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MiRNAs as Potential Biomarkers for The Diagnosis of Fibromyalgia

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ABSTRACT

Fibromyalgia is a worldwide, non-inflammatory rheumatological syndrome considered by extensive musculoskeletal pain, which is the furthermost public sign. Fibromyalgia as well is associated with a diversity of additional multipart symptoms, including depression, fatigue, neuropathic pain, and irritable bowel syndrome, that often intersect with those of further diseases. Due to the inadequate understanding of the pathogenesis of Fibromyalgia, in addition to the lack of exact biomarkers and laboratory tests, the diagnosis and treatment of this disorder keep on challenging.

In this review, we sightsee the probable efficacy of microRNAs as diagnostic biomarkers for Fibromyalgia. Recently, miR-145-5p and miR-451a have been proposed to be dysregulated in entities with Fibromyalgia. At the time miR-145-5p is involved in the regulation of pain perception and the modulation of inflammatory and neuropathic pain pathways; conversely, miR-451a has been concerned with the pathogenesis of depression, frequently comorbid conditions in Fibromyalgia patients.

We emphasize these two microRNAs, miR-145-5p and miR-451a, and inspect their mechanisms and pathways in the framework of Fibromyalgia. By inspecting the underlying mechanisms through which these microRNAs contribute to the multifaceted symptomatology of Fibromyalgia, we goal to clarify their probable diagnostic use as biomarkers.

Keywords: Depression, Fibromyalgia, MiR-145-5p, MR-451a, Pain.

1. INTRODUCTION

Fibromyalgia (FM) is a common rheumatologic syndrome with an unclear etiology. FM is distinguish with the most characteristic primary manifestation; pain which prolonged at least three months [1]. This pain begins locally, after that, widespread at numerous parts of the body [2]. Geographic variety is also noted, where industrialized countries reporting a greater prevalence than economically weak regions or

rural [3]. FM affecting approximately 5.0% of the world's population, and this percentages vary from country to another due to the different methods of determining them. The age groups involved are also vary in addition, variations in sociocultural standards [4]. The percentage found in Europe, America, Asia, Spain, and Saudi Arabia are 2.64%, 2.41%, 1.62%, 2.4%, 13.4% respectively [5] [6] [7].

FM has become worldwide prevalence, occurs at any age, but the most common age is 30 and 60, and affects 80-96% more women than men [8]. Research illustrated that the prevalence in women between 30 and 39 is 3.5%, 5% between 40 and 49, and elevate to 10.1% between 50 and 59, while this percentage decrease between 60 and 64 to reach to 7.2%, and in older people than 65 is 5.5% [9]. This can be explained on the basis of the prospective role of gonadal sex hormones in perception of pain, that is obvious also in other phases that related to hormones, like the premenstrual and postmenopausal periods [10]. Commonly, women have greater sensitivity to pain three times more than men as they both differ in their responses to pain [11].

Common comorbidities symptoms accompanied with FM

This musculoskeletal pain is described as a neuroinflammatory process that widespread and affect the central nervous system (CNS) [12]. There are complex symptomatology accompanied with FM comprising of chronic fatigue syndrome (CFS), anxiety, memory impairment, irritable bowel syndrome (IBS), joint stiffness, sleep deprivation, depression, restless leg, psychiatric disturbances, mood disorders, and neuropathic myofascial pain, hence all these comorbidities symptoms complicate the diagnosis and treatment of FM [13].

Psychiatric comorbidities represent a high prevalence among patients with FM (13–80%), such as major depressive and anxiety-like behavior reported by more than 50% of people with FM (19–65%), and their negative effects often lower quality of life [14]. Anxiety may be related to the irregular and persistent nature of symptoms, whereas depression caused by prolonged hyperalgesia [15].

Approximately 20-70% of FM patients coordinate with the diagnostic criteria for CFS [16] thus, it might be difficult to differentiate between FM and CFS due to similarities in symptoms [17].

Interestingly, 30-70% of FM patients are suffering from IBS [18]. Abdominal pain, altered bowel habits, constipation, and bloating are the common gastrointestinal symptoms comorbidity with FM that reflect chronic pain [19].

In addition, there are other several comorbidity diseases associated with FM patients and have similar symptoms which complicating the diagnostic process as autoimmune disorders [20]. These diseases are as rheumatological conditions, systemic lupus erythematosus (SLE), and rheumatoid arthritis [21].

Moreover, restless leg syndrome is a another comorbidity disease can be concurrently diagnosed with FM patients, that included 64% of FM females [22]. In addition, interstitial cystitis, Headaches, and migraine are also co-morbidities conditions in patients with FM and represent 40% [23].

Temporomandibular Joint Disorder (TMJ), is a form of pain diseases which affect 31% of FM patients especially soft tissues in various body regions as joints, muscles, and ligaments. The stress, and depression are also the most common symptoms characterized this disease [24].

Etiology of Fibromyalgia

Although the main etiology of FM is still unknown, there are numerous factors responsible for pathophysiology, etiopathogenesis, and the development of FM [25]. It is thought by many to be multifactorial and include potent interactions between genetic, environmental, as well as neurological variables [26]. Accordance with current studies, FM defined predominantly as a condition of central sensitization; it is a regulatory mechanism in which CNS becoming hypersensitive to pain stimuli [27, 28]

Dysregulation in neurotransmitters including serotonin, norepinephrine, as well as dopamine concentration which are regulator factors in the pathophysiology of FM resulting in alteration of pain pathways, and increase pain sensitization [29]. Also, genetic predisposition contributes to increased susceptibility to FM, and affect pain perception [30]. Additionally, psychological and environmental

alterations that involve infections, sleep deprivation, physical trauma, and emotional stress are thought to cause hypothalamic pituitary adrenal axis (HPA) dysregulation which precipitate FM symptoms, and increase response to pain [31, 32]. Chronic pain is believed to be influenced by immune system dysregulation and inflammation and abnormalities in them lead to aggregate FM symptoms [33]. The precise mechanisms of understanding FM keep elusive despite all these noticeable causes and insights thus, this makes diagnosis, managing, and treatment of FM very difficult [34].

Diagnosis criteria and limitations of FM

The diagnosis of pain has been assessed according to the American College of Rheumatology (ACR) classification at eighteen body sites [35]. Thus, FM's pain features must be understanding for best diagnosis of FM and effective treatment [36]. The diagnosis of FM is very complicate because lack of comprehensive understanding of several states of musculoskeletal, and existence of resemblances of symptomatic, definitions, and pathogenesis in musculoskeletal diseases thus, accompanying diagnosis must be understood in overlapping conditions [37]. Symptom Severity Scale (SSS), and Widespread Pain Index (WPI) were updated in 2010 by the ACR criteria to involve both fatigue, and cognitive symptoms [38]. Nevertheless, patient diversity in symptoms yet causes inconsistent diagnosis of the condition [39]. On the other hand, the subjective nature of FM symptoms, which mainly depend on patient self-reporting, presents difficulties for clinicians as well particularly in primary care centers [40].

Furthermore, the diagnosis of FM involves that organic diseases shouldn't be the main cause of symptoms [41]. Unfortunately, FM patients resort to numerous clinical visits, specialist sessions, and investigations thus, this leading to increasing their anxiety, disappointment and discontent [2]. Subsequently, due to absence of specific laboratory tests for FM, and there isn't ideal standard for FM diagnosis, the criteria of the 1990 ACR classification have been applied in clinical states, but it isn't perfect for diagnosing every patient [42].

Treating FM is very difficult because there isn't any drug or treatment can work on all symptoms or is suitable for all patients. Thus, the purpose of the treatment is to enhance the life's quality and existing with pain rather than treating pain [43]. Non-pharmacological methods, psychological therapy, as well as, exercise programs are very important for treating FM [44]. Despite, FM Pharmacotherapy is various that involve; pregabalin, amitriptyline, duloxetine, amitriptyline, cyclobenzaprine, tramadol, in addition milnacipran, but all of these drugs are unsatisfactory [45].

Frequency of misdiagnosis and delayed diagnosis

According to research, patients with FM often experience prolonged suffering due to misdiagnosis or delayed diagnosis. The frequency of delayed or incorrect diagnosis has been measured in a number of studies [46]. It was reported that more than 60% of FM patients have a delay in diagnosis, with an average delay of (2 -5) years following the onset of symptoms [47]. The overlap of FM symptoms with lupus, rheumatoid arthritis, and chronic fatigue syndrome is the main reason for this delay [37, 48].

Similarly, prior study illustrated that a comprehensive European study conducted in 2009 by the European Network of Fibromyalgia Associations (ENFA), and Pfizer Inc found that the average time it took to diagnose FM was eight years from the onset of symptoms [49]. Furthermore, 38% of patients surveyed indicated that they had received at least one wrong diagnosis prior to receiving an appropriate diagnosis of FM [50, 51].

In addition, because FM has a strong correlation with mental health comorbidities, it is misdiagnosed mostly as depression or other psychiatric diseases [52]. Women especially are more susceptible than males to be diagnosed with symptoms of both FM and depression [53].

Moreover, delays in diagnosis are also influenced by geographic differences. According to a Brazilian study, FM patients in rural areas had greater diagnosis delays than those in urban areas sometimes lasting

up to 10 years [54, 55]. This may be because there is a lack of contact to specialists who are knowledgeable about FM and healthcare resources [56].

Consequently, these statistics suggest a serious problem with FM diagnosis, as many patients have prolonged periods of misdiagnosed or unclear symptoms [57]. As well as, early and accurate diagnosis is further complicated by the lack of specific biomarkers and a lack of awareness among clinicians [58], resulting in useless therapies and a decline in their quality of life [59].

2. Diagnostic tools

2.1. Neuroimaging Techniques

Researchers are able to discover irregularities in the CNS in FM patients preclinically and clinically. Positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) can visualize neuroinflammation, occupancy of neuroreceptors related to pain [60, 61]. These imaging techniques have been used in studies that have shown disrupted connections in brain regions like the anterior cingulate cortex and insula that are linked to pain processing [62]. These results reveal that neuroimaging techniques are not specific as a diagnostic tool for detecting particular brain patterns linked to FM [63].

2.2. Autonomic Nervous System Testing

Patients with FM frequently involvement autonomic dysfunction, which can present as symptoms like orthostatic intolerance, dizziness, cognitive impairment, anxiety, and irregular heart rate variability [64]. Assessing the autonomic nervous system or heart rate variability analysis may offer an extra diagnostic tool for symptoms, but these symptoms diagnosis may be not distinguish FM from other chronic pain conditions [65].

2.3. Cytokine Profiling

Considering that FM is thought to be influenced by chronic inflammation, some research is looking into cytokine profiles as potential diagnostic indicators [66]. FM patients exhibit elevating of pro-inflammatory cytokines levels, as tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) which may indicate their involvement in the pathophysiology of the condition [67]. Cytokine profiling is still not a focused method for identifying FM from other chronic pain syndromes [68].

2.4. Metabolomic and Proteomic Approaches

Remarkably, both previous and recent studies investigated that Proteomics; is the study of proteins, and metabolomics; is the study of tiny molecules involved in metabolism, and both are an emerging method used in the FM diagnosis [69, 70]. Researchers examining the metabolic profiles of FM patients are observing unique metabolic alterations, as lipids and amino acids, that related to pain, fatigue, and cognitive failure [71]. Study demonstrated that inflammation and neuropathic pain are linked to elevated levels of ceramides, and Sphingomyelins [72]. Also, it has been found that pro-inflammatory eicosanoids, like prostaglandins are capable of intensify pain [73]. In addition, dysregulation in triglyceride levels, and phospholipid indicate problems with energy storage, and mitochondrial membranes disorders which may be a factor in fatigue and energy deficiencies [74,75]. Furthermore, cognitive function, neuroprotection,

depression, and myelin integrity influenced by low concentrations of polyunsaturated fatty acids as omega-3 fatty acids [76], and alteration in cholesterol metabolism [77, 78].

Likewise, studies confirmed that proteomic analysis is used to detect protein markers in FM patients' serum and cerebrospinal fluid, hence this in turn facilitate the differentiation FM from other diseases [79,80]. The synthesis of neurotransmitters, and the regulation of oxidative stress all depend on amino acids, and FM symptoms have been connected to altered amino acid levels [81]. It was illustrated that chronic pain and increased central sensitization are linked to elevated glutamate levels in the CSF [82]. Moreover, aspartate contributes to excitatory neurotransmission and may be connected to increased pain perception [83]. Otherwise, low levels of tryptophan can result in less serotonin being synthesized, which can affect mood and fatigue [84]. Decreased levels of leucine, isoleucine, and valine, three branched-chain amino acids (BCAAs), can affect muscles' ability to produce energy and cause fatigue [85]. Reduced amounts of tyrosine, affects cognitive processes including memory, and attention, and may lead to cognitive deficiencies [86]. Additionally, phenylalanine imbalance can have an indirect effect on neurotransmitter balance [87].

Recent updates for diagnostic tools

MicroRNA (miRNA) Biomarkers

Current studies have been focused on discovering biological markers and creating alternatives diagnostic equipment in order to overcome the disadvantages of conventional FM diagnostic techniques [88, 89]. Interestingly, using MicroRNA (miRNA) biomarkers as non-invasive blood-based biomarkers may provide a more precise and accurate way to diagnose FM and effective treatment [90, 58]. It has been found that there are specific miRNAs as miR-145-5p and miR-451a are dysregulated in FM patients [91, 92].

Although these alternative biomarkers have a great potential, their application in clinical practice is still in its early phases, and they haven't been widely applied. To verify the accuracy and specificity of these possible diagnostic instruments, extensive validation research is required [93].

Understanding microRNA (miRNA) biomarkers

MicroRNAs (miRNAs) are small non-coding RNA molecules, the normal mature miRNA consists of 21 or 22 nucleotides (nt) in the length [94]. Two decades ago, the information about existence of miRNAs and their vital role in the diagnosis of diseases were completely unknown, but the genes that encode the protein were well known [95]. After that, with adequate understanding of transcribing DNA into RNA, and then translating it into protein, the scientists paid attention to the study and research of all non-protein-coding sequences [96]. According to transcript lengths of non-coding RNAs, they can be

classified into two main types; small non-coding RNAs that <200 nt in length including microRNAs, while long non-coding RNAs (lncRNA) that longer than >200 nt [97].

For studying miRNA, and their target genes, there have been about 1000 computational tools were identified as bioinformatics algorithm since 2003 that contributed to the analysis of miRNA expression. MiRNA were classified according to their influence on physiological processes, development, and diseases [98].The first miRNA was discovered in 1993 in the Victor R. Ambros laboratory [99]. The real development of miRNAs were in 2007 through intercellular RNAs that is released into the extracellular space in vesicles, transferring RNA cargo to receiver cells [100]. Thereafter, it was reported in 2008 that miRNAs can be detected in all body fluids, particularly serum, cerebrospinal fluids (CSF), and plasma, and can be used as biomarkers and therapeutic targets, and dysregulation of their concentration either up or downregulation used as disease biomarkers [101].

3. MicroRNA biogenesis and functional networks

There is a clear process for miRNA biogenesis, which begins with transcription and concludes with the production of mature miRNAs **Figure (1)**:

3.1. Transcription step

In the biogenesis of miRNA, both RNA polymerases II and III are responsible for generation of miRNA precursors, then passes on series of cleavage occur in the nucleus and cytoplasm resulting in production of mature miRNA. This can occur through transcription of microRNAs as primary transcripts (pri-miRNAs) [102].

3.2. Processing in the Nucleus

In the nucleus, the pri-miRNAs cut into precursor microRNAs (pre-miRNAs) via DiGeorge syndrome critical region 8 (DGCR8) and Drosha within the nucleus [103]. After this processing stage, pre-miRNAs are created, these molecules are roughly 70 nucleotides long [104].

3.3. Export to the Cytoplasm

Further, they transported to the cytoplasm by Exportin-5 (XPO5), and it depends on energy and performs transport via Ran-GTP [105].

3.4. Cytoplasmic Processing

After entering the cytoplasm, the pre-miRNAs are processed further by the Dicer ribonuclease enzyme [106]. Dicer splits them and creates mature duplex miRNA, and they usually consisting of 22 nucleotides-long RNA duplexes [107].

3.5. Incorporation into RISC

Following the strand mature RNA duplexes, it combined with RNA-induced gene silencing complex (RISC), and finally form mature microRNAs, whereas the second strand is typically broken down [108].

3.6. Target Gene Regulation

The 3' untranslated region (3' UTR) of target mRNAs is often where the miRNA-RISC complex attaches to complementary sequences. Depending on the level of complementarity, this binding may

reduce translation or cause the target mRNA to degrade [109]. By adjusting gene expression at the post-transcriptional level, this regulatory mechanism enables miRNAs to regulate a number of biological processes [110], such as inflammation, development, differentiation, and apoptosis [111].

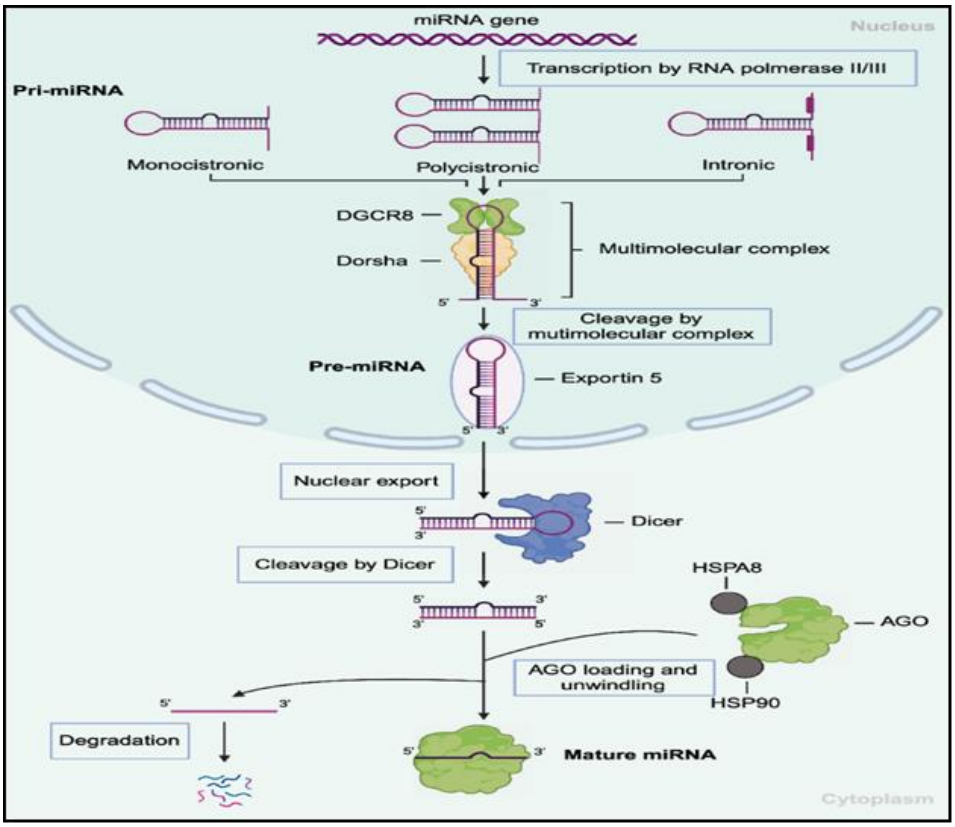

Figure (1): Biogenesis and maturation of microRNAs, Pri-miRNAs (primary microRNAs); Precursor microRNAs (pre-miRNAs); DGCR8 (DiGeorge syndrome critical region 8); RISC (RNA-induced gene silencing complex) [112].

The advantages of miRNAs

Dysregulated miRNAs have the potential to change cellular homeostasis and have a role in the development of diseases. The advantages of miRNAs as biomarkers are distinct [113]. The specificity of miRNAs plays a vital role in providing targeted diagnostics [114] because of their tissue- and disease-specific expression patterns [115], as miR-122, which is a specific biomarker for liver disorders [116]. Furthermore, miR-21, is one of cancer-specific miRNAs due to overexpression in almost types of cancer, which reveal information regarding the types and growth of tumors as gastrointestinal cancers [117], lung cancer [118], and prostate cancer [119]. Due to the resistance of miRNAs to degradation, they can be reliably detected in various clinical samples like urine, CSF [120], blood, and saliva which provide stability [121]. Additionally, studies confirmed that microRNAs play an important role in regulation of the levels of the target genes expression via RISC by using various mechanisms [122]. Gene silencing mechanism is evaluated according to the relation between the nature, and the amount of miRNAs and the target genes [123]. When miRNA and its target exhibit partial complementarity, the RNA-induced silencing complex, or miRNA-RISC, prevents mRNA from being translated into protein without causing mRNA degradation [124]. The miRNA-RISC complex encourages the degradation of the target mRNA in case of the complementarity between the miRNA and mRNA is high, which results in decreased gene expression [125].

4. Functionality of miRNAs

4.1. Regulation of developmental processes

Furthermore, the effectiveness of miRNAs and their dysregulation has been shown to regulate numerous biological functions and linked to pathological processes. These processes are involving proliferation, differentiation, growth, cell cycle, apoptosis, inflammation, cellular development, disease conditions, metabolism, and metastasis due to they control highest percentage of the human protein-coding genome [126]. In particular, many researches have pointed out notably the relation between miRNAs, as well as circular RNAs, and lncRNAs, in the diagnosis of various human diseases including neurological disorders, cardiovascular, infectious diseases, and human cancers [127]. Studies have emphasized that a single miRNA may be an ideal regulator for more than 200 genes [128].

In contrast, many miRNAs can control a single gene, thus reaching to target miRNAs that are very important issue in biomedical research as therapeutic targets and biomarkers of diseases [129,130]. Certain miRNAs control the synthesis of cytokines and inflammatory pathways, which in turn affects the immune response. MiR-146a play a vital role in the suppression of inflammation, but miR-21 has been demonstrated to enhance inflammatory responses [131]In addition, miRNAs contribute in the embryogenesis, brain's growth, and development of CNS [132] due to they control numerous biological processes like organ formation, and cell proliferation, tissue differentiation [104].

MiR-290 cluster has a critical role in the pluripotency and differentiation in embryonic stem cells via regulation MAPK signaling pathway [133]. It has been found that miR-124 affect the development of neuronal pathways in the nervous system [134, 135], also miR-9 [136] and both play a role in the differentiation of neural stem cells into neurons [137].

4.2. MiRNAs act as oncogenes (oncomiRs) or tumor suppressors

There are two types of miRNAs including oncomiRs and tumor suppressors. OncomiRs induce cancer progression via blocking tumor suppressor genes as miR-21considers oncomiRs in several types of cancers involving breast, colorectal cancer, and lung [138]. Whereas tumor-suppressive miRNAs downregulate the growth of cancer by targeting oncogenes [139].

4.3. Neuroplasticity and Pain

MiRNAs control neuronal transmission and neuroplasticity [140], as they can control pain perception via control genes which regulate neurotransmitter receptors, ion channels, and signaling pathways [140]. It is well recognized that miRNAs affect inflammation and brain functions to modify pain perception in diseases such as FM. Chronic pain syndromes as rheumatoid arthritis can be impacted by miRNAs that regulate inflammation and pain pathways, like miR-145-5p and miR-451a [141]. It was reported that certain miRNAs like miR-29 and miR-132 affect neurological disorders as Alzheimer's disease by modifying genes linked to the processing of amyloid precursor proteins, and neuroinflammation [142]. Also, miR-7 and miR-153 influence Parkinson’s disease through regulating alpha-synuclein, that produce aggregation of toxins in Parkinson’s disease [143].

4.4. Stress and Hormonal Regulation:

MiRNAs has direct effect on the hypothalamic-pituitary-adrenal (HPA) axis, which controls stress hormones as cortisol [144]. Also, dysregulation of miR-34a and miR-124a lead to chronic stress conditions that involve depression and anxiety disorders.

4.5. Cardiovascular disease

Heart muscle development, and vascular function are influenced by some miRNAs, such as miR-1 and miR-133a [145]. MiR-33, miR-126, as well as miR-21 protect from atherosclerosis because they have a vital role in regulation cholesterol metabolism and endothelial function [146]. The dysregulation in the levels of such miRNAs used in the diagnosis of heart failure and myocardial infarction [147].

4.5. The miRNAs' role in the immune system regulation, and in inflammatory and autoimmune diseases

miRNAs have the ability to modulate immune responses via regulation of the inflammatory pathways, modulating immune cells, and control both innate and adaptive immune processes [148]. It was documented that rheumatoid arthritis and many sclerosis are under controlling by some miRNAs as miR-146a, and miR-155 via inhibition of pro-inflammatory signaling pathways [149]. Furthermore, thymic development and T-cell receptor sensitivity are regulated by miR-181a, which helps in the appropriate maturation of immune cells [150].

4.6. Involvement in metabolic disorders

Because miRNAs regulate metabolism-related genes, they are associated with metabolic disorders such as diabetes and obesity [151]. Insulin secretion and beta-cell activity in the pancreas are mediated by the most abundant miRNA in pancreatic islets as miR-375, which accounts for 10% of β-cell miRNAs [152]. Insulin resistance and Type 2 diabetes have been linked to the dysregulation of numerous of miRNA as miR-29, miR-146, miR-24, miR-25, miR-96, and miR-34a [153].

MiR-33 controls genes related to fatty acid metabolism and cholesterol transport, which in turn maintains cholesterol homeostasis, lipid metabolism, and inflammation [154]. Thus, the potential role of miR-33 exhibited in the treatment of dyslipidemia, obesity, diabetes, and atherosclerosis [155] .

Generally, miRNAs are being researched as possible treatment targets for a number of disorders because of their participation in so many important pathways. Two methods for modifying miRNA activity include miRNA mimics and antagomiRs (anti-miRNA oligonucleotides) [156]. The function of downregulated miRNAs can be restored by introducing these synthetic miRNAs into cells [157]. AntagomiRs types of mRNA are designed to suppress the action of particular specific miRNAs which are pathogenic and upregulated [158].

Exploring the influence of miRNAs as key regulators on inflammation, pain, stress responses, and immune response in FM

The heterogeneity of FM symptoms and the lack of a clear etiology make it very difficult to determine specific miRNAs involved [159]. Recent studies have found that certain miRNAs are differentially expressed in FM patients compared to healthy controls [88,160]. Research is ongoing to understand the exact mechanisms by which these miRNAs contribute to the symptoms of FM and to explore their potential as therapeutic targets. Overall, miRNAs hold promise in enhancing our understanding of FM and developing new diagnostic and therapeutic approaches [161].

MiRNAs can influence pain perception by targeting genes involved in the development of nervous systems and function through regulation of ion channels, neurotransmitter receptors, and other molecules critical for nerve signaling and pain processing [162]. Chronic inflammation is a feature of FM, and it has been found that miRNAs are known to modulate inflammatory pathways either inducing or suppressing inflammatory signaling pathways as miR-21 that capable of eliciting pro-inflammatory responses via regulating macrophage polarization [163].

Recent study indicated that some miRNAs contributed in the pathogenesis of chronic inflammatory conditions affecting the production and release of cytokines, chemokines, and other inflammatory mediators, potentially contributing to the chronic pain and fatigue seen in FM [99]. In addition, it has been showed that there are some miRNAs can influence the nuclear factor kappa-B (NF-κB), and mitogen-activated protein kinases (MAPK) signaling pathway [164]. The hypothalamic-pituitary-adrenal (HPA) axis which regulates the body's response to stress, is often dysregulated in FM [165]. Also, miRNAs may play a role in this dysregulation by modulating the expression of stress-related genes [166].

Some of these miRNAs that have been identified as downregulated in FM include miR-320a, miR-103a-3p, and miR-22-3p, miR-151a-5p, miR-23a-3p [167]. Also, miR-139-5p, miR-107, miR-1, let-7a-5p [91], miR-133a, and miR-30b-5p all of these miRNAs are downregulated in FM. In addition, miR-142-3p, miR-346, miR-320b, and miR-374b-5p and this in the line with [168].

There are various miRNAs studies in FM patients as explained in (Table.1). Different mechanisms are often presented in various studies that identify miRNAs, as biomarkers for FM and other disorders [58, 169]. In addition, pathways are vary and they typically contain down or up regulation [170] depending on the disease under investigation [171 ,172].

Table. 1 Various miRNA in FM patients

No.	miRNA Name	Regulation in FM	Mechanism	Pathway	References
1	miR-145-5p	Downregulated	Positively correlates with pain and fatigue; its downregulation may lead to increased expression of pro-inflammatory cytokines as IL-6, TNF-α, contributing to FM symptoms.	Inflammatory pathways, as NF-κB pathway	[58, 88]
2	miR-320a	Downregulated	Regulates inflammatory pathways and neuronal regeneration; its downregulation is linked to chronic inflammation and impaired neuronal repair mechanisms.	Inflammatory pathways and neuronal regeneration pathways as NF-κB Pathway	[173,174]
3	miR-103a-3p	Downregulated	Plays a role in neural plasticity and pain regulation; decreased expression leading to increased inflammation and pain sensitivity.	SNRK/NF-κB/p65 signaling pathway	[175, 176]
4	miR-130a-3p	Downregulated	Targets genes involved in pain modulation and inflammatory responses; its downregulation may result in the upregulation of pro-inflammatory genes, exacerbating pain and inflammation.	Inflammatory pathways as JAK-STAT Pathway	[177]
5	miR-1-3p	Downregulated	Modulates pain and inflammatory responses; decreased levels may lead to increased expression of pain-related genes and inflammatory mediators.	Pain signaling and inflammatory pathways as Inflammatory pathways as JAK-STAT Pathway	[178]
6	miR-22-3p	Downregulated	Acts as a neuroprotective agent; regulates genes related to immune response, apoptosis, and autophagy. Its downregulation may impair these processes, contributing to neuronal damage and FM symptoms.	Immune response, apoptosis, and autophagy pathways, as PI3K-AKT-mTOR Pathway	[179, 180]
7	miR-151a-5p	Downregulated	Influences cytokine regulation and pain signaling pathways; reduced expression may lead to increased pro-inflammatory cytokine production and heightened pain perception.	Cytokine regulation and pain signaling pathways as TRPV1-Mediated Pain Signaling	[181]
8	miR-23a-3p	Downregulated	Modulates cytokines and chemokines; its downregulation is linked to increased pain sensitivity and inflammation due to the upregulation of pro-inflammatory mediators.	Cytokine and chemokine signaling pathways as JAK-STAT Pathway	[91,182]

9	miR-223	Downregulated	Associated with CNS injury and neuropathic pain; affects inflammation pathways. Its reduced levels in CSF, and serum may lead to increased inflammatory responses and neuronal damage.	Inflammatory pathways as JAK-STAT Pathway, and NF-κB Pathway	[183]
10	miR-29a-3p	Downregulated	Modulates chronic fatigue and pain; its downregulation may disrupt these pathways, leading to increased fatigue and pain.	Systemic cholinergic as Cholinergic Anti-Inflammatory Pathway, and Wnt pathways	[88]
11	miR-128-3p	Downregulated	Regulates pain and fatigue; influences BDNF. Decreased levels may result in altered BDNF expression, affecting neuronal function and contributing to FM symptoms.	Wnt pathway and BDNF modulation	[88,184]
12	miR-199a-3p	Downregulated	Inhibits inflammatory cytokines; its downregulation is linked to increased production of pro-inflammatory cytokines, leading to persistent pain and fatigue.	Inflammatory pathways as JAK-STAT Pathway	[185,186]
13	miR-375	Downregulated	Involved in neurological functions and pain perception; its reduced expression is linked to cognitive dysfunction and altered pain perception in FM patients.	Neurological function and pain perception pathways as TRPV1-Mediated Pain Signaling	[172]
14	miR-150-5p	Downregulated	Central regulator of immune responses; suppresses B-cell activation. Its downregulation may lead to increased B-cell activity and autoimmunity, contributing to FM pathology.	Immune response pathways as PI3K-AKT-mTOR Pathway	[187, 188]
15	miR-139-5p	Downregulated	Regulates chronic fatigue and pain; its downregulation may alteredt these pathways, leading to increased fatigue and pain.	Systemic cholinergic and Wnt pathways	[140]
16	miR-143-3p	Upregulated	Linked to mental fatigue and muscle functioning; elevated levels in FM patients may disrupt normal muscle function and contribute to fatigue.	Muscle function and fatigue pathways, and Wnt/β-Catenin Pathway	[189,190]
17	miR-320a	Upregulated	Correlated with fatigue and insomnia; inversely related to pain. Increased expression may affect sleep regulation and fatigue levels in FM patients.	Sleep regulation and fatigue pathways	[191]

18	miR-21-5p	Upregulated	Regulates inflammation and immune responses; modulates pro-inflammatory cytokines. Its upregulation may lead to increased inflammation and immune dysregulation in FM patients.	Inflammatory and immune response pathways, and NF-κB Pathway	[192]
19	miR-155	Upregulated	Vital in immune regulation; contributes to inflammation and pain. Elevated levels may enhance pro-inflammatory pathways, leading to increased pain perception in FM patients.	Oxidative stress-TRPA1 pathways	[161, 193]

Clinical applications of miRNAs as diagnostic and prognostic biomarkers

MiRNAs have the potential to be used as diagnostic tools to distinguish between diseases similar with symptoms as miR-122 and miR-21 which are employed in cancer diagnostics to distinguish between colorectal and liver tumors, respectively [194]. Likewise, miRNA profiles have the ability to differentiate FM from other chronic pain conditions [195]. On the other hand, miRNAs levels may indicate the development of diseases such as cancer, FM, and heart disease. MiR-155 levels are directly proportional with severity of the disease which is elevated in patients with chronic rheumatoid arthritis [196]. This enable medical professionals to evaluate inflammatory activity thus modify the treatment [197]. In addition, myocardial damage is correlated with miR-208a and miR-499 levels, which indicate the probability of heart failure following an infarction [198].

Patient sensitivities to particular treatments can be predicted using miRNA profiles as miR-375 and miR-141 levels, which are specific miRNA that have direct effects on chemotherapy responses in patients of breast cancer [199]. Moreover, to improve modified treatment strategies for FM, miRNA profiles may be able to predict the response of patients towards certain drugs like duloxetine and pregabalin [168].

miR-145–5p is a microRNA encoded in the human by MIR145 gene on chromosome 5, it can be used as biomarker in the pathogenesis of different diseases as aplastic anemia [200]. These diseases also involving FM [176], diabetic nephropathy [201], and rheumatoid arthritis [202]. MiR-145–5p playing pivotal roles in various biological processes, including inflammation, cell differentiation, and proliferation, as well as involved in the regulation of gene expression [203]. It has been showed that miR-145–5p down-regulated in bladder cancer cells [204], and asthma [205].

However, miR-145–5p elevated in cerebral ischemia reperfusion injury [206]. Interestingly, it has been suggested that up-regulation of miR-145–5p used as tumor suppressor in the diagnosis of various types of malignant diseases as breast cancer, gastrointestinal cancers, bladder cancer, renal cancer, prostate cancer, and cervical cancer [207]. On the other hand, the levels of biomarker miR-145–5p one of the most important miRNA that can help in distinguishing FM patients from healthy individuals because of the strong relation between its levels with FM in more than one type of body fluid [208]. Also, miR-145–5p help in diagnosing of FM and assessing the severity of symptoms, and in monitoring the response to therapeutic interventions aimed at alleviating inflammation and pain [209].

Role of miR-145-5p, and miR-451a in FM

Particular miR-145-5p, and miR-451a influence the central sensitization process and pain pathways in chronic pain disorders as FM [210]. MiR-145-5p controls cytokine signaling pathways associated with FM and chronic pain, as well as inflammatory response and neuropathic pain pathways [88]. On the other hand, previous and recent studies confirmed that miR-451a regulates psychological stress and mood, depression and other prevalent FM comorbidities are linked to it [211, 212]. Also, its levels might be able

to reveal alterations in mental health, which would help with FM's comprehensive treatment [213]. Hence, clinicians can evaluate the complexity of symptoms and even estimate the effect of treatment by using these miRNAs as biomarkers for psychiatric states, intensity of pain, and inflammatory status in FM [214].

Numerous investigations have observed notable variations in the expression of miR-145-5p. According to a study, FM patients' CSF levels of miR-145-5p were around 30% reduce than those of controls, and this was correlated with the severity of their symptoms, including fatigue and pain intensity [177]. Moreover, it was observed that miR-145-5p was downregulated by roughly 25% in settings where inflammatory markers were also raised, confirming its involvement in inflammatory pathways [215]. In contrast, previous study noted that miR-451a's overexpression is constant across various inflammatory situations, confirming its function as a general inflammatory marker, and it has been showed that its levels upregulated by roughly 50% in FM patients with chronic inflammation [216].

Furthermore, to demonstrating the variations in miRNA expression in FM patients, these statistics support the validity of these miRNAs as biomarkers, which facilitates the creation of specific diagnostic test. To improve their predictive and therapeutic relevance in clinical settings, researchers are extending these findings through longitudinal investigations to investigate whether miRNA levels correspond with the course of FM symptoms or response to treatment.

MiR-145-5p regulates inflammatory responses and pain pathways in FM

Interestingly, miR-145-5p contributed in the pathogenesis of FM via its role in influencing gene expression, and its levels can reflect the underlying inflammatory status and potentially the intensity of pain and other symptoms in FM patients [177]. Current study has been showed that miR-145-5p modulate inflammation and pain pathways, which are central to the symptoms of FM, so it could be a potential therapeutic target for managing FM symptoms [215].

Furthermore, miR-145-5p has anti-inflammatory properties by targeting specific pathways and molecules involved in inflammatory responses, and it has been found that its downregulation linked to overexpression of inflammatory mediators which can exacerbate inflammation [217]. Various studies reported that this miRNA can regulate the inflammatory response and apoptosis, and influences the expression of cytokines and other inflammatory mediators, contributing to chronic pain and fatigue experienced by FM patients [214, 218].

Additionally, miR-145-5p has been noted to play a role in the development and function of neural processes, and musculoskeletal systems which might affect pain perception and nerve signaling in FM [88]. In FM, the downregulation of miR-145-5p may affect nerve signaling and pain perception, leading to the widespread pain and fatigue characteristic of the condition [91].

Potential role of miR-451a as a biomarker and therapeutic target in FM symptomatology

Study has highlighted the potential of miR-451a as a biomarker and therapeutic target in different conditions, and it has been studied for its regulatory functions in inflammation and its expression patterns in various diseases, specifically it is involved in modulating inflammatory responses [219]. Also, miR-451a has been shown to play a significant role in vascular inflammation and the modulation of vascular smooth muscle [220]. So miR-451a used as a therapeutic target for inflammatory conditions, and this could have relevance for FM [214, 221].

Although miR-451a is primarily studied in relation to conditions as major depressive disorder and myocardial infarction, its role in FM is developed [212]. It was reported that the cellular miR-451a

expression significantly associated with decreasing levels of serotonin through brain derived neurotrophic factor (BDNF) expression [222]. Also, miR-451a is elevating cortisol activity in patients with depression [223]. Depression stimulates oxidative stress and thus enhances downregulation of miR-451-a in the brain tissues and serum of patients [224]. Generally, research has indicated that miR-451a might be relevant in neurological and psychiatric conditions [225].

As well as, miR-451a is implicated in the regulation of inflammatory pathways [226]. Various studies suggested that miR-451a might influence the pain perception and inflammation, two key aspects contribute to the symptomatology of FM [227, 228].

Additionally, miR-451a has been found to be a biomarker in different diseases due to its involvement in regulating stress responses, apoptosis, and cellular metabolism thus, it can relief pain, and fatigue via modulating oxidative stress pathways [229]. Hence, this regulatory function could extend to FM, where it might modulate the expression of genes involved in pain and inflammation, potentially providing a target for therapeutic intervention, and the downregulation of miR-451a in CSF of patients correlated with cognition and depression [230].

5. CONCLUSION

MicroRNAs (miRNAs) regulate numerous biological functions and linked to pathological processes involved in FM. The exploration of miRNAs in FM reveals that they hold potential as biomarkers and therapeutic targets, contributing significantly to our understanding and management of this complex disorder. Ongoing research into miRNAs in FM is crucial for building a comprehensive understanding of their role in disease mechanisms and clinical management. The researches focus on miR-145-5p, miR-451a which are often dysregulated in FM implicated in pain pathways and neuroinflammatory processes. Thus, understanding which miRNAs modulate pain pathways could lead to targeted therapies that alleviate pain more effectively, enhancing the personalization of FM treatment plans. Lastly, optimizing FM care and enhancing patients' quality of life may be possible by incorporating miRNA findings into a multidisciplinary strategy that includes pharmaceutical, physical, and psychosocial therapies.

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