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MiRNA a new insight in metabolic and human diseases: A review

Ibrahim Jafri*

Department of Biotechnology, College of Sciences, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia

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ABSTRACT

The purpose of this research is to examine existing studies on the association between microRNAs (miRNA) and age-related disorders. The miRNAs are small, noncoding RNA molecules with the ability to regulate gene expression. These are well-established in extracellular circulation, including various types of diseases such as cancer, cardiovascular diseases, and diabetes. Similarly, several miRNAs are associated with certain age-related conditions, such as increased miR-21 expression in cancer patients. Besides that, the miR-122 in atherosclerosis patients played an essential role in gene expression and disease. Therefore, the miRNA has the potential to serve as a reliable biomarker for the early detection, monitoring of progression, and regression of age-related diseases. To have a complete understanding of the mechanisms and the direct long-term effects that the miRNA has on the pathophysiology and development of diseases, additional research is required.

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Introduction

The first microRNA (miRNA) was discovered in a roundworm called *Caenorhabditis Elegans*, leading to the discovery of over 2,400 mature miRNAs. In general, miRNAs are small, non-coding RNA molecules between 18 and 25 nucleotides in length that can regulate gene expression . They have been linked to a variety of human diseases including diabetes, hypertension, and neurodegenerative disorders. The synthesis of miRNA begins to start in the nucleus with the formation of primary miRNA. Subsequently, it transforms into its precursor miRNA, and then terns to mature the miRNA. In fact, miRNA primarily modulates gene expression, and is produced as circulatory miRNA.

Circulatory miRNAs are known to be stable in extracellular circulation, but numerous studies have impacted negatively on their ability to serve as a viable bio-indicator for ageing and to develop age-related diseases, such as certain types of cancer, cardiovascular diseases, cataracts, dementia, diabetes and hypertension. Therefore, minimally invasive or even non-invasive miRNAs are beneficial in the early detection of diseases (1). They are also present in the body fluids such as blood, breast milk, cerebrospinal fluids, saliva, and tears. These fluids are stable which contain higher level of miRNA, and this miRNA is considered to be ideal for possible diagnosis, and may be used as health progression markers (2).

Effects of miRNA

Aging

The condition known as “cell senescence,” which indicates age-related deterioration and causes cells to lose their ability to divide and develop, is critical in the ageing process. It refers to the intricate cellular and molecular changes that occur in cells over time (2). Numerous miRNAs regulate pathways involved in the ageing process. A study by Hooten found a decrease in miR-151a-5p, miR-181a-5p, and miR1248 expression in older adults (with an average age of 64) compared to young people (with an average age of 30) (1). Furthermore, it was discovered that older adults have higher levels of miR-92a, miR-222, and miR-375 expression than young individuals (3). Increased expression of miR-144 and miR-451 in type 2 diabetes patients have been identified as potential biomarkers of red blood cell aging (2). All the data were shown in table 1.

Arthritis

Rheumatoid arthritis is an inflammatory, auto-immune disease associated with aging. Patients with rheumatoid arthritis would benefit from an early-stage detection stra-

Table 1. Studies on the correlation between miRNA and aging.

Article title	Correlation	Subjects	Ref
Age-related changes in micro-RNA levels in serum	↓ miR-151a-5p, miR-181a-5p, miR-1248	Human	(1)
Effect of aging and sex on circulating micro-RNAs in humans	↓ miR-20a	Human	(4)
Investigation of microRNA expression in human serum during the aging process	↑ miR-92a, miR-222, miR-375	Human	(3)

* Corresponding author. Email: i.jafri@tu.edu.sa

tegy that would prevent long-term joint damage. In fact, a study revealed lower levels of miR-146a, miR-155 and miR-16, and the researchers hypothesized that miR-223 could be used as a marker for the progression of rheumatoid disease (5). Similarly, another study found elevated miR-4634, miR-181d, and miR-4764-5p levels, and decreased miR-342- 3p, miR-3926, miR-3925-3p, miR-122-3p, and miR-9-5p levels (6). Additionally, a separate study demonstrated that miRNA expression can be used as a biomarker to monitor disease progression before and after anti-tumor necrosis factor (anti-TNF) therapy in patients with rheumatoid arthritis due to the regulation of miR-16, miR-23, miR-125 and miR-126 serum levels (7). Number of studies have shown the correlation between miRNA and arthritis as shown in table 2.

Cancer

Cancer is one of the leading causes of death worldwide, accounting for 8.2 million people per year (World Health Organization). The most prevalent forms of cancer in men are prostate, lung, colorectal, stomach, and liver. Women are more likely to be affected by breast, colorectal, lung, and uterine cervical cancers (10). Since cancer arises from uncontrolled cell differentiation and proliferation, and its relationship with miRNA biomarkers must be thoroughly investigated. In fact, numerous biomarkers are already employed in the diagnosis of certain cancers. For instance, alpha-fetoprotein is currently utilized as a biomarker for liver cancer. The use of chromogranin for neuroendocrine tumors is another example. Additionally, carbohydrate antigen 125 is used as a biomarker for ovarian cancer. On the other hand, ongoing research is still being conducted to explore and discover more superior biomarkers because many types of cancer are still not detected until they are in advanced stages. For example, the majority of cancers (if not all) are nearly seven times more prevalent in older men (i.e., prostate, lung, and colon cancers), and four times more recurrent in older women (i.e., breast, colon, lung, and stomach cancers) than in young individuals.

Numerous studies have shown that miR-21 is the most prevalent miRNA associated with cancer. Meanwhile, the miR-152 has been identified as the most common tumor suppressor (10). Patients diagnosed with lung, colorectal, and breast cancer exhibited a significant increase in miR-21 and miR-152. In contrast, the miR-21 and miR-152 were not significantly expressed in prostate cancer patients. Instead, patients with prostate cancer had lower expression of miR-200, miR-605, miR-135, and miR-106, as well as a significant increase in miR-410 (11). In contrast, a different study involving prostate cancer patients revealed upregulation of miR-21 and miR-375 (12). These outcomes are supported by the findings of other studies that found increased concentrations of miR-21, miR-141, miR-100, and miR-375 in the serum and plasma of prostate cancer patients (13). In contrast, patients with non-small cell lung cancer exhibited significant down-regulation of miR-195, and upregulation of miR-182, miR-183, and miR-210 (13). Another study on non-small cell lung cancer revealed abnormal miRNA expression based on deregulated levels of miR-423, miR-148, miR-18, miR-574, and miR-26 (14).

Additionally, breast cancer is the second leading cause of cancer-related deaths among women. In this type of cancer, circulating miRNA can be used as a biomarker to track the recurrence of breast cancer. Recent research found an increase in miR-21, miR-375, and miR-205, as well as a decrease in miR-382, miR-376, and miR-411, in patients with recurrent breast cancer (12). Another study on breast cancer revealed that miR-148 was significantly up-regulated, whereas the miR-15b was significantly down-regulated in the patients (22).

Eventually, the miR-23, miR-27, miR-142, and miR-376 were the most up-regulated miRNA in patients with colorectal cancer (16). Patients with advanced colorectal cancer, and advanced polyps had high levels of miR-34 but low levels of miR-150 (23). Furthermore, it was found that let-7a, miR-1229, miR-1246, and miR-150 levels were significantly higher in patients with primary colorectal cancer compared to healthy individuals (25). Table 3 demonstrate many studies on the correlation between miRNA and cancer.

Cardiovascular diseases

Cardiovascular diseases continue to be the leading cause of death and morbidity worldwide. It includes conditions such as atherosclerosis, diabetes, hypertension,

Table 2. Studies on the correlation between miRNA and arthritis.

Article title	Correlation	Subjects	Ref
Association of circulating miR-223 and miR-16 with disease activity in patients with early rheumatoid arthritis.	↓ miR-146a, miR-155, miR-16	Human	(5)
Circulating miRNA-125b is a potential biomarker predicting response to rituximab in rheumatoid arthritis	↑ miR-125b	Human	(8)
Plasma microRNA expression profiles in Chinese patients with rheumatoid arthritis.	↑ miR-4634, miR-181d, miR-4764-5p	Human	(6)
Plasma microRNA expression profiles in Chinese patients with rheumatoid arthritis	↓ miR-342-3p, miR-3926, miR-3925-3p, miR-122-3p, miR-9-5p, miR-219-2-3p	Human	(6)
MicroRNA-125b: association with disease activity and the treatment response of patients with early rheumatoid arthritis.	↓ miR-125b	Human	(9)
Circulating miRNAs as potential biomarkers of therapy effectiveness in rheumatoid arthritis patients treated with anti-TNF alpha	↑ miR-16-5p, miR-23-3p, miR-125b-5p, miR-126-3p, miR-146a-5p, miR-223-3p	Human	(7)
Circulating miRNAs as potential biomarkers of therapy effectiveness in rheumatoid arthritis patients treated with anti-TNF alpha	↑ miR-23, miR-223	Human	(7)

Table 3. Studies on the correlation between miRNA and cancer.

Article title	Correlation	Subjects	Ref
Circulating microRNA signature for the diagnosis of very high-risk prostate cancer	↑ 200c, miR-605, miR-135a*	Human	(11)
	↓ miR-433, miR-106a		11
Identification of a circulating microRNA signature to distinguish recurrence in breast cancer patients.	↑ miR-21-5p, miR-375, miR-205-5p, miR-194-5p	Human	(12)
	↓ miR-382-5p, miR-376c-3p, miR-411-5p	Human	(13)
Diagnostic value of serum miR-182, miR-183, miR-210, and miR-126 levels in patients with early-stage nonsmall cell lung cancer.	↑ miR-182, miR-183, miR-210	Human	(13)
Diagnostic value of serum miR-182, miR-183, miR-210, and miR-126 levels in patients with early-stage non-small cell lung cancer	↓ miR-126	Human	(13)
A unique set of 6 circulating micro-RNAs for early detection of non-small cell lung cancer.	↑ miR-429, miR-205, miR-200b, miR-203, miR-125b, miR-34b	Human	(15)
Serum-based microRNA signatures in early diagnosis and prognosis prediction of colon cancer.	↑ miR-23a-3p, miR-27a-3p, miR-142-5p, miR-376c-3p	Human	(16)
MicroRNA expression profiling on individual breast cancer patients identifies novel panel of circulating microRNA for early detection.	↑ miR-4270, miR-1225-5p, miR-188-5p, miR-1202, miR-4281, miR-1207-5p, miR-642b-3p, miR-1290, miR-3141	Human	(17)
The utility of urine-circulating miRNAs for detection of prostate cancer.	↑ miR-375	Human	(18)
The utility of urine-circulating miRNAs for detection of prostate cancer.	↓ miR-148	Human	(18)
Analysis of circulating miRNAs 21 and 375 as potential biomarkers for early diagnosis of prostate cancer.	↑ miR-21, miR-375	Human	(19)
Evaluation of plasma miR-21 and miR-152 as diagnostic biomarkers for common types of human cancers.	↑ miR-21, miR-152	Human	(10)
Diagnostic and prognostic value of plasma micro-RNA-195 in patients with non-small cell lung cancer.	↓ miR-195	Human	(20)
MicroRNA-410-5p as a potential serum biomarker for the diagnosis of prostate cancer.	↑ miR-410-5p	Human	(21)
Circulating microRNA-based screening tool for breast cancer.	↑ miR-148a	Human	(22)
Circulating microRNA-based screening tool for breast cancer	↓ miR-15b	Human	(22)
Circulating miRNAs miR-34a and miR-150 associated with colorectal cancer progression.	↑ miR-34a	Human	(23)
Circulating miRNAs miR-34a and miR-150 associated with colorectal cancer progression.	↓ miR-150	Human	(23)
Expression of the microRNAs hsa-miR-15a and hsa-miR-16-1 in lens epithelial cells of patients with age-related cataract.	↑ miR-141	Human	(24)
Circulating exosomal microRNAs as biomarkers of colon cancer	↑ let-7a, miR-1229, miR-1246, miR-150, miR-21, miR-223, miR-23a	Human	(25)
Circulating neutrophil microRNAs as biomarkers for the detection of lung cancer	↑ miRs-423-3p, 148a-3p, 18a-3p, 574-3p	Human	(14)
Circulating neutrophil microRNAs as biomarkers for the detection of lung cancer	↓ miR-26a-2-3p	Human	(14)
Circulating miR-200c and miR-141 and outcomes in patients with breast cancer.	↑ miR-200c, miR-141	Human	(26)
Potentiality of a triple microRNA classifier: miR-193a-3p, miR-23a and miR-338-5p for early detection of colorectal cancer.	↑ miR-193a-3p, miR-23a, miR-338-5p	Human	(27)

and obesity (20). The expression of miR-92a, miR-126, miR-130a, miR-222, and miR-370 was found to be lower in patients with pre-atherosclerosis compared to patients with atherosclerosis in several studies (28). Patients with atherosclerosis also had higher levels of miR-21, miR-122, miR-130a, and miR-211 (28). Elevated expression of miR-106b/25, miR-17/92a, miR-21/590-5p, miR-126, and miR-451 was found in patients with unstable angina (29). However, patients with heart failure had significant down-regulation of miR-103, miR-142, and miR-30b (30). Number of studies have shown the correlation between miRNA and cardiovascular diseases as shown in table 4.

Cataract and glaucoma

Cataract is the most common cause of blindness worldwide when it comes to aging. The primary miRNA associated with cataracts is elevated miR-34 expression (32). In the meantime, other researchers discovered an increase in miR-15 and miR-16 levels in cataract patients (32). In contrast, a study of glaucoma patients found an increase in the expression of miR-4484, miR-6515, and miR-12 (33). Numbers of studies have shown the correlation between miRNA and Cataract and Glaucoma as shown in table 5.

Diabetes and obesity

Diabetes mellitus has become a global public health problem due to growing concern about an increasing number of obese people worldwide. It has had an impact on the lives of over 450 million people worldwide. Type 1 diabetes is caused by the body's inability to produce enough insulin, whereas type 2 diabetes is caused by ineffective insulin synthesis. A study found a link between miRNA and plasma hormone concentrations in pre-diabetic African American adults, and type 2 diabetes mellitus patients. Furthermore, in the pre-diabetic Mellitus group, a strong association between the miRNA-15 and total ghrelin and C peptide was discovered (35). Furthermore, it was discovered that decreased miRNA-15b expression resulted in insulin resistance, and increased plasma ghrelin, demonstrating the relationship between C-peptide and miRNA-15b(35).Meanwhile, the miR-126 was found to be a viable biomarker for the early detection of type 2 diabetes mellitus in high-risk patients, as miR-126 expression was significantly reduced in high-risk patients (36). Another study discovered significant up-regulation of miR-661, miR-571, miR-770, and miR-1303 expression in type 2 diabetes mellitus patients (37). Apart from these findings, obesity was identified as an age-related public health issue that is strongly linked to metabolic disorders such as diabetes. Thus, the miR-138 and miR-376 have been proposed as potential tools for predicting among control patients, diabetes patients, and obese diabetic patients (38). Table 6 shows numbers of studies on the correlation between miRNA and diabetes and obesity.

Table 4. Studies on the correlation between miRNA and cardiovascular diseases .

Article title	Correlation	Subjects	Ref
Peripheral blood miRNAs as a biomarker for chronic cardiovascular diseases.	↑ miR-21, miR-122, miR-130a, miR-211	Human	(28)
Peripheral blood miRNAs as a biomarker for chronic cardiovascular diseases.	↓ miR-92a, miR-126, miR-222	Human	(28)
Signature of circulating microRNAs as potential biomarkers in vulnerable coronary artery disease	↑ miR-106b/25, miR-17/92a, miR-126*, miR-451 miR-21/590-5p family	Human	(29)
Circulating microRNAs as candidate markers to distinguish heart failure in breathless patients	↓ miR-103, miR-142-3p, miR-342-3p, miR-30b	Human	(31)
Circulating microRNAs characterizing patients with insufficient coronary collateral artery function	↑ miR-423-5p, miR-10b, miR-30d, miR-126	Human	(30)

Table 5. Studies on the correlation between miRNA and cataract and glaucoma.

Article title	Correlation	Subjects	Ref
Correlation between microRNA-34a levels and lens opacity severity in age-related cataracts.	↑ miR-34a	Human	(32)
Expression of the microRNAs hsa-miR-15a and hsa-miR-16-1 in lens epithelial cells of patients with age-related cataract.	↑ miR-15a-5p, miR-15a-3p, miR-16-1-5p	Human	(24)
Expression of the microRNAs hsa-miR-15a and hsa-miR-16-1 in lens epithelial cells of patients with age-related cataract.	↓ miR-16-1-3p	Human	(24)
Profiles of extracellular miRNAs in the aqueous humor of glaucoma patients assessed with a microarray system.	↑ miR-4484, miR-6515-3p, miR-3663-3p, miR-4433-3p, miR-6717-5p, miR-4725-3p, miR-1202, miR-3197	Human	(33)
Profiles of extracellular miRNAs in the aqueous humor of glaucoma patients assessed with a microarray system.	↓ miR-4507, miR-3620-5p, miR-5001-5p, miR-6132, miR-4467, miR-187-5p, miR-6722-3p, miR-4749-5p, miR-1260b, miR-4634	Human	(33)
MicroRNA profiling in aqueous humor of individual human eyes by next-generation sequencing.	↑ miR-451a, miR-21, miR-16	Human	(34)
MicroRNA profiling in aqueous humor of individual human eyes by next-generation sequencing.	↑ miR-184, miR-4448, miR-30a, miR-29a, miR-29c, miR-19a, miR-30d, miR-205, miR-24, miR-22, miR-3074	Human	(34)

Table 6. Studies on the correlation between miRNA and diabetes and obesity.

Article title	Correlation	Subjects	Ref
Plasma miR-126 is a potential biomarker for the early prediction of type 2 diabetes mellitus in susceptible individuals.	↓ miR-126	Human	(36)
Circulating microRNAs as biomarkers for type 1 diabetes mellitus	↑ miR-101, miR-200a, miR-148b, miR-210, miR-155, miR-320, miR-103, miR-145, miR-21*, miR-126, miR-148a	Human	(39)
Circulating microRNAs as biomarkers for type 1 diabetes mellitus	↓ miR-93, miR-146a	Human	(39)
Age- and glycemia-related miR-126-3p levels in plasma and endothelial cells	↑ miR-126-3p	Human	(40)
Identification of microRNA biomarkers in type 2 diabetes: a meta-analysis of controlled profiling studies.	↑ miR-142-3p	Human	(41)
Identification of microRNA biomarkers in type 2 diabetes: a meta-analysis of controlled profiling studies.	↓ miR-126a	Human	(41)
Peripheral blood microRNA-15a is a potential biomarker for type 2 diabetes mellitus and pre-diabetes.	↓ miR-15a	Human	(35)
Significance of serum microRNAs in pre-diabetes and newly diagnosed type 2 diabetes: a clinical study	↑ miR-9, miR-29a, miR-30d, miR34a, miR-124a, miR-146a, miR-375	Human	(42)
Increased serum microRNAs are closely associated with the presence of microvascular complications in type 2 diabetes mellitus.	↑ miR-661, miR-571, miR-770-5p, miR-892b, miR-1303	Human	(37)
Circulating levels of microRNA from children with newly diagnosed type 1 diabetes and healthy controls: evidence that miR-25 associates to residual beta-cell function and glycaemic control during disease progression.	↑ miR-25	Human	(43)
Circulating microRNA-223 as a potential biomarker for obesity.	↓ miR-223	Human	(44)

Table 7. Studies on the correlation between miRNA and hypertension.

Article title	Correlation	Subjects	Ref
Role of circulating miRNAs as biomarkers in idiopathic pulmonary arterial hypertension: possible relevance of miR-23a	↑ miR-1-2, miR-1957, miR-20a, miR-145, miR-27a, miR-23a, miR-23b, miR-191, miR-130	Human	(45)
Role of circulating miRNAs as biomarkers in idiopathic pulmonary arterial hypertension: possible relevance of miR-23a.	↓ miR-30c-2, miR-99a, miR-328, miR-199a, miR-330, miR-204	Human	(45)
Circulating miR-92a expression level in patients with essential hypertension: a potential marker of atherosclerosis	↑ miR-92a	Human	(47)
Low levels of microRNA-21 are a marker of reduced arterial stiffness in well-controlled hypertension	↑ miR-1, miR-133a, miR-26b, miR-208b, miR-499, miR-21	Human	(48)
MicroRNA-9 and microRNA-126 expression levels in patients with essential hypertension: potential markers of target- organ damage	↓ miR-9 and miR-126	Human	(46)
Hypertrophic and antihypertrophic microRNA levels in peripheral blood mononuclear cells and their relationship to left ventricular hypertrophy in patients with essential hypertension.	↑ miR-1, miR-208b, miR-499, miR-21	Human	(49)
Hypertrophic and antihypertrophic microRNA levels in peripheral blood mononuclear cells and their relationship to left ventricular hypertrophy in patients with essential hypertension	↓ miR-133a, miR-26b	Human	(49)

Hypertension

Hypertension is a medical condition that usually leads to the development of cardiovascular diseases such as chronic kidney disease, coronary artery disease, and heart failure. A better understanding of miRNA and its role in hypertension could lead to better care and monitoring for patients with hypertension and other related conditions. Microarray expression profiling of miRNAs in patients with idiopathic pulmonary hypertension revealed a down-regulation of miR-1-2, miR-1957, imR20a, and miR-145 (45). MiR-23a, on the other hand, was the most important due to the patients' pulmonary function status and PGC1 alpha (45). Other studies found lower expression of miR-9 and miR-126 in hypertensive patients, and plasma miR-92a revealed a compelling positive correlation with hypertensive individuals (46). Table 7 shows numbers of studies on the correlation between miRNA and hypertension.

Neurodegenerative diseases

Neurodegenerative diseases associated with aging include Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, and Parkinson's disease. For instance, the miRNA profiling of Parkinson's disease patients revealed a down-regulation of miR-1, miR-22, and miR-29, whereas another study found an up-regulation of miR-191, miR331, and miR-454 relative to the control

Table 8. Studies on the correlation between miRNA and Neurodegenerative diseases.

Article title	Diseases	Correlation	Subjects	Refs
Plasma micro-RNA biomarkers for detection of mild cognitive impairment: a biomarker validation study.	Dementia	↑ miR-128, miR-132, mir-874, miR-134, miR-323-3p, miR-382	Human	(51)
MicroRNA expression in Alzheimer's blood mononuclear cells.	Alzheimer's	↑ miR-34a, miR-181b	Human	(53)
MicroRNA-seq data analysis pipeline to identify blood biomarkers for Alzheimer's disease from public data.	Alzheimer's	↑ 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	Human	(52)
MicroRNA-seq data analysis pipeline to identify blood biomarkers for Alzheimer's disease from public data	Alzheimer's	↓ let-7a-5p, let-7e-5p, let-7f-5p, let-7g-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 is	Human	(52)
MicroRNA profiling of CSF reveals potential biomarkers to detect Alzheimer‘s disease.	Alzheimer's	↑ miR-146a, miR-100, miR-505, miR-4467, miR-766, miR-3622b-3p, miR-296	Human	(54)
MicroRNA profiling of CSF reveals potential biomarkers to detect Alzheimer‘s disease.	Alzheimer's	↓ miR-449, miR-1274a, miR-4674, miR-335, miR-375, miR-708, miR-219, miR-103	Human	(54)
MicroRNA (miRNA) speciation in Alzheimer's disease (AD) cerebrospinal fluid (CSF) and extra-cellular fluid (ECF).	Alzheimer's	↑ miR-9, miR-125b, miR-146a, miR-155	Human	(55)
Circulating miRNAs as potential biomarkers in Alzheimer's disease	Alzheimer's	↓ miR-125b, miR-23a, miR-26b	Human	(56)
Blood serum miRNA: non-invasive biomarkers for Alzheimer's disease	Alzheimer's	↓ miR-137, miR-181c, miR-9, miR-29a, miR-29b	Human	(57)
Circulating miR-125b as a biomarker of Alzheimer's disease.	Alzheimer's	↑ miR-9	Human	(58)
Circulating miR-125b as a biomarker of Alzheimer's Disease	Alzheimer's	↓ miR-125b, miR-181c	Human	(58)
Genome-wide serum microRNA expression profiling identifies serum biomarkers for Alzheimer's disease.	Alzheimer's	↑ miR-3158-3p, miR-27a-3p, miR-26b-3p, miR-151b	Human	(59)
Genome-wide serum microRNA expression profiling identifies serum biomarkers for Alzheimer's disease.	Alzheimer's		Human	(59)
Serum microRNA profiles serve as novel biomarkers for the diagnosis of Alzheimer's disease.	Alzheimer's	↓ miR-31, miR-93, miR-143, miR-146a	Human	(60)
Prognostic serum miRNA biomarkers associated with Alzheimer's disease shows concordance with neuropsychological and neuroimaging assessment.	Alzheimer's	↑ 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	Human	(61)
Prognostic serum miRNA biomarkers associated with Alzheimer's disease shows concordance with neuropsychological and neuroimaging assessment.	Alzheimer's	↓ miR-1306-5p, miR-342-3p, miR-15b-3p	Human	(61)
Circulating miRNA biomarkers for Alzheimer's disease.	Alzheimer's	↑ miR-323b-5p, miR-545-3p, miR-563, miR-600, miR-1274a, miR-1975	Human	(62)
Circulating miRNA biomarkers for Alzheimer's disease.	Alzheimer's	↓ let-7d-5p, let-7 g-5p,miR-15b-5p, miR-142-3p, miR-191-5p, miR-301a-3p, miR-545-3p,	Human	(62)
Circulating microRNAs in Huntington's disease: emerging mediators in metabolic impairment.	Huntington's	↑ miR-877-5p, miR-223-3p, miR-223-5p, miR-30d-5p, miR-128, miR-22-5p, miR-222-3p, miR-338-3p, miR-130b-3p, miR-425-5p, miR-628-3p, miR-361-5p, miR-942	Human	(63)

A panel of four decreased serum microRNAs as a a novel biomarker for early Parkinson's disease.	Parkinson's	↓ miR-141, miR-214, miR-146b-5p, and miR-193a-3p	Human	(50)
Identification of circulating microRNAs for the differential diagnosis of Parkinson's disease and multiple system atrophy.	Parkinson's	↑ miR-223*, miR-324-3p, mir-24	Human	(64)
Identification of circulating microRNAs for the differential diagnosis of Parkinson's disease and multiple system atrophy.	Parkinson's	↓ miR-339-5p	Human	(64)
Identification of plasma microRNAs as a biomarker of sporadic amyotrophic lateral sclerosis.	ALS	↑ miR-4258, miR-663b, miR-4649-5p	Human	(65)
Identification of plasma microRNAs as a biomarker of sporadic amyotrophic lateral sclerosis.	ALS	↓ miR-26b-5p, miR-4299, let-7f-5p, miR-4419a, miR-3187-5p, miR-4496	Human	(65)

Table 9. Studies on the correlation between miRNA and osteoporosis.

Article title	Correlation	Subjects	Ref
MiR-422a as a potential cellular microRNA biomarker for postmenopausal osteoporosis.	↑ miR-422a	Human	(68)
MiR-133a in human circulating monocytes: a potential biomarker associated with postmenopausal osteoporosis.	↑ miR-133a	Human	(67)
Circulating microRNA signatures in patients with idiopathic and postmenopausal osteoporosis and fragility fractures	↑ miR-152-5p, miR-335-5p, miR-320a	Human	(69)
Circulating microRNA signatures in patients with idiopathic and postmenopausal osteoporosis and fragility fractures.	↓ miR-30e-5p, miR-140-5p, miR-324-3p, miR-19b-3p, miR-19a-3p, miR-550a-3p, miR-186-5p, miR-532-5p, miR-93-5p, miR-378a-5p, miR-16-5p, miR-215-5p, let-7b-5p, miR-29b-3p, miR-7-5p, miR-365a-3p	Human	(69)
Serum circulating micro-RNAs as biomarkers of osteoporotic fracture.	↑ miR-122-5p, miR-125b-5p, miR-21-5p	Human	(70)
Five freely circulating miRNAs and bone tissue miRNAs are associated with osteoporotic fractures.	↑ miR-21, miR-23a, miR-24, miR-93, miR-100, miR-122a, miR-124a, miR-125b, miR-148a	Human	(66)
Identification of miR-194-5p as a potential biomarker for postmenopausal osteoporosis.	↑ miR-194-5p	Human	(71)

(50). In ALS patients, the miR-206 is typically up-regulated, while the miR-4299 is down-regulated. In patients with ALS, the miR-4258, miR-663, and miR4649 are up-regulated, whereas the miR-3187 and miR-4496 are down-regulated (50).

Both the miR-132 and miR-134 were also found to have strong associations with dementia (51). Alzheimer's disease is one of the most prevalent health concerns among the elderly because it is a neurodegenerative disease associated with ageing. The microRNAs miR-26b, miR-28, miR-30c, and miR-30d were up-regulated in Alzheimer's patients, while the let-7a, let-7e, and miR-15b were down-regulated (52). Another study on Alzheimer's disease found down-regulation of miR31, miR-93, and miR-143.

Parkinson's disease is the second most common neurodegenerative disorder in the United States after Alzheimer's disease. Patients with Parkinson's disease have decreased levels of R-141, miR-214, miR-193, and miR-146 and upregulation of miR-223 and miR-24 (50). Number of studies have shown the correlation between miRNA and neurodegenerative diseases as shown in table 8.

Osteoporosis

Osteoporosis is a condition associated with an increased risk of bone fracture due to decreased bone mass and weakened bones as a result of ageing (66). For instance, hip fractures have been prevalent but have also become a growing concern among the elderly population, as falls can easily result in a fracture, causing morbidity and mortality as well (66). According to another study, the miR-133 is a miRNA associated with low bone mineral density and osteoporosis (67). It was discovered that postmenopausal osteoporosis is associated with an increase of the miR-422 and miR-191 (68). A miRNA analysis study revealed significant upregulation of miR-21, miR-23, and miR-24 in osteoporosis patients (66). Table 9 shows the correlation between miRNA and Osteoporosis.

Conclusion

In conclusion, sufficient evidence has been summarized in this survey to demonstrate that miRNAs play a crucial and indispensable role in gene expression. In addition, it has been revealed that a stronger relationship exists the between specific miRNAs and diseases or conditions, which strengthens the evidence that miRNAs can serve as biomarkers that can aid and enable early detection, monitor the progression and regression of age-related diseases

and conditions, and facilitate their early detection and monitoring. However, there is a discrepancy in sensitivity and specificity for each miRNA and condition. On the other hand, additional research is required for better understanding of miRNA, its mechanisms, and their impact on the pathophysiology and development of age-related conditions or diseases. These findings have important implications for future research and potential solutions that would support accurate, focused, and effective management and treatment of aging-related diseases and conditions.

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