would contribute to improve cognitive function in T2D patients (Zhao et al. 2018), what we could suggest also to be better addressed in AD. The identification of how AET influences the regulation of miRNAs in T2D and AD may also identify molecular targets for pharmacological interventions. Here, we have performed a narrative review to try to link some of these mechanisms. This study evaluated the potential novel effects of AET on AD and T2D.

Classic mechanisms of AD

AD is the most common cause of dementia and related neurodegenerative disorders (Alzheimer´s Association 2010). Aging is the greatest risk factor for AD, but the development of the pathophysiology is not a normal part of aging. The amyloid cascade hypothesis based on the role of Aβ peptide has been the major point investigated in the last 30 years (Folch et al. 2019). However, medicines developed that had as main target β-secretase 1 (BACE1), which is the major beta secretase for the generation of β-peptides, have failed in clinical trials (Hawkes 2017; Egan et al. 2018).

The amyloid hypothesis consists in the cleavage of amyloid precursor protein (APP) by β- and gamma-secretase what will lead to an increased number of cytotoxic residues, which will form oligomers that will cause neuron damage (De Sousa et al. 2020a). Inflammation, oxidative stress and insulin resistance can be also seen in the brain of AD patients and animal models (Zhao et al. 2004; Lee et al. 2009). Another hypothesis for the development of AD is Tau hyperphosphorylation (Gratuze et al. 2018). Synaptic dysfunction is related to accumulation of hyperphosphorylated tau protein in AD (Smith et al. 2015). The third mostly studied hypothesis in AD reveals the existence of cholinergic neurons loss and nicotinic acetylcholine receptors (nAChRs) reduction throughout the brain (Magdesian et al. 2005).

Nevertheless, all listed hypothesis can be found in AD patients and in animal models suggesting multiple harmful effects of this disease to the brain. However, it seems that insulin resistance, a common feature between AD and T2D, develops a pivotal role between Aβ and tau pathologies (Mullins et al. 2017; Rad et al. 2018).

Classic mechanisms of T2D

Several processes are associated with T2D and the main known mechanisms linked to this disease are: hyperglycemia, insulin resistance, hyperinsulinemia, hyperlipidemia, increase in reactive oxygen species, inflammation, fibrosis and apoptosis (Roden and Shulman 2019).

State of overnutrition generates metabolic imbalance, promoting activation of the renin–angiotensin–aldosterone system, which stimulates the mechanistic of rapamycin (mTOR)-S6 kinase 1 (S6K1), inhibiting insulin signaling on IRS-1 and IRS-2, decreasing the activation of via PI3K-AKT. Another described molecular mechanism that leads to the inactivation of the PI3K-AKT signaling pathway and insulin resistance is the phosphorylation of serine residues from IRS-1 or IRS-2 that attenuates glucose uptake by this signaling pathway (Jia et al. 2016).

These long-term metabolic and molecular changes will promote dysfunction of some cell organelles, such as: mitochondria, generating mitochondrial dysfunction; in the endoplasmic reticulum, leading to endoplasmic reticulum stress and impaired calcium handling (Jia et al. 2016); and in the cell nucleus and DNA, due to epigenetic alterations linked to changes in DNA methylation, histone acetylation and deacetylation (Kang et al. 2016), modified expression of miRNAs, long-non coding RNA, among many other non-coding RNAs (Raciti et al. 2015), resulting in remodeling and dysfunction of specific organs such as the brain (Biessels and Despa 2018), heart (Dillmann 2019), blood vessels (Shi and Vanhoutte 2017), adipose tissue (Roden and Shulman 2019), kidneys (Assayag et al. 2017) and gut (Hashimoto et al. 2020).

However, a simple session of aerobic exercise activates the AMP kinase, which in turn induces the translocation of GLUT4 to the cell surface, increasing glucose uptake (Musi et al. 2001), demonstrating that exercise is an important tool in combating insulin resistance, T2D and AD (Improta-Caria et al. 2020).

AET features

Physical exercise is considered an excellent non-pharmacological strategy to prevent and help treat AD (De la Rosa et al. 2020) and T2D (Sampath Kumar et al. 2019). AET

Table 1 Circulating miRNAs in T2D (Clinical studies)

MicroRNA	Samples	Targets	References
↓miR-130a	Diabetic Patients Peripheral blood samples	PPARγ	(Jiao et al. 2015)
↑miR-128, miR-130b-3p, miR-374a-5p	Diabetic Patients – south asians Serum samples	IRS-1, PI3KR1, SOCS4	(Prabu et al. 2015)
↑miR-572 ↓miR-1249, miR-320b	Prediabetic and newly-diagnosed Diabetic Patients Plasma samples	FOXO1, EIF2AK3	(Yan et al. 2016)
↓miR-146a	Diabetic Patients Plasma samples	TRAF6	(Balasubramanyam et al. 2011)
↑miR-29a, miR-34a, miR-375	Prediabetic and newly-diagnosed Diabetic Patients Serum samples		(Kong et al. 2011)
↓let-7	Diabetic Patients Carotid endarterectomy specimens samples Aortic samples	NF-kB	(Brennan et al. 2017)
↓miR-503	Patients with T2DM, obesity or both Serum samples	Insulin	(Pescador et al. 2013)
↑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 Plasma samples	INS, IRS-1 PI3KR2, CXCL2, NFKBIZ	(Ortega et al. 2014)
↑miR-144	Diabetic Patients Serum samples	IRS-1	(Karolina et al. 2011)
↑miR-455-5p; miR-454-3p; miR-144-3p; miR-96-5p ↓miR-409-3p; miR-665; miR-766-3p	Diabetic Patients Serum samples	SOCS3, TNF, PRKAA2, PRKAA1; PPARA, FOXO1, MAP2K; AKT1, IRS1, IRS2	(Yang et al. 2017)
↑miR-101, miR-375, miR-802	Diabetic Patients Serum samples	INS, Mtpn, EZH2, Hnf1b	(Higuchi et al. 2015)
↓miR-23a, miR-186, miR-191, miR-146a, let-7i	Diabetic Patients Serum samples	NF-kB	(Yang et al. 2014)
↑miR-1, miR-133a	Diabetic Patients Serum samples	MEF2a	(de Gonzalo-Calvo et al. 2017)
↓miR-126	Diabetic Patients Plasma samples	PI3KR2, SPRAD1	(Zampetaki et al. 2010)
↓miR-126	Diabetic Patients Plasma samples	PI3KR2, SPRAD1	(Zhang et al. 2015b)
↓miR-126	Diabetic Patients Serum samples	PI3KR2, SPRAD1	(Liu et al. 2014d)
↓miR-126	Diabetic Patients Plasma samples	PI3KR2, SPRAD1	(Olivieri et al. 2015)
↓miR-15a	Diabetic Patients Peripheral blood samples		(Al-Kafaji et al. 2015)
↑miR-30a-5p, miR-150 ↓miR-15a, miR-375	Diabetic Patients Plasma samples		(Jiménez-Lucena et al. 2018)
↑miR-424	Diabetic Patients Serum samples	KEAP1, NRF2	(Sun et al. 2017)
↓miR-146a	Diabetic Patients Serum samples		(Baldeón et al. 2014)

Table 1 (continued)

MicroRNA	Samples	Targets	References
↑miR-21, miR-24, miR-34a, miR-148	Diabetic Patients Blood samples	SFRP4	(Nunez Lopez et al. 2017)
↑miR-21, miR-30d, miR-34a, miR-148a	Diabetic Patients	Insulin	(Seyhan et al. 2016)
↑miR-210 ↓ miR-126	Diabetic Patients Plasma samples		(Amr et al. 2018)
↑miR-1, miR-133	Diabetic Patients Peripheral blood samples		(Al-Muhtaresh et al. 2019)
↑miR-34a, miR-375 ↓ miR-146a	Diabetic Patients Serum samples		(García-Jacobo et al. 2019)
↑miR-21	Diabetic Patients Plasma samples		(La Sala et al. 2019)
↑miR-217	Diabetic Patients Serum samples	HIF-1 α	(Lin et al. 2019)
↑miR-20b-5p	Diabetic Patients Plasma samples	Wnt9b	(Xiong et al. 2020)
↑miR-23c ↓ miR-23a, miR-23b	Diabetic Patients PBMCs samples	SDF-1α	(Amin et al. 2020)
↓miR-24	Diabetic Patients Plasma samples		(Li et al. 2020)
↑miR-15a	Diabetic Patients Plasma samples	GCC	(Sangalli et al. 2020)
↑miR-122 ↓ miR-126, miR-146a	Diabetic Patients Plasma samples	TNF- α, IL-6	(Zeinali et al. 2020)
↑miR-34c	Diabetic Patients Plasma samples		(Wu et al. 2021)

more specifically is the type of exercise that is widely studied in the literature and shows several positive effects on the human body (Hillman et al. 2008). AET improves cell function of the innate and adaptive immune system (Improta-Caria et al. 2021), improves the function of endocrine hormones (Hackney and Lane 2015), promotes changes in the morphology and function of several organs, especially the brain (Colcombe et al. 2006), heart (Schüttler et al. 2019) and blood vessels (Hurley et al. 2019), which are very affected organs in both AD and T2D.

In recent years, the effects of AET on molecular mechanisms have been investigated, mainly mechanisms associated with miRNAs in both healthy (Baggish et al. 2011; Nielsen et al. 2014) and diseased individuals (Fernandes et al. 2012; Gomes et al. 2017; Improta-Caria and Aras 2021). However, the molecular mechanisms regulated by AET-induced miRNAs in AD and T2D are poorly studied.

MiRNAs: links between AET, T2D and AD

MiRNAs are small non-coding single-stranded RNAs, having usually 22 nucleotides, that play a role in post-transcriptional mechanisms of the regulation of gene expression (Ha and Kim 2014). MiRNAs are involved with obesity (Iacomino et al. 2016) and adipocyte differentiation and proliferation, and target PPAR´s during the process (Tyagi et al. 2019). They also influence cardiovascular inflammation (Nemecz et al. 2016), T2D (Baroukh et al. 2007), AD (Liu et al. 2014c), and AET (Silva et al. 2017). MiRNAs regulate up to 60% of the protein-coding genes in the human genome (Muljo et al. 2010). A portion of our genome generates functional small RNAs that will not be translated into protein, but that will instead play a very important role in regulating gene expression (Caria et al. 2018). Moreover, miRNA expression profiles are evidently able to identify different types of cancers, however the role of miRNAs in cell biology or organisms remains unclear. In order to understand the roles of miRNAs, it is necessary to systematically identify the targets they regulate.

Expression of miRNAs are associated with many pathophysiological mechanisms involved in T2D (insulin synthesis, insulin resistance, glucose intolerance, hyperglycemia, intracellular signaling, and lipid profile) (Caria et al. 2018). MiRNA regulation is related to several comorbidities and complications of T2D, such as impaired angiogenesis, micro- and macrovascular damage (Stępień et al. 2018). There is a strong possibility that miR-126 is involved in the pathogenesis of micro- and macrovascular complications of T2D (Caria et al. 2018). A number

Table 2 Circulating miRNAs in AD (clinical studies)

Circulating MicroRNAs in Alzheimer´s Disease				
MicroRNAs	Targets	Source	Models	Reference
	Clinical Studies			
↓miR-137, miR-181c, miR-9, miR-29a, miR-29b	SPTLC1 SPTLC2	Serum samples	AD patients	(Geekiyanage et al. 2012)
↑miR-26b-3p, miR-28-3p, miR-30c-5p, miR-30d-5p, miR-148b-5p, miR-151a-3p, miR-186-5p, miR-425-5p, miR-550a-5p, miR-1468, miR-4781-3p, miR-5001-3p, miR-6513-3p ↓ let-7a-5p, let-7e-5p, let-7f-5p, let-7 g-5p, miR-15a-5p, miR-17-3p, miR-29b-3p, miR-98-5p, miR-144-5p, miR-148a-3p, miR-502-3p, miR-660-5p, miR-1294, miR-3200-3p		Blood samples	AD patients	(Satoh et al. 2015)
↓miR-384	APP	Plasma and serum samples	AD patients	(Liu et al. 2014c)
↑miR-34a, miR-181b	BCKDK, AHCY	Blood samples	AD patients	(Schipper et al. 2007)
↓miR-101-3p, miR-144-3p, miR-153-3p, miR-381-3p, miR-383-5p	APP	Plasma samples	AD patients	(Zhou et al. 2019)
↓miR-15b, miR-34a, miR-142, miR-545	TAU	Blood and CSF samples	AD patients	(Cosín-Tomás et al. 2017)
↓miR-214-3p	ATG12	Cerebrospinal fluid samples	AD patients	(Zhang et al. 2016a)
↑miR-125 ↓ miR-16, miR-451a, miR-605		Cerebrospinal fluid samples	AD patients	(McKeever et al. 2018)
↓miR-135b	BACE1	Peripheral blood samples	AD patients	(Zhang et al. 2016b)
↓miR-29c	BACE1	Peripheral blood samples	AD patients	(Yang et al. 2015)
↓miR-200a-3p	BACE1	Blood plasma samples	AD patients	(Wang et al. 2019)
↓miR-193b	APP	Cerebral spinal fluid samples	AD patients	(Liu et al. 2014a)
↓miR-135a, miR-200b	APP, BACE1, Aβ42	Cerebral spinal fluid samples	AD patients	(Liu et al. 2014b)
↓miR-125b, miR-23a, miR-26b		Serum and CSF samples	AD patients	(Galimberti et al. 2014)
↑miR-9 ↓ miR-125b, miR-181c		Serum samples	AD patients	(Tan et al. 2014a)
↑miR-3158-3p, miR-27a-3p, miR-26b-3p, miR-151b ↓ miR-36, miR-98-5p, miR-885-5p, miR-485-5p, miR-483-3p, miR-342-3p, miR-30e-5p, miR-191-5p, let-7 g-5p, let-7d-5p		Serum samples	AD patients	(Tan et al. 2014b)
↓miR-31, miR-93, miR-143, miR-146a		Serum samples	AD patients	(Dong et al. 2015)
↑miR-361-5p, miR-30e-5p, miR-93-5p, miR-15a-5p, miR-143-3p, miR-335-5p, miR-106b-5p, miR-101–3p, miR-425-5p, miR-106a-5p, miR-18b-5p, miR-3065-5p, miR-20a-5p, miR-582-5p ↓ miR-1306-5p, miR-342-3p, miR-15b-3p		Serum exosomes samples	AD patients	(Cheng et al. 2015)
↑miR-323b-5p, miR-563, miR-600, miR-1274a, miR-1975 ↓ let-7d-5p, let-7 g-5p,miR-15b-5p, miR-142-3p, miR-191-5p, miR-301a-3p, miR-545-3p		Plasma samples	AD patients	(Kumar et al. 2013)
↑miR-548at-5p, miR-138-5p, miR-5001-3p, miR-659-5p ↓ miR-185-5p, miR-342-3p, miR-141-3p, miR-342-5p, miR-23b-3p, miR-338-3p, miR-3613-3p		Plasma exosomes samples	AD patients	(Lugli et al. 2015)
↑miR-9, miR-125b, miR-146a, miR-155		Cerebral spinal fluid samples	AD patients	(Alexandrov et al. 2012)

Table 2 (continued)

Circulating MicroRNAs in Alzheimer´s Disease				
MicroRNAs	Targets	Source	Models	Reference
↑miR-146a, miR-100, miR-505, miR-4467, miR-766, miR-3622b-3p, miR-296 ↓ miR-449, miR-1274a, miR-4674, miR-335, miR-375, miR-708, miR-219, miR-103		Cerebral spinal fluid samples	AD patients	(Denk et al. 2015)
↑miR-10a-5p, miR-22-3p, miR-26a, miR-100-5p, miR-204-5p		Cerebral spinal fluid samples	AD patients	(Jain et al. 2019)
↑miR-206		Serum samples	AD patients	(Xie et al. 2017)
↑miR-519 ↓ miR-29, miR-125b, miR-223		Serum samples	AD patients	(Jia and Liu 2016)
↓miR-107		Plasma samples	AD patients	(Wang et al. 2015)
↑miR-34c	BCL2, SIRT1	Plasma and PBMC samples	AD patients	(Bhatnagar et al. 2014)
↑miR-135a, miR-384 ↓ miR-193b		Serum samples	AD patients	(YANG et al. 2018)
↓miR-501-3p		Serum samples	AD patients	(Hara et al. 2017)
↑miR-106b-3p, miR-660-5p, miR-1246, miR-6119-5p ↓ miR-22-3p, miR-26a-5p, miR-126-5p, miR-148b-5p, miR-181c-3p		Serum samples	AD patients	(Guo et al. 2017)
↑miR-15a		Cerebral spinal fluid and plasma samples	AD patients	(Bekris et al. 2013)
↑miR-112, miR-161, let-7d-3p, miR-5010-3p, miR-26a-5p, miR-1285-5p, miR-151a-3p ↓ miR-103a-3p, miR-107, miR-532-5p, miR26b-5p, let-7f-5p		Blood samples	AD patients	(Leidinger et al. 2013)
↑miR-146a-5p, miR-106b-3p, miR-195-5p, miR-20b-5p, miR-497-5p ↓ miR-125b-3p, miR-29c-3p, miR-93-5p miR-19b-3p		Serum samples	AD patients	(Wu et al. 2017)
↑miR-455-3p		Serum samples	AD patients	(Kumar et al. 2017)
↓miR-146a		Cerebral spinal fluid samples	AD patients	(Müller et al. 2014)
↑miR-29a, miR-29b ↓ miR-34a, miR-125b, miR-146a		Cerebral spinal fluid and plasma samples	AD patients	(Kiko et al. 2014)
↑miR-29a, miR-125b		Cerebral spinal fluid samples	AD patients	(Müller et al. 2016)
↑miR-125b, miR-222		Cerebral spinal fluid samples	AD patients	(Dangla-Valls et al. 2017)
↓miR-27a-3p		Cerebral spinal fluid samples	AD patients	(Frigerio et al. 2013)
↑miR-361-5p, miR-30e-5p, miR-93-5p, miR-15a-5p, miR-143-3p, miR-335-5p, miR-106b-5p, miR-101-3p, miR-424-5p, miR-106a-5p, miR-18b-5p, miR-3065- 5p, miR-20a-5p, miR-582-5p ↓ miR-1306-5p, miR-342-3p, miR-15b-3p		Serum samples	AD patients	(Cheng et al. 2015)
↓miR-146a-5p		Venous blood samples	AD patients	(Zhang et al. 2015a)
↑miR-590-5p, miR-486-5p ↓ miR-129-3p, miR-139- 3p, miR-181-5p, miR-210, miR-223-5p, miR-374b, miR-519-3p, let-7a,, miR-424-3p, miR-532-3p, miR-758		Cerebral spinal fluid samples	AD patients	(Van Harten et al. 2015)
↑miR-130a-3p, miR-339-5p, miR-425-5p, miR-3607-3p, miR-4297 ↓ miR-25-5p, miR-639, miR-5000-5p, miR-5699		PBMC blood samples	AD patients	(Ren et al. 2016)

Table 2 (continued)

Circulating MicroRNAs in Alzheimer´s Disease				
MicroRNAs	Targets	Source	Models	Reference
miR-29c, miR-136-3p, miR-16–2, miR-331-5p, miR-132-5p, miR-151, miR-485-5p		Cerebral spinal fluid samples	AD patients	(Gui et al. 2015)
↑miR-27b, miR-128, miR-155		PBMC blood samples	AD patients	(Guedes et al. 2016)
↓miR-9-5p, miR-106a-5p, miR-106b-5p, miR-107		Blood samples	AD patients	(Yllmaz et al. 2016)
↑miR-613	BDNF	Cerebral spinal fluid and sérum samples	AD patients and mice model	(Li et al. 2016)
↑miR-378a-3p, miR-1291 ↓ miR-15b-5p, miR-19b-3p, miR-30d-5p, miR-125b-5p, miR-140-5p, miR-142-3p, miR-143-3p,miR-193a-5p, miR-195-5p, miR-223-3p, miR-328-3p, miR-340-5p		Cerebral spinal fluid samples	AD patients	(Lusardi et al. 2017)
↑miR-200c		Plasma samples	AD patients	(Wu et al. 2016)
↑miR-200a-3p, miR-320a, miR-320b, miR-320c, miR-483-5p, miR-486-5p, miR-502-3p, miR-1260a ↓ miR-18a-5p, miR-30b-5p, miR-33a-5p, miR-103a-3p, miR-142-3p, miR-151a-5p, miR-301a-3p		Plasma samples	AD patients	(Nagaraj et al. 2017)
↓miR-9-5p, miR-598		Cerebral spinal fluid samples	AD patients	(Riancho et al. 2017)
↑miR-26a-5p, miR-26b-5p, miR-103a-3p, miR-107		Blood samples	AD patients	(Chang et al. 2017)
↓miR-222		Serum samples	AD patients	(Zeng et al. 2017)
↓miR-144-5p, miR-221, miR-374		Blood samples	AD patients	(Manzine et al. 2018)
↑let-7b		Cerebral spinal fluid samples	AD patients	(Liu et al. 2018)
↑miR-1908	APOE	Plasma samples	AD patients	(Wang et al. 2018b)
↑miR-18b-5p, miR-20a-5p, miR-22-3p, miR-24-3p, miR-26a-5p, miR-26b-5p, miR-27a-3p, miR-29b-3p, miR-30a-5p, miR-30b-5p, miR-30e-5p, miR-99b-5p, miR-103a-3p, miR-106a-5p, miR-106b-5p, miR-124-3p, miR-125a-5p, miR-140-3p, miR-142-3p, miR-143-3p, miR-197-3p, miR-223-3p, miR-301a-3p, miR-338-3p, miR-491-5p, let-7b-5p, let-7 g-5p ↓ miR-15a-5p, miR-22-3p, miR-92a-3p miR-99a-5p, miR-100-5p, miR-132-3p, miR-146a-5p, miR-320a, miR-320b, miR-335-5p, miR-1246		Cerebral spinal fluid and serum samples	AD patients	(Denk et al. 2018)
↑miR-125b	SPHK1	Cerebral spinal fluid samples	AD patients	(Jin et al. 2018)
↑let-7b, let-7e		Cerebral spinal fluid samples	AD patients	(Derkow et al. 2018)
↓miR-21, miR-23a, miR-126, miR-151a, miR-451a, let-7i		Plasma samples	AD patients	(Gámez-Valero et al. 2019)
↓miR-133b		Serum samples	AD patients	(Yang et al. 2019)
↓miR-4422	BACE1 GSAP	Serum samples	AD patients	(Hajjri et al. 2020)
↓miR-9		Blood samples	AD patients	(Souza et al. 2020)
↓miR-103, miR-107		Plasma samples	AD patients	(Wang et al. 2020)
↓miR-149	BACE1	Serum samples	AD patients	(Du et al. 2021)
↓miR-374b	BACE1	Serum samples	AD patients	(Zhang and Wang 2021)

Table 3 Circulating miRNAs in AET (response during and after exercise in clinical studies)

Circulating 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		Healthy men	Acute Response Cycle ergometer exercise (10 × 2 min bouts, 1 min rest interval between each bout, 76% VO2peak)	(Radom-Aizik et al. 2010)
↓ 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		Serum samples		
↑ miR-21, miR-146a, miR-221, miR-222, miR-20a	PTEN PDCD4 p27/KIP1 p21/WAF1	Healthy men 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)
↑ 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		Healthy men 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)
↓ 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				
↑ miR-149 ↓ miR-146a, miR-221		Healthy men Serum samples	Acute Response Resistance exercise (bench press and leg press) 3 days after exercise	(Sawada et al. 2013)

Table 3 (continued)

Circulating MicroRNAs	Targets	Source	Exercise protocols	Reference
↓ miR-486	PTEN	Healthy men 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)
↑ 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 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)
↑ miR-181b, miR-214miR-1, miR-133a, miR-133b, miR-208b		Healthy men Plasma samples	Acute Response Uphill treadmill test (concentric) Immediately after Downhill treadmill test (eccentric) 2–6 hs after exercise	(Banzet et al. 2013)
↑ miR-126, miR-133	CPK	Healthy men Plasma samples	Acute Response Single symptom-limited spiroergometry test Cycling 4 h at 70% of anaerobic threshold Marathon run	(Uhlemann et al. 2014)
↑ miR-1, miR-126, miR-133a, miR-134, miR-146a, miR-208a, miR-499	CPK NT-proBNP hsCRP	Healthy men Plasma samples	Acute Response Marathon run Immediately after run (decreased after 24 h)	(Baggish et al. 2014)
↑ 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)
↑ miR-1, miR-133a, miR-206		Healthy men Plasma samples	Acute Response Marathon run Immediately after run	(Gomes et al. 2014)

Table 3 (continued)

Circulating MicroRNAs	Targets	Source	Exercise protocols	Reference
↑ miR-15a, miR-29b, miR-29c, miR-30e, miR-140, miR-324, miR-338, miR-362, miR-532, miR-660		Healthy men	Acute Response	(Radom-Aizik et al. 2014)
↓ miR-23b, miR-130a, miR-151, miR-199a, miR-221		Serum samples	Cycle ergometer exercise (10 × 2 min bouts, 1 min rest interval between each bout, 82% VO2max)	
↑ miR-1, miR-133a, miR-133b, miR-139-5p, miR-143, miR-145, miR-223, miR-330-3p, miR-338-3p, miR-424		Healthy men (n = 32)	Acute Response cycle ergometry test at 65% Pmax 1–3 hs after exercise Immediately after exercise	(Nielsen et al. 2014)
↓ miR-30b, miR-106a, miR-146, miR-151-3p, miR-151-5p, miR-221, miR-652, let-7i		Plasma samples	Adaptation (12 weeks total) Systematic endurance cycle ergometry training, 3–5 days after training	
↑ 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				
↑ miR-150 ↓ miR-125b, miR-146a, miR-210,		Healthy individuals and CKD patients Plasma samples	Acute and Adaptation 12-wk home-based aerobic training	(Van Craenenbroeck et al. 2015)
↑ let-7f, miR-21, miR-29c, miR-223		Healthy adults	Adaptation (18 weeks) Running exercise (3 ×/week, 60 min)	(Dias et al. 2015)
↓ let-7f, miR-21, miR-29c, miR-223		PBMCs samples		
↑ miR-222	HIPK1	Heart failure patients Blood samples	Acute Response Heart failure patients Bicycle Ergometry Test	(Liu et al. 2015)

Table 3 (continued)

Circulating MicroRNAs	Targets	Source	Exercise protocols	Reference
↑ 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 Serum samples	Acute Response Marathon run Immediately after run (decreased after 24 h)	(de Gonzalo-Calvo et al. 2015)
↑ miR-1, miR-30a, miR-133a ↓ miR-26a, miR-29b		Healthy adults Plasma samples	Acute Response Marathon run Immediately after run (decreased after 24 h) Immediately after run	(Clauss et al. 2016)
↑ miR-1, miR-133a, miR-206		Statin and nonstatin-using runners Plasma samples	Acute Response Marathon run Immediately after run (decreased after 24 h)	(Min et al. 2016)
↑ 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 Plasma samples	Acute Response Immediately after Vigorous intensity continuous exercise Immediately after	(Cui et al. 2016)
↑ miR-1, miR-486, miR-494	HDAC4 PAX7 PTEN FOXO1A	Healthy men Blood samples	Acute Response Aerobic exercise VO2max test (Endurance athletes, runners, cyclists and triathletes)	(Denham and Prestes 2016)
↑ miR-376a ↓ miR-16, miR-27a, miR-28		Obese older adults Plasma samples	Adaptation (5 months total) Aerobic run exercise training 30 min, 65–70% heart rate res. (4 days/week)	(Zhang et al. 2017)

Table 3 (continued)

Circulating MicroRNAs	Targets	Source	Exercise protocols	Reference
↑ miR-7154-3p, miR-200b-5p, miR-5582-3p, miR-6859-3p, miR-6751-5p, and miR-4419a, miR-1273f, miR-181b, miR-7852, miR-548ac, miR-6737, miR-1915, miR-200a, miR-4418, miR-4488, miR-6124, miR-302e ↓ miR-3671, miR-5095, miR-7154, miR-9, miR-5698, miR-181a, miR-4253, miR-4251, miR-429, miR-936, miR-605		Healthy individuals Saliva samples	Aerobic long run Run exceeding 55 min and comprising ≥ 20% of weekly running distance	(Hicks et al. 2018)
↑ miR-221 ↓ miR-208b, miR-221, miR-21, miR-146a, miR-210		Healthy men Serum samples	Acute Response and Adaptation Basketball Exercise (3-months)	(Li et al. 2018)
↑ 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 Serum samples	Acute Response 10 km race, half-marathon, marathon	(de Gonzalo-Calvo et al. 2018)
↓ miR-21-5p, miR-150-5p		Myasthenia Gravis patients Serum samples	Adaptation Aerobic and resistance training twice weekly for 12 weeks	(Westerberg et al. 2017)

Table 3 (continued)

Circulating MicroRNAs	Targets	Source	Exercise protocols	Reference
↑ miR-142-3p, miR-221-3p, miR-126-3p, miR-146a-5p, and miR-27b-3p ↓ miR-486-5p, let-7b-5p, miR-29c-3p, let-7e-5p, miR-93-5p, miR-7-5p, miR-25-3p, miR-92a-3p, and miR-29b-3p		Healthy individuals Serum samples	Adaptation 20 weeks of endurance exercise training	(Barber et al. 2019)
↑ let-7a, let-7f, let-7 g, miR-17, miR-15a, miR-26b, miR-20a, miR-16, miR-98, miR-20b, miR-17, miR-144, miR-18a, miR-1246, miR-195, miR-199a, miR-93, miR-126, miR-374a, miR-374b, miR-454, miR-7107 ↓ miR-30b, miR-30c, miR-16–2, miR-30a, miR-199a, miR-192, miR-223, miR-199a, miR-326, miR-30d, miR-331, miR-340, miR-378a, miR-484, miR-550a, miR-7977		Healthy individuals Blood samples		(Kern et al. 2019)

Table 3 (continued)

Circulating MicroRNAs	Targets	Source	Exercise protocols	Reference
↑ miR-33a, miR-345, miR-424, miR-505, miR-1260a ↓ miR-199b, miR-551a, miR-1537, miR-223, miR-150, let-7b, miR-423, miR-346, miR-425, miR-338, miR-339, miR-106b, miR-502, miR-27a, miR-660, miR-100, miR-22, miR-30e, miR-497, miR-1972, miR-940, miR-130b, miR-223, miR-145, miR-181c, miR-501, miR-675, miR-424, miR-1, miR-34a, miR-629, miR-30a, miR-148a, miR-596, miR-10b, miR-30d, miR-320d, miR-192, miR-20b, miR-103a, miR-106b, miR-144, miR-665, miR-486		Healthy individuals Plasma samples	Individuals performed 10-km race, a half-marathon and a Marathon	(Fernández-Sanjurjo et al. 2020)
↑ miR-150, miR-221		Healthy men Serum samples		(Sapp et al. 2020)
↓ miR-146a, miR-191		HFrEF patients Plasma samples	Aerobic training intensity was set at 90% of heart rate at the respiratory compensation point for 15 weeks	(Witvrouwen et al. 2021a)
↑ miR-409, miR-501				(Goldberg et al. 2021)
↑ let-7b, miR-23a, miR-140, miR-146a, miR-191, miR-210, and miR-339-5p				(Witvrouwen et al. 2021b)

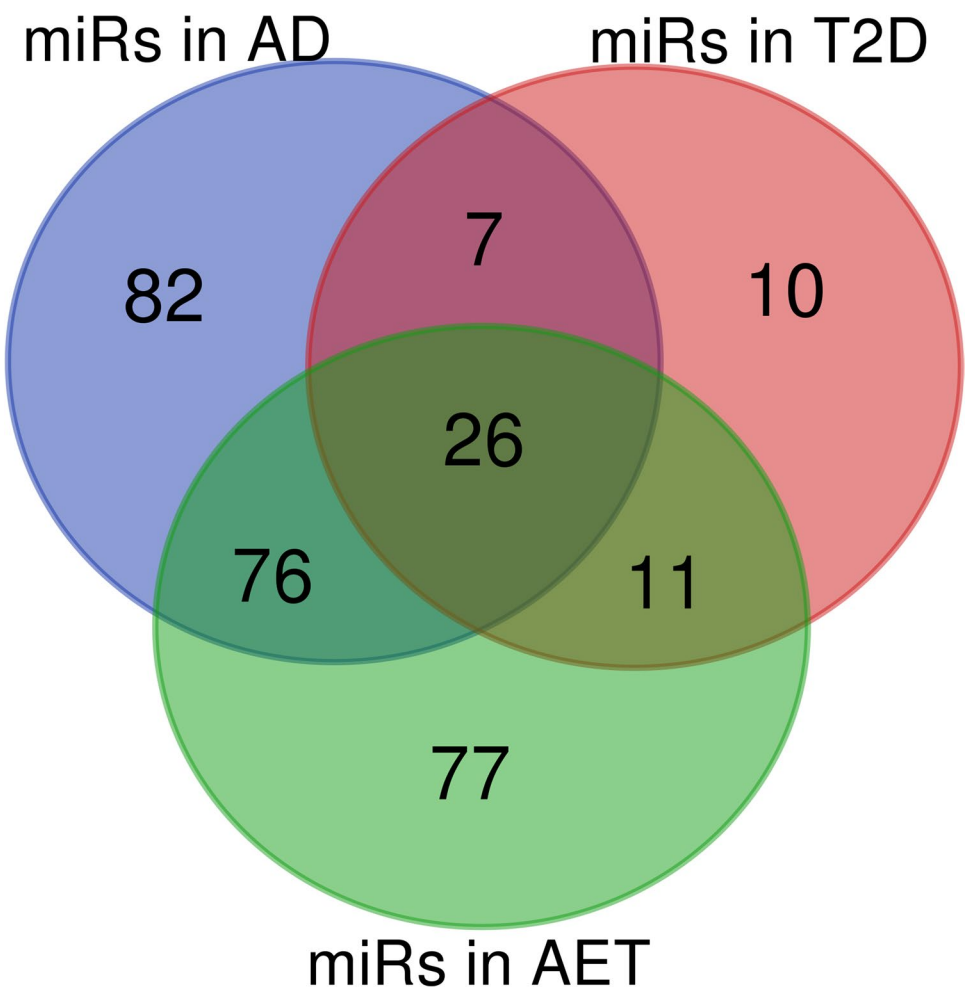

Fig. 1 Venn diagram representing overlaps of circulating miRNAs in AD, T2D AND AET. The Venn diagram depicts miRNAs that were identified and dysregulated in AD, T2D AND AET, and showing the overlaps in the three conditions

of miRNAs have been identified as regulators of insulin transcription and translation at higher levels of blood glucose, such as miR-124, miR-107, miR-30a, and miR-30d (Baroukh et al. 2007; Tang et al. 2009; Aaltonen et al. 2010). Downregulation of miR-484, miR-690, and miR-296 was observed in mice models of T2D, and is related to the inhibition of insulin transcription (Tang et al. 2009). Insulin secretion is also regulated by a few miRNAs, including miR-375 and miR-9 (Poy et al. 2004; Joglekar et al. 2009). The regulation of the molecular mechanisms involved in T2D patients seems to be regulated by mir375, miR-101 and miR-802 (Kong et al. 2011; Higuchi et al. 2015). These are a few examples only of how miRNAs are crucial in several pathophysiological roles in T2D and associated comorbidities and conditions (Table 1).

MiRNA dysregulation is also evident in AD and has been associated with several neuropathological alterations (Table 2), including altered expressions of species that are known to be involved in AD pathology, including microglia and astrocytes (Shaik et al. 2018). MiR-132/212 was reported to be down-regulated in the frontal cortex in mild cognitive decline (Smith et al. 2015). MiRNA 153 is also downregulated in the AD brain and it is associated with higher expressions and mutations of APP (Long et al. 2012). MiR-195 is suggested to be downregulated in the AD brain leading to increased production of Aβ40 and Aβ42, the strongest cytotoxic forms of the peptide, contributing to a greater formation of pathogenic amyloid plaques (Shaik et al. 2018). Future studies must investigate drugs that can target dysregulation of miRNAs in T2D and AD. Nevertheless, the investigation of alternative signaling pathways and mechanisms, including the changes induced in miRNAs by AET is necessary (Table 3). Identifying the changes caused by AET hold potential for the development of novel therapies for the treatment of T2D and AD.

AET induces changes in miRNAs in both T2D and AD

AET is capable of improving insulin resistance and dyslipidemia (De Sousa 2018). Cellular homeostasis is markedly affected by a single exercise session and in response to

chronic exercise training, which induce marked changes in the circulating miRNA profile (Caria et al. 2018). AET promotes positive effects in miRNA-mediated gene regulation among healthy participants, but clinical studies focusing on people with T2D and AD have not been well-explored to date (Muljo et al. 2010; Caria et al. 2018; Shaik et al. 2018).

The identification of the miRNAs regulated by AET in people with T2D and/or AD is important in order to understand the molecular alterations in signaling pathways, proteins, enzymes and interleukins. These findings are crucial for the development of new therapies, drug-related or not, in order to prevent or combat TD2M and AD.

Circulating miRNAs overlaps between AD, T2D and AET

Here, we show what is currently known about identified circulating miRNAs in AD, T2D and AET, and the common miRNAs to all three on a Venn diagram (Fig. 1). We identified 7 circulating miRNAs deregulated and associated with AD and T2D, 76 circulating miRNAs deregulated in AD and AET and 11 circulating miRNAs deregulated in T2D and AET. In particular, we identified 26 circulating miRNAs deregulated in the 3 situations, they are: miR-532, let-7i, miR-144, miR-140, miR-30a, miR-375, miR-222, miR-30d, miR-125b, miR-126, miR-21, miR-142, miR-34a, miR-20b, miR-146a, miR-148a, miR-15a, miR-23a, miR-766, miR-210, miR-195, miR-130a, miR-424, miR-23b, miR-29a and miR-191. After an analysis of the expression pattern of these 26 miRNAs, it was found that 2 miRNAs (miR-23a and miR-532) showed an expression pattern different from the pattern in the AET. Both miR-23a and miR-532 are downregulated in disease and upregulated in AET.

Inflammation is a very common situation in AD and T2D and NF-κB is an overexpressed transcriptional factor in this situation. The NF-κB p-65 subunit binds to miR-23a promoter and decreases its expression (Rathore et al. 2012), favoring an increase in the inflammatory profile. Dysregulation of miR-23a has also been associated with dyslipidemia (Karolina et al. 2012). On the other hand, AET increases the expression of miR-23a, suggesting that AET can decrease the inflammatory process and attenuate dyslipidemia through the regulation of this miRNA in AD and T2D.

Under conditions of inflammation, miR-532 is downregulated and this miRNA targets the proapoptotic gene BCL2 antagonist/killer 1 (BAK1). Thus, BAK1 is overexpressed, elevating the inflammatory profile and promoting apoptosis (Chen et al. 2020). In contrast, AET increases miR-532 expression, suggesting that it may be a molecular mechanism induced by AET to reduce BAK1 expression and subsequently decrease inflammation and apoptosis in AD and T2D. These remarkable data are further strong evidence that scientific research should be driven to investigate the changes induced in miRNA´s by AET in T2D and AD. Such identification will also facilitate finding possible targets for new therapies.

Conclusions

AET is a non-pharmacological tool that can prevent and be used as a therapy in T2D and AD, helping to avoid memory loss and several pro-inflammatory mechanisms in both diseases. We suggest that investigating molecular mechanisms of the actions of AET on molecular pathways and the regulation of miRNAs will not only provide all known benefits of how better prescribe physical exercise, but will also illuminate new targets to the ultimate aim that is to find a cure to these diseases. AET will at the very least likely diminish the suffering of patients through the development of new and effective therapies. AET and physical exercise in general is a therapy itself.

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Author's contribution Ricardo Augusto Leoni De Sousa: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing—original draft; Writing—review & editing. Alex Cleber Improta-Caria: Data curation; Formal analysis; Investigation; Supervision; Validation; Visualization; Roles/Writing—original draft; Writing—review & editing.

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Declarations

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