**The Open Medicinal Chemistry Journal**
*DOI: 10.2174/0118741045337675241003055149, 2024, 18, e18741045337675*
**ISSN: 1874-1045**
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**REVIEW ARTICLE** **OPEN ACCESS**

# MicroRNAs as Indicators of Alterations in Reaction to Endurance Training

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**Abstract:**
Without a doubt, endurance sports are beneficial for heart health and general fitness; regular physical exercise is thought to be one of the best ways to avoid cardiovascular disease. Gene expression is regulated by tiny molecules known as microRNAs, which are generated subsequent to transcription. Translational repression, mRNA deadenylation, and decapping are all caused by miRNAs when they attach to a certain region at the 3′ UTR of their target mRNAs (40, 41). Along with promoter regions, additional mRNA regions such as the 5′ UTR and coding sequence have also been shown to include miRNA binding sites. While it has been shown that miRNA contact with a promoter region may drive transcription, miRNA binding to the 5′ UTR and coding sections silences the expression of genes. According to preliminary research, miRNAs may serve as helpful indicators of the systemic changes brought on by exercise before they are identified using traditional imaging or laboratory methods. This study focused on four important physiological processes that help the body adapt to various endurance workouts. We found that miR-27, miR-221, miR-210, miR-328, miR-133a, miR-134a, and miR-20a are essential for adaptive response to exercise after conducting a thorough literature search.

**Keywords:** MicroRNA, Endurance exercises, Adaptive changes, Biomarker, Sport.



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*Cite as:* Mourgan F, Al Shamli A, Al Qasimi A, Hefny N, Hasan L. MicroRNAs as Indicators of Alterations in Reaction to Endurance Training. Open Med Chem J, 2024; 18: e18741045337675.
http://dx.doi.org/10.2174/0118741045337675241003055149

Received: June 30, 2024
Revised: September 14, 2024
Accepted: September 25, 2024
Published: October 10, 2024



## 1. INTRODUCTION

High dynamic long-term activities with low-to-high energy demand, such as cycling, running, rowing, swimming, or a mix of these, are referred to as endurance training [1]. Physiologically, the primary goal of endurance training is to push the anaerobic metabolism and lactate generation thresholds closer together. A persistent increase of up to 5- to 6-fold in cardiac output is required for an extended period of time during high-intensity training. The “athlete's heart,” is defined by an elevated thickness of the left ventricular (LV) wall, a proportioned increase in the size of the left and right ventricular walls, as well as an increase in the size of the atrial capacity, is a structural, functional, and electrical cardiac adaptation that further compensates for repetitive effort [2]. Endurance exercise can have unquestionably positive effects, but it can also have negative effects. Adolescents and young athletes who engage in intense activity may infrequently experience an increased possibility of sudden cardiac failure which is mostly prevalent in young athletes with hereditary cardiomyopathies, which can coexist with LV hypertrophy, and increased and/or reduced ejection fraction [3]. Because of this, it is still difficult to differentiate an athlete's heart from pathologic conditions using current approaches; hence, new biomarkers are required to achieve this differentiation between pathology

and physiology. MicroRNAs, or miRNAs, have gained attention recently as possible biomarkers for adaptations made in response to exercise. MicroRNAs are short non-coding RNAs that control the expression of genes that are expressed after transcription by blocking the translation of proteins or increasing messenger RNA (mRNA) degradation. Normal, functioning cardiac tissue development is influenced by microRNAs. In addition to being implicated in the pathogenesis of cardiovascular disorders such as hypertrophy, fibrosis, and injury to cardiomyocytes, they regulate cell development, differentiation, apoptosis, and proliferation [4]. In most tissues, microRNAs make up the predominant class of small RNAs. While miRNA genes can be found in different genomic locations, introns, or noncoding transcripts, encode the bulk of human miRNAs. RNA polymerase II produces primary miRNA, which is the first step in the synthesis of miRNA. Next, a complex made up of the endoribonuclease Drosha and the RNA bingeing protein DGCR8 microprocessor subunit further processes miRNAs. After being exported to the cytoplasm, primary miRNAs are further broken down by endoribonuclease Dicer and then incorporated into proteins belonging to the Argonaute family to form an effector complex [5]. Circulating miRNAs have generated interest as possible therapeutic targets and indicators of many disease states due to their accessibility and biochemical stability. Their predictive significance in CVDs has received much research interest from the academic community [5, 6]. Circulating miRNAs can be involved in the adaptations to exercise and are changed in response to both acute and endurance exercise [7]. Prior research that measured the plasma levels of miRNAs in marathon runners revealed elevated levels of some miRNAs following marathon runs and their correlation with conventional fitness metrics [8]. Previous research has also shown correlations between the expression of miRNAs and markers of cardiac injury, including troponin plasma levels, creatine kinase-MB (CK-MB), and NT-pro-BNP (n-terminal b-type natriuretic peptide). As such, they may serve as biomarkers for the processes involved in the heart's response to exercise [9-11]. Circulating miRNAs may enhance the assessment of exercise and make it easier to distinguish between pathological and adaptive alterations [12]. Thus, this article is aimed at summarizing what is currently known about the role of miRNAs in endurance training.

### 1.1. Biogenesis and Use of microRNAs

MicroRNAs, when expressed, are small, non-coding post-translational proteins that alter the target genes [13-15]. An estimated 60% of all human proteins and enzymes involved in important physiological processes are thought to be regulated by microRNAs [13, 14] as many different types of cells produce microRNAs [13-16]. For instance, numerous cell lineages involved in the pathogenesis of cardiovascular disease, such as macrophages, platelets, fibroblasts, endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and cardiomyocytes, are known to produce microRNAs [15-17]. Hence, there is still ongoing debate regarding the nature of microRNAs sourced from different cells. MicroRNAs attach to the 3′-or, less frequently, the 5′-untranslated regions of target messenger RNAs (mRNAs), thereby controlling gene expression at the post-transcriptional level. This process inhibits translation and/or causes the targeted mRNA to degrade [13]. A single microRNA can change the way several mRNAs operate by using this technique. Additionally, since they are concealed by apoptotic bodies, micro-particles, and other structures, circulating microRNAs in serum are persistent against RNase and resistant to lysis [13]. The biosynthesis of microRNA is highly intricate [14]; RNA polymerase II mediates the transcription of a DNA strand in the cell nucleus, which yields primary microRNA, or Prim-miRNA [14]. Following transcription, the enzyme complex DROSHA cleaves Pri-miRNA to produce pre-miRNA, a precursor to microRNA. Pre-miRNA is transported to the cytoplasm by exportin-5, where it is broken down into roughly 22 nucleotide RNA duplexes by the RNA-degrading enzyme Dicer. The microRNA seed sequence is attached to the recognition site of the microRNA on the target mRNA, facilitating the transport of the microRNA strand to the Argonaute complex (AGO) for the creation of an RNA-induced silencing complex (RISC); this complex directs the microRNA strand to pair with the target mRNA. Exosomes facilitate the release of microRNAs from cells [14]; according to reports (www.mirbase.org), there are currently over 2000 identified human microRNAs and some of these are implicated in atherosclerotic processes [16, 17]. Numerous pro-thrombotic and microRNAs overwhelm microRNAs that have anti-atherogenic properties, causing the onset and progression of atherosclerosis. In both ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI) myocardial infarction, as well as in cardiac remodeling and fibrosis after ACS, the major cause of cardiovascular death is atherosclerotic plaque rupture [16-18].

### 1.2. MicroRNAs and $VO_{2max}$

$VO_{2max}$, or maximal oxygen uptake, is the highest oxygen consumption rate experienced during progressive exercise. It serves as an indicator of the combined ability of the heart, lungs, and muscles to take in and use oxygen. While there are many exercises that raise $VO_{2max}$, aerobic high-intensity training has been the most implicated [19]. In both healthy persons and patients with CAD, $VO_{2max}$ has been a dependable predictor of cardiovascular death and all-cause mortality [20]. Being that elite endurance athletes have a high cardiac output due to a high LV chamber size, they normally have high $VO_{2max}$. Numerous miRNAs were found to be linked with the aerobic performance metrics; for instance, increases in miR-1, miR-133a, miR-206, miR-208b, and miR-499 have been reported following a marathon run due to exertion. At the individual anaerobic lactate threshold (VIAS), additional investigation showed that miR-1, miR-133a, and miR-206 were positively linked with $VO_{2max}$ and running speed [8]. Among the muscle-sourced miRNAs are miR-133a,

miR-206, and miRNA-1. MicroRNA-1, miR-206, and miR-133a are thought to be anti-hypertrophic factors, and they control the development of skeletal myoblasts. It's possible that the aforementioned miRNAs' special ability to affect both tissues qualifies them as potential cardiopulmonary fitness indicators. According to Denham *et al*., miR-1 may have a role in aerobic performance capacity and, when coupled with miR-486, may serve as a stand-alone predictor of $VO_{2max}$. Studies have shown that following a four-week training program, microRNA-1 and miR-486 were considerably raised and linked with the VO2max values, while miR-486 was negatively correlated with resting heart rate [21]. Furthermore, both before and after the training program, there was a linear correlation between the increase in peak oxygen consumption and miRNA associated with inflammation, such as miR-146a. Considering the similarity in the expression patterns of miR-146a and miR-20a to miR-20, both may be considered possible plasma-based cardiovascular fitness indicators (refer to Table **1**) [22]. Finally, from 4631 participants in the HUNT Fitness Study, 12 patients with the highest and 12 with the lowest $VO_{2max}$ were chosen for miRNA expression profiling. Consequently, miR-210 had a negative correlation with $VO_{2max}$ values and was considerably greater in a validation cohort. Although there was a weak correlation between microRNA-21 and miR-222 and $VO_{2max}$, their values were thought to be indicative of CVD [23]. Six potential miRNA clusters that can be used to predict phenotypic $VO_{2max}$ levels were highlighted by Kern *et al*., who also demonstrated that regular endurance training can change miRNA expression (see Table **1**). Clusters 1, 2, and 6 remained among the top negative feature coefficients. Moreover, miR-532-5p was proposed as a possible biomarker of $VO_{2max}$ alterations following carbohydrate ingestion. Given that $VO_{2max}$ was substantially correlated with the insulin signaling pathway, it is consistent with the results of their miRNA enrichment research [24]. $VO_{2max}$ values were positively linked with miR-1, miR-133, miR-206, miR-146a, and miR-20, indicating their potential as biomarkers for cardiopulmonary fitness. Remarkably, differing outcomes were noted in connection to miR-486 and its association with $VO_{2max\ [25]}$. These discrepancies most likely result from a multitude of variables that differ throughout studies, such as (i) Disparities in training protocols (*e.g*., short-term $VO_{2max}$ ergometer test *versus* long-term steady-state cycling program); (ii) individual differences among participants (*e.g*., young healthy subjects that engage in no regular exercise regimen against a healthy endurance athlete that trains more than three times per week for at least one year); (iii) variations in blood sample collection schedules; and (iv) variations in data analysis. It is hardly unexpected that the literature is conflicting given these numerous differences. Hence, the role of miR-486 as a cardiopulmonary fitness biomarker may only be explored *via* more research [24]. It is becoming more widely acknowledged that miRNAs are potential circulating biomarkers of disease and injury. Initial studies on mTBI have demonstrated possible changes in the circulating levels of specific miRNAs following injury; however, little is known about how miRNA modifications evolve following mTBI. Our prospective study of Australian football players, both male and female, provides evidence that lower plasma levels of miR-27a and miR-221 occur throughout the sub-acute phase following SRC. Furthermore, an inverse correlation was observed between the severity of SRC symptoms and the plasma levels of these miRNAs. These encouraging results suggest that miRNA may be useful in supporting SRC treatment, even if they still need more research and validation in larger cohorts.

**Table 1. MicroRNA characteristics investigated in endurance sports.**

| miRNAs | Exercise | Training Protocol | Outcome | Reference |
|---|---|---|---|---|
| miR-20a, miR-210, miR-221, miR-222, miR-328, miR-21, miR-146a, miR-21, miR-133a, miR-21, miR-146a, and miR-210 | Cycling | At rest and during acute exhaustive exercise testing on upright cycle ergometer, before and after a 90-day period of aerobic exercise training | Elevated by acute exercise before and after sustained training: miR-146a, miR-222 elevated by acute exercise before but not after sustained training: miR-21, miR-221 elevated after sustained training: miR-20a nonresponsive: miR-133a, miR-210, miR-328 | [19] |
| miR-133a, miR-206 | Half-marathon | Before and immediately after the halfmarathon—21.1 km | Elevated after the half-marathon run: miR-133a and miR-206 | [98] |
| Global miRNA screening (752 miRs) | Running | Before and immediately after: 10 km race, half-marathon, and marathon | After 10 km run Upregulated: miR-199b-5p, miR-424-3p, miR-33a-5p, miR-551a, miR-1537, miR-223-5p, miR-1260q, let-7b-3p, miR-150-5p, miR-423-5p, miR-223-3p, miR-345-5p, miR-505-3p | [99] |

*(Table 1) contd.....*

| miRNAs | Exercise | Training Protocol | Outcome | Reference |
|---|---|---|---|---|
| miR-1, miR-133a, miR-181a, miR-486, and miR-494 | Running-sprint | Before and after 4 weeks (thrice weekly) of sprint interval training and a single bout of maximal aerobic treadmill exercise | Endurance athletes, increased: miR-1, miR-486, and miR-494 after endurance training<br>Healthy, young men decreased: miR-1, miR-133a, and miR-486 immediately after maximal aerobic exercise | [18] |
| Global miRNA | Running | Before, after 8 weeks of endurance training, after 8 weeks of wash-out phase, and after another 8 weeks of endurance training | Most important miRNA associated with VO2max<br>Cluster 1:miR-4465, miR-5581-5p, miR-6879-5p, miR-6869-5p<br>Cluster 2: miR-7975<br>Cluster 6: miR-326-5p, miR-502-5p, miR-502-3p, miR-340-5p | [21] |

### 1.3. Potential Clinical Significance of Subacute Decrease of miR-27a and miR-221 after SRC

Even though self-reporting of symptoms is a well-known drawback for SRC management and research, our SCAT tests' independence from RTP decisions gives us some assurance that such assessments would be less susceptible to bias. Therefore, the miRNA correlations with the observed symptoms offer more proof of a relationship with SRC, even though they still need to be validated. Most remarkably, there was an inverse correlation between plasma miR-27a and the severity of SCAT symptoms at various time points [26]. for instance, discovered an inverse correlation between symptoms at 2-days post-SRC (*i.e.*, the overall peak of symptom reporting of the time-points in this study) and plasma miR-27a levels at 6- and 13-days; additionally, there was a correlation between plasma miR-27a levels at 2- and 6-days and symptoms at 13-days. Only the symptom severity at 6 days was linked with miR-221 levels at 13 days. These miRNA results not only offer more proof of SRC specificity but also suggest that miRNAs have served as potential biomarkers in the management of SRC. For instance, the inverse correlation seen between the 2- and 6-day levels of miR-27a and the 13-day symptoms may indicate that miR-27a can be utilized to predict and track the recovery of symptoms. Although higher blood levels of tau (13 days), neurofilament light (NfL; 6 and 13 days), and glial fibrillary acidic protein (GFAP; 2 days) were detected in the males of this cohort in our prior protein biomarker investigations, Sandy R. Schultz *et al*. 2022 did not find any relationships with symptoms [27]. However, it is crucial to recognize that pathophysiological recovery may not always follow symptom relief. As a result, biomarkers may serve distinct purposes in identifying various facets of “recovery” following SRC. Research on several neurological disorders suggests that miR-221 might play significant roles in neurobiology and that brain injury or disease is associated with lower levels of miR-221 in the blood. One of the most prevalent miRNAs in the human brain is miR-221, and studies conducted *in vitro* indicate that miR-221 is essential for the survival and development of neural cells. Because miR-221 inhibits endothelial cell proliferation and motility [28-30], it is also believed to play significant roles in vascular homeostasis. As a result, changes in circulating levels may indicate a reaction to neurovascular injury. Furthermore, it has been demonstrated that serum miR-221 levels drop during the first week following an ischemic stroke [31, 32], and that pre-treatment with a miR-221 mimic decreases neuro-inflammation and infarct size in mice following an ischemic stroke. 39 Additionally, there is *in vitro* evidence that Parkinson's disease-associated loss-of-function mutations of DJ-1 led to decreased levels of miR-221, as well as clinical data indicating patients with the condition have lower serum miR-221 levels [33-35]. Six days following SRC [26], also observed a drop in plasma miR-27a levels. It has been observed that miR-27a appears to have a number of roles in the pathogenesis of traumatic brain injury (TBI), including disruption of the blood-brain barrier, protection against neuronal apoptosis, and negative control of neuroinflammation [36-38]. It has been noted through experimental TBI studies that within the first 24 hours of injury, both mice [37] and rats [39] showed miR-27a down-regulation in the injured brain tissue. This was observed when intra-cerebro-ventricular administration of a miR-27a mimic or lentivirus encoding miR-27a [39] reduced lesion volume and neuronal cell death. These investigations offer some support for the theory that the decreased plasma miR-27a found in the current investigation may reflect post-trauma brain alterations. To date, there has been no report of altered miR-27a in fluids following traumatic brain injury (TBI) possibly because of the acute sampling time points used in earlier research. However, several clinical investigations in different types of brain damage and disease have demonstrated comparable reductions in miR-27a levels in circulation. For instance, serum taken 48 hours after admission showed lower levels of miR-27a in patients who had experienced intracerebral hemorrhage[45]. Two groups of AD patients had lower CSF levels of miR-27a than controls, and it was discovered that this reduction correlated with AD pathology (poor β-amyloid[42] and high CSF tau and phosphorylated tau). Shultz *et al*. (2022) [26] investigation of the KEGG pathways targeted by miR-27a & miR-221 also identified important pathways that might be involved in the pathophysiology of mTBI, even if these findings needed to be confirmed using luciferase assays. In light of the previously described research on the role of these miRNA in brain damage and disease [26], postulate that the pathophysiological implications of mTBI may be linked to the lower plasma levels of miR-221 and miR-27a following SRC.

### 1.4. Altered Circulating MicroRNA Profiles Post-Endurance Training (Ultramarathon Runners)

Eyileten *et al*. (2021) [40] assessed a distinct group of ultra-marathon athletes for the impact of high physical fitness on changes in miRNA expression linked to muscle hypertrophy, cardiac muscle functioning, angiogenesis, hemopoiesis; these miRNAs were chosen based on bioinformatics analysis. Among the various approaches to choosing miRNAs for validation research, *in-silico* bioinformatics analysis is advantageous since it calls upon all relevant data and produces predictions for specific targets and molecular interactions. By using this paradigm, the study was the first to validate its findings on a highly precise sample of elite athletes and to pinpoint the most pertinent targets. The obtained results were considered helpful in identifying novel physiological adaption biomarkers in endurance athletes. Bioinformatics and computational analysis of literature data have identified the most potential circulating miRNAs that can be induced by endurance training. Given that *in silico* research was unable to discover the miRNAs that would be unique to either chronic or acute training [40], postulate that the variation in miRNA profiles has more to do with the miRNA's level than its presence or absence [40]. verified that following a 100-kilometer race, there were significantly higher levels of miR-125a-5p, miR-126, and miR-223 among 23 elite endurance athletes. Furthermore [40], discovered using enrichment analysis a number of associations between miRNAs and pathways, such as the BDNF and insulin signaling pathway, that could be involved in physiological differentiation or regeneration in endurance sports [41]. BDNF is one of the well-known mediators in the development of the nervous system; it is a neurotrophin that promotes neurogenesis and helps neurons survive [42-44]. Cell survival is stimulated by BDNF through a variety of mechanisms, such as the PI3K-Akt cascade and the MAPK pathway [45]. It is commonly known that BDNF can be crucial for maintaining glucose/energy homeostasis in addition to the neurological system. It is interesting to note that numerous investigations have produced strong proof of miRNAs' ability to control BDNF's post-transcriptional levels [44, 45]. Exercise raises blood BDNF levels, according to a number of human research [46] and meta-analyses [47]. Exercise raises blood lactate levels and the cardiovascular response by causing the release of BDNF [48]. Since platelets are the main source of BDNF [44, 49], increased sympathetic activity during intense physical exercise can activate platelets [50] which in turn helps release BDNF into the bloodstream [51]. The bio-informatics study revealed that the examined miRNAs controlled magnesium and guanosine triphosphate, in addition to other significant pathways. Notably, research on animals has shown that magnesium can improve blood circulation, and brain, and muscle glucose availability by preventing or postponing the buildup of lactate in the muscles, which in turn reduces fatigue during exercise [52]. Moreover, it has been demonstrated that free extracellular guanosine 5′-triphosphate (GTP) promotes myogenic cell development in both mouse and human cell lines. According to [53], this finding suggests that guanosine triphosphate may modulate miRNA-myogenic regulatory factors, which in turn affect how the body adapts to physical activity. Following the run [40], discovered a negative correlation between miR-1-3a and hs-CRP. More significantly, runners who completed the race in less than 10 hours were found to have levels of expression of miR-1-3p than those who finished more than 10 hours. MiR-1 belongs to the subset of myomiRs, which are muscle-enriched or striated muscle-specific miRNAs. These molecules play a role in muscle development, homeostasis, and cell regeneration. They also have an effect on the apoptosis of cardiomyocytes caused by hypoxia and re-oxygenation [54]. According to Roms *et al*. (2021), there is evidence that myomiRs exhibit a dose-response correlation at varying levels of exercise duration and intensity; also the pattern of miR-1 expression is dose-dependent with exercise intensity; finally, the duration of exercise affects the levels of other miRNAs like miR-133a or miR-222. Studies on young male runners have shown that after high-intensity interval training (HIIT), miR-1 responds specifically to aerobic exercise as its concentration increases post-marathon [56]. The results were in line with the notion that specific circulating miR-1 was significantly up-regulated 3 h post-exercise but not immediately or shortly after (within 1 h) [57], even though blood samples for analysis were taken within 30 min of the race's conclusion. Much research has found increased miR-1-3p in response to endurance training, but just a few studies [58, 59] related this finding to myoglobin 24 hours after the run. Furthermore, a negative correlation was observed between the levels of miR-1-3p and CRP following the 100 km race. After and during endurance exercise, there is a brief increase in blood CRP concentration, which, as per [60], is caused by the acute phase response post-exercise that is controlled by cytokines, particularly IL-6. According to [61], endurance sports that are both short- and long-term can cause both pro- and anti-inflammatory reactions. Additionally, it has been previously documented that CRP levels substantially correspond with the distance covered and may grow continually during ultra-endurance runs [62]. As a result, miR-1-3p may be used as a marker for the reparative mechanisms activated in response to stressful external stressors. Furthermore, it was shown that miR-1 adversely regulates phosphoinositide 3-kinases catalytic subunit alpha (PIK3CA) expression and that its expression is reduced in cardiac injury caused by epirubicin. Therefore, downregulating PIK3CA results in a notable reduction in the phosphorylation of mTOR, or mammalian target of rifampicin kinase, and protein kinase B (Akt). mTOR is an important downstream target gene of the PI3K/Akt pathway, which can reduce cardiac injury by increasing autophagy and inhibiting apoptosis [63]. Wade *et al*.(2014) [64] have reported the angiogenic function of MiR-125a in endothelium and cardiac muscle hypoxia and inflammation. While one study found that miR-125a-5p expression was downregulated in the ischemic myocardium following an MI episode, another study found

that patients with heart failure, particularly those with low ejection fraction, had higher levels of miR-125a-5p in their bloodstreams [65]. Additional research revealed that paroxysmal atrial fibrillation was associated with elevated expressions of miR-125a-5p [66]. Furthermore, several publications show a dynamic character in their circulatory presence following myocardial damage [67, 68]. In conclusion, a damaged heart may release miR-125a into the bloodstream. Furthermore, it has been demonstrated by *in vitro* research that shear rates, which are also seen during intense training, trigger the endothelial secretion of miR-125a-5p [69]. Since HIIT caused a large increase in miR-125a-5p, which may be impacted by HIIT's intermittent nature, it was discovered that this kind of training had an impact on alterations in miRNA expression [69]. In fact, research comparing MOD exercise to HIIT exercise revealed the possible presence of an intensity-dependent pattern of miRNA release from CV cells for different miRNA species; participants in the 100-kilometer run showed greater expression of miR-125a-5p [70]. Male participants in the HUNT study had low VO2 max, a measure of cardiopulmonary fitness, which was linked to higher levels of miR-125a. Additionally, Eyileten *et al*. (2021) [45] discovered that miR-125a-5p was expressed less frequently in ultramarathon runners who were in the highest quartile of VO2 max [45]; the study also found a negative connection between maximal lactate concentration and miR-125a-5p. The energy used by ultramarathon runners is primarily produced in aerobic processes [71]; hence, more active oxidative enzymes are found in these athletes [72]. It has previously been documented [73, 74] that mean running speed and lactate concentration are correlated, and that mean lactate accumulation increases with distance run [75-77]. These results led to the conclusion that marathon runners should modify their pace to maximize oxygen intake and minimize the rise in blood lactate concentration, hence avoiding an exponential rise in lactate. Numerous cancer forms have been linked to miR-125a-5p's propensity to obstruct aerobic glycolysis and lactate generation [78]; data on the healthy and active population is, however, extremely limited. The metabolism of cancer cells is distinct in that, regardless of the availability of oxygen, the majority of glucose is converted to lactate. This is accomplished by overexpressing a number of proteins involved in glucose metabolism, including the hexokinase (HK2), mono-carboxylate transporters, and glucose transporter (GLUT) 1. They function by transferring glucose metabolites from catabolic to anabolic pathways, which speeds up the invasion, migration, and multiplication of cells. Remarkably, additional research indicated that miR-125a had a detrimental effect on the control of HK2, an enzyme that limits the rate of glycolysis [79, 80]. One study Sun *et al*. (2017) [81] found miR-125a as a potential biomarker for laryngeal squamous cell carcinoma (LSCC), based on its ability to target HK2 and suppress LSCC progression; however, these results are yet to be implemented in clinical settings. Cellular energy disorders may also involve miR-125a-regulated mitochondrial fission. In fact, it is thought that increased mitochondrial fission hinders the synthesis of mitochondrial ATP by decreasing electron transport chain activity [82]. This, in turn, causes a decrease in the consumption of glucose and the formation of lactate. These results support the notion that miR-125a is the primary regulator of cell energy metabolism. miR-125a expression is enhanced by the downregulation of the PI3K/Akt/mTOR signaling pathway, which further decreases cell proliferation and improves the pro-inflammatory cascade. According to Chen *et al*.(2019) [83], PI3K inhibition enhanced miR-125a's capacity to control the PI3K/Akt/mTOR signaling pathway and elicit an inflammatory response. Many biological pathways, such as apoptosis, angiogenesis, cell cycle, and glucose metabolism, are centered on the PI3K/Akt signaling pathway. According to Xie *et al* (2019) [84], PI3K/Akt can control the decrease in glycogen synthesis and promote glycolysis. It is possible, therefore, that miR-125a-5p suppresses the generation of lactate during prolonged, high-intensity physical exercise by regulating pyruvate synthesis and, therefore, acetyl-coenzyme A, which is a component of the tricarboxylic acid cycle that produces ATP. To fully understand the function of miR-125a-5p in energy metabolism in endurance athletes, more research is necessary. Furthermore, there may be other adaptive functions of miR-1, miR-125a-5p, and miR-126 in ultra-marathon athletes. They may also mitigate endothelial cell damage by restoring autophagic flux *via* PI3K/Akt/mTOR signaling inhibition [63, 85]. It is noteworthy that Eyileten *et al*. (2021) [45] assessed a number of common changes in CV-related biomarkers in elite athletes throughout a 100-kilometer race; however, for most runners, taking part in a 100 km ultra-marathon results in a small but noteworthy increase in hs-TnT. Furthermore, Małek (2021) [86] found a correlation between the change in hs-CRP and the mean lactate concentration during the race and the change in troponin. miR-15a is another miRNA that might be crucial for the metabolism of glucose during exercise. Numerous *in vivo* and *in vitro* analyses Chakraborty (2019) [87] revealed that miR-15a controls transcription factor expression, which contributes to the development of cell resistance to insulin. Type 2 diabetes mellitus (T2DM) induced downregulation of MiR-15a has been discovered among T2DM patients in some studies [88]. Additionally, miR-15a may affect blood coagulation, platelet activation, glucose metabolism, and insulin signaling pathways, according to many bioinformatics studies [89]. In keeping with earlier research, Eyileten *et al*. (2021) [40] discovered a negative relationship between glucose levels and miR-15a expression following the race. It's interesting to note that miR-15a expression did not change before or after the run. More research is necessary to fully understand this problem, although the miR-15a expression may be possibly linked to the complex insulin action on peripheral tissues, which may affect other regulatory mechanisms that prevent high glucose levels. Endurance training causes a number of adjustments and processes; it can lead to oxidative stress, and injury to the skeletal muscles which is one of the causes promoting inflammation connected to exercise [90, 91]. Moreover, transient acute volume overload of the atria and right

ventricle may be caused by high-intensity endurance training [92]. It is therefore speculated that these occurrences could be connected to post-race higher miR-223 levels in ultramarathon athletes. It is believed that muscle ischemia and injured myofibrils induce the synthesis of miR-223. Furthermore, miR-223's overexpression is associated with the infiltration of inflammatory cells into the body [93], most likely as a result of its critical role in macrophage formation and function [94, 95]. MiR-223 can polarize macrophages into anti-inflammatory types by targeting PBX/knotted 1 homeobox 1 [96]. The blockage of the synthesis and excessive accumulation of NLRP3, a component of the inflammasome that reacts to cellular injury, may be another way MiR-223 helps to control inflammation [93]. Skeletal muscle regeneration may benefit from all of the previously outlined regulatory activities that uphold the harmony between inflammatory and anti-inflammatory factors [97]. It is also thought that miR-223 influences metabolic signaling, which may be useful for endurance athletes. In fact, miR-223 may affect adipose tissue's sensitivity to insulin and improve cardiomyocytes' GLUT4 expression, allowing those cells to absorb glucose at a higher rate [93]. Along with this occurrence, it has been observed that deletion of miR-223 leads to increased production of nitric oxide synthase 2 (NOS2) caused by IFNγ/LPS. NOS2 is an enzyme that is central to insulin resistance and a strong inducer of oxidative stress [21]. These findings support the proposal that inflammation, skeletal muscle injury, and metabolic adaption are associated with miR-223 overexpression in ultramarathon runners. Table **1** summarize most of relevant studied regarding miRNA as a biomarker in endurance sports

## CONCLUSION

A thorough summary of the existing literature on the role of miRNA in endurance exercise and how they are regulated both during and after endurance training has been presented in this review. The review showed that miR-1, miR-133, miR-21, and miR-155 are essential for adaptive response to exercise. Available studies demonstrated that the type of exercise has no significant impact on inflammatory-related miRNA expression. However, there is a need for more studies to understand the relationships between miRNAs and genes involved in adaptive changes depending on the length and type of training.

## AUTHORS' CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

## ACKNOWLEDGEMENTS

Declared none.

## REFERENCES

[1] Hughes, D.C.; Ellefsen, S.; Baar, K. Adaptations to endurance and strength training. *Cold Spring Harb. Perspect. Med.*, **2018**, *8*(6), a029769. http://dx.doi.org/10.1101/cshperspect.a029769 PMID: 28490537

[2] Sharma, S.; Merghani, A.; Mont, L. Exercise and the heart: the good, the bad, and the ugly. *Eur. Heart J.*, **2015**, *36*(23), 1445-1453. http://dx.doi.org/10.1093/eurheartj/ehv090 PMID: 25839670

[3] Mavrogeni, S.I.; Bacopoulou, F.; Apostolaki, D.; Chrousos, G.P. Sudden cardiac death in athletes and the value of cardiovascular magnetic resonance. *Eur. J. Clin. Invest.*, **2018**, *48*(7), e12955. http://dx.doi.org/10.1111/eci.12955 PMID: 29782639

[4] Wojciechowska, A.; Osiak, A.; Kozar-Kamińska, K. MicroRNA in cardiovascular biology and disease. *Adv. Clin. Exp. Med.*, **2017**, *26*(5), 868-874. http://dx.doi.org/10.17219/acem/62915 PMID: 29068585

[5] Feinberg, M.W.; Moore, K.J. MicroRNA regulation of atherosclerosis. *Circ. Res.*, **2016**, *118*(4), 703-720. http://dx.doi.org/10.1161/CIRCRESAHA.115.306300 PMID: 26892968

[6] Romaine, S.P.R.; Tomaszewski, M.; Condorelli, G.; Samani, N.J. MicroRNAs in cardiovascular disease: an introduction for clinicians. *Heart*, **2015**, *101*(12), 921-928. http://dx.doi.org/10.1136/heartjnl-2013-305402 PMID: 25814653

[7] Zhou, Q.; Shi, C.; Lv, Y.; Zhao, C.; Jiao, Z.; Wang, T. Circulating microRNAs in Response to Exercise Training in Healthy Adults. *Front. Genet.*, **2020**, *11*, 256. http://dx.doi.org/10.3389/fgene.2020.00256 PMID: 32256529

[8] Mooren, F.C.; Viereck, J.; Krüger, K.; Thum, T. Circulating micrornas as potential biomarkers of aerobic exercise capacity. *Am. J. Physiol. Heart Circ. Physiol.*, **2014**, *306*(4), H557-H563. http://dx.doi.org/10.1152/ajpheart.00711.2013 PMID: 24363306

[9] Baggish, A.L.; Park, J.; Min, P.K.; Isaacs, S.; Parker, B.A.; Thompson, P.D.; Troyanos, C.; D'Hemecourt, P.; Dyer, S.; Thiel, M.; Hale, A.; Chan, S.Y. Rapid upregulation and clearance of distinct circulating microRNAs after prolonged aerobic exercise. *J. Appl. Physiol.*, **2014**, *116*(5), 522-531. http://dx.doi.org/10.1152/japplphysiol.01141.2013 PMID: 24436293

[10] Silva, D.C.P.; Carneiro, F.D.; Almeida, K.C.; Fernandes-Santos, C. Role of miRNAs on the Pathophysiology of Cardiovascular Diseases. *Arq. Bras. Cardiol.*, **2018**, *111*(5), 738-746. http://dx.doi.org/10.5935/abc.20180215 PMID: 30484515

[11] Nappi, F.; Avtaar Singh, S.S.; Jitendra, V.; Alzamil, A.; Schoell, T. The Roles of microRNAs in the Cardiovascular System. *Int. J. Mol. Sci.*, **2023**, *24*(18), 14277. http://dx.doi.org/10.3390/ijms241814277 PMID: 37762578

[12] Gomes, C.P.C.; Oliveira-, G.P., Jr; Madrid, B.; Almeida, J.A.; Franco, O.L.; Pereira, R.W. Circulating miR-1, miR-133a, and miR-206 levels are increased after a half-marathon run. *Biomarkers*, **2014**, *19*(7), 585-589. http://dx.doi.org/10.3109/1354750X.2014.952663 PMID: 25146754

[13] Yates, L.A.; Norbury, C.J.; Gilbert, R.J.C. The long and short of microRNA. *Cell*, **2013**, *153*(3), 516-519. http://dx.doi.org/10.1016/j.cell.2013.04.003 PMID: 23622238

[14] Creemers, E.E.; Tijsen, A.J.; Pinto, Y.M. Circulating MicroRNAs. *Circ. Res.*, **2012**, *110*(3), 483-495. http://dx.doi.org/10.1161/CIRCRESAHA.111.247452 PMID:

22302755
[15] Ren, J.; Zhang, J.; Xu, N.; Han, G.; Geng, Q.; Song, J.; Li, S.; Zhao, J.; Chen, H. Signature of circulating microRNAs as potential biomarkers in vulnerable coronary artery disease. *PLoS One*, **2013**, *8*(12), e80738. http://dx.doi.org/10.1371/journal.pone.0080738 PMID: 24339880
[16] Sayed, D.; Abdellatif, M. MicroRNAs in development and disease. *Physiol. Rev.*, **2011**, *91*(3), 827-887. http://dx.doi.org/10.1152/physrev.00006.2010 PMID: 21742789
[17] Badacz, R.; Przewłocki, T.; Legutko, J.; Żmudka, K.; Kabłak-Ziembicka, A. microRNAs Associated with Carotid Plaque Development and Vulnerability: The Clinician's Perspective. *Int. J. Mol. Sci.*, **2022**, *23*(24), 15645. http://dx.doi.org/10.3390/ijms232415645 PMID: 36555285
[18] Nie, P.; Yang, F.; Wan, F.; Jin, S.; Pu, J. Analysis of MicroRNAs Associated With Carotid Atherosclerotic Plaque Rupture With Thrombosis. *Front. Genet.*, **2021**, *12*, 599350. http://dx.doi.org/10.3389/fgene.2021.599350 PMID: 33679879
[19] Helgerud, J.; Høydal, K.; Wang, E.; Karlsen, T.; Berg, P.; Bjerkaas, M.; Simonsen, T.; Helgesen, C.; Hjorth, N.; Bach, R.; Hoff, J. Aerobic high-intensity intervals improve VO2max more than moderate training. *Med. Sci. Sports Exerc.*, **2007**, *39*(4), 665-671. http://dx.doi.org/10.1249/mss.0b013e3180304570 PMID: 17414804
[20] Keteyian, S.J.; Brawner, C.A.; Savage, P.D.; Ehrman, J.K.; Schairer, J.; Divine, G.; Aldred, H.; Ophaug, K.; Ades, P.A. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *Am. Heart J.*, **2008**, *156*(2), 292-300. http://dx.doi.org/10.1016/j.ahj.2008.03.017 PMID: 18657659
[21] Denham, J.; Prestes, P.R. Muscle-enriched microRNAs isolated from whole blood are regulated by exercise and are potential biomarkers of cardiorespiratory fitness. *Front. Genet.*, **2016**, *7*, 196. http://dx.doi.org/10.3389/fgene.2016.00196 PMID: 27895662
[22] Baggish, A.L.; Hale, A.; Weiner, R.B.; Lewis, G.D.; Systrom, D.; Wang, F.; Wang, T.J.; Chan, S.Y. Dynamic regulation of circulating microRNA during acute exhaustive exercise and sustained aerobic exercise training. *J. Physiol.*, **2011**, *589*(16), 3983-3994. http://dx.doi.org/10.1113/jphysiol.2011.213363 PMID: 21690193
[23] Bye, A.; Røsjø, H.; Aspenes, S.T.; Condorelli, G.; Omland, T.; Wisløff, U. Circulating microRNAs and aerobic fitness--the HUNT-Study. *PLoS One*, **2013**, *8*(2), e57496. http://dx.doi.org/10.1371/journal.pone.0057496 PMID: 23469005
[24] Kern, F.; Ludwig, N.; Backes, C.; Maldener, E.; Fehlmann, T.; Suleymanov, A.; Meese, E.; Hecksteden, A.; Keller, A.; Meyer, T. Systematic assessment of blood-borne microRNAs highlights molecular profiles of endurance sport and carbohydrate uptake. *Cells*, **2019**, *8*(9), 1045. http://dx.doi.org/10.3390/cells8091045 PMID: 31500139
[25] World health statistics overview 2019: Monitoring health for the SDGs, sustainable development goals. **2019**. Available from: https://www.who.int/publications/i/item/9789241565707
[26] Shultz, S.R.; Taylor, C.J.; Aggio-Bruce, R.; O'Brien, W.T.; Sun, M.; Cioanca, A.V.; Neocleous, G.; Symons, G.F.; Brady, R.D.; Hardikar, A.A.; Joglekar, M.V.; Costello, D.M.; O'Brien, T.J.; Natoli, R.; McDonald, S.J. Decrease in Plasma miR-27a and miR-221 After Concussion in Australian Football Players. *Biomark. Insights*, **2022**, *17* http://dx.doi.org/10.1177/11772719221081318 PMID: 35250259
[27] McDonald, S.J.; O'Brien, W.T.; Symons, G.F.; Chen, Z.; Bain, J.; Major, B.P.; Costello, D.; Yamakawa, G.; Sun, M.; Brady, R.D.; Mitra, B.; Mychasiuk, R.; O'Brien, T.J.; Shultz, S.R. Prolonged elevation of serum neurofilament light after concussion in male Australian football players. *Biomark. Res.*, **2021**, *9*(1), 4. http://dx.doi.org/10.1186/s40364-020-00256-7 PMID: 33422120
[28] Terasawa, K.; Ichimura, A.; Sato, F.; Shimizu, K.; Tsujimoto, G. Sustained activation of ERK1/2 by NGF induces microRNA-221 and 222 in PC12 cells. *FEBS J.*, **2009**, *276*(12), 3269-3276. http://dx.doi.org/10.1111/j.1742-4658.2009.07041.x PMID: 19438724
[29] Hamada, N.; Fujita, Y.; Kojima, T.; Kitamoto, A.; Akao, Y.; Nozawa, Y.; Ito, M. MicroRNA expression profiling of NGF-treated PC12 cells revealed a critical role for miR-221 in neuronal differentiation. *Neurochem. Int.*, **2012**, *60*(8), 743-750. http://dx.doi.org/10.1016/j.neuint.2012.03.010 PMID: 22465943
[30] Celic, T.; Meuth, V.; Six, I.; Massy, Z.; Metzinger, L. The mir-221/222 Cluster is a Key Player in Vascular Biology *via* the Fine-Tuning of Endothelial Cell Physiology. *Curr. Vasc. Pharmacol.*, **2016**, *15*(1), 40-46. http://dx.doi.org/10.2174/1570161114666160914175149 PMID: 27633456
[31] Peng, H.; Yang, H.; Xiang, X.; Li, S. MicroRNA-221 participates in cerebral ischemic stroke by modulating endothelial cell function by regulating the PTEN/PI3K/AKT pathway. *Exp. Ther. Med.*, **2020**, *19*(1), 443-450. PMID: 31885694
[32] Tsai, P.C.; Liao, Y.C.; Wang, Y.S.; Lin, H.F.; Lin, R.T.; Juo, S.H.H. Serum microRNA-21 and microRNA-221 as potential biomarkers for cerebrovascular disease. *J. Vasc. Res.*, **2013**, *50*(4), 346-354. http://dx.doi.org/10.1159/000351767 PMID: 23860376
[33] Ma, W.; Li, Y.; Wang, C.; Xu, F.; Wang, M.; Liu, Y. Serum miR-221 serves as a biomarker for Parkinson's disease. *Cell Biochem. Funct.*, **2016**, *34*(7), 511-515. http://dx.doi.org/10.1002/cbf.3224 PMID: 27748571
[34] Roser, A.E.; Caldi Gomes, L.; Schünemann, J.; Maass, F.; Lingor, P. Circulating miRNAs as Diagnostic Biomarkers for Parkinson's Disease. *Front. Neurosci.*, **2018**, *12*, 625. http://dx.doi.org/10.3389/fnins.2018.00625 PMID: 30233304
[35] Oh, S.E.; Park, H.J.; He, L.; Skibiel, C.; Junn, E.; Mouradian, M.M. The Parkinson's disease gene product DJ-1 modulates miR-221 to promote neuronal survival against oxidative stress. *Redox Biol.*, **2018**, *19*, 62-73. http://dx.doi.org/10.1016/j.redox.2018.07.021 PMID: 30107296
[36] Li, X.Q.; Lv, H.W.; Wang, Z.L.; Tan, W.F.; Fang, B.; Ma, H. MiR-27a ameliorates inflammatory damage to the blood-spinal cord barrier after spinal cord ischemia: reperfusion injury in rats by downregulating TICAM-2 of the TLR4 signaling pathway. *J. Neuroinflammation*, **2015**, *12*(1), 25. http://dx.doi.org/10.1186/s12974-015-0246-3 PMID: 25876455
[37] Sabirzhanov, B.; Zhao, Z.; Stoica, B.A.; Loane, D.J.; Wu, J.; Borroto, C.; Dorsey, S.G.; Faden, A.I. Downregulation of miR-23a and miR-27a following experimental traumatic brain injury induces neuronal cell death through activation of proapoptotic Bcl-2 proteins. *J. Neurosci.*, **2014**, *34*(30), 10055-10071. http://dx.doi.org/10.1523/JNEUROSCI.1260-14.2014 PMID: 25057207
[38] Xi, T.; Jin, F.; Zhu, Y.; Wang, J.; Tang, L.; Wang, Y.; Liebeskind, D.S.; Scalzo, F.; He, Z. miR-27a-3p protects against blood–brain barrier disruption and brain injury after intracerebral hemorrhage by targeting endothelial aquaporin-11. *J. Biol. Chem.*, **2018**, *293*(52), 20041-20050. http://dx.doi.org/10.1074/jbc.RA118.001858 PMID: 30337368
[39] Sun, L.; Zhao, M.; Wang, Y.; Liu, A.; Lv, M.; Li, Y.; Yang, X.; Wu, Z. Neuroprotective effects of miR-27a against traumatic brain injury *via* suppressing FoxO3a-mediated neuronal autophagy. *Biochem. Biophys. Res. Commun.*, **2017**, *482*(4), 1141-1147. http://dx.doi.org/10.1016/j.bbrc.2016.12.001 PMID: 27919684
[40] Eyileten, C.; Wicik, Z.; Fitas, A.; Marszalek, M.; Simon, J.E.; De Rosa, S.; Wiecha, S.; Palatini, J.; Postula, M.; Malek, L.A. Altered Circulating MicroRNA Profiles After Endurance Training: A Cohort Study of Ultramarathon Runners. *Front. Physiol.*, **2022**, *12*, 792931. http://dx.doi.org/10.3389/fphys.2021.792931 PMID: 35145424
[41] Walsh, E.I.; Smith, L.; Northey, J.; Rattray, B.; Cherbuin, N. Towards an understanding of the physical activity-BDNF-cognition triumvirate: A review of associations and dosage. *Ageing Res. Rev.*, **2020**, *60*, 101044. http://dx.doi.org/10.1016/j.arr.2020.101044 PMID: 32171785

[42] Gasecka, A.; Siwik, D.; Gajewska, M.; Jaguszewski, M.J.; Mazurek, T.; Filipiak, K.J.; Postuła, M.; Eyileten, C. Early Biomarkers of Neurodegenerative and Neurovascular Disorders in Diabetes. *J. Clin. Med.,* **2020**, *9*(9), 2807. http://dx.doi.org/10.3390/jcm9092807 PMID: 32872672

[43] Li, Y.; Li, F.; Qin, D.; Chen, H.; Wang, J.; Wang, J.; Song, S.; Wang, C.; Wang, Y.; Liu, S.; Gao, D.; Wang, Z.H. The role of brain derived neurotrophic factor in central nervous system. *Front. Aging Neurosci.,* **2022**, *14*, 986443. http://dx.doi.org/10.3389/fnagi.2022.986443 PMID: 36158555

[44] Eyileten, C.; Mirowska-Guzel, D.; Milanowski, L.; Zaremba, M.; Rosiak, M.; Cudna, A.; Kaplon-Cieslicka, A.; Opolski, G.; Filipiak, K.J.; Malek, L.; Postula, M. Serum Brain-Derived Neurotrophic Factor is Related to Platelet Reactivity and Metformin Treatment in Adult Patients With Type 2 Diabetes Mellitus. *Can. J. Diabetes,* **2019**, *43*(1), 19-26. http://dx.doi.org/10.1016/j.jcjd.2018.01.014 PMID: 29891331

[45] Eyileten, C.; Sharif, L.; Wicik, Z.; Jakubik, D.; Jarosz-Popek, J.; Soplinska, A.; Postula, M.; Czlonkowska, A.; Kaplon-Cieslicka, A.; Mirowska-Guzel, D. The Relation of the Brain-Derived Neurotrophic Factor with MicroRNAs in Neurodegenerative Diseases and Ischemic Stroke. *Mol. Neurobiol.,* **2021**, *58*(1), 329-347. http://dx.doi.org/10.1007/s12035-020-02101-2 PMID: 32944919

[46] Mrówczyński, W. Health Benefits of Endurance Training: Implications of the Brain-Derived Neurotrophic Factor—A Systematic Review. *Neural Plast.,* **2019**, *2019*, 1-15. http://dx.doi.org/10.1155/2019/5413067 PMID: 31341469

[47] Ruiz-González, D.; Hernández-Martínez, A.; Valenzuela, P.L.; Morales, J.S.; Soriano-Maldonado, A. Effects of physical exercise on plasma brain-derived neurotrophic factor in neurodegenerative disorders: A systematic review and meta-analysis of randomized controlled trials. *Neurosci. Biobehav. Rev.,* **2021**, *128*, 394-405. http://dx.doi.org/10.1016/j.neubiorev.2021.05.025 PMID: 34087277

[48] Schiffer, T.; Schulte, S.; Sperlich, B.; Achtzehn, S.; Fricke, H.; Strüder, H.K. Lactate infusion at rest increases BDNF blood concentration in humans. *Neurosci. Lett.,* **2011**, *488*(3), 234-237. http://dx.doi.org/10.1016/j.neulet.2010.11.035 PMID: 21094220

[49] Eyileten, C.; Zaremba, M.; Janicki, P.K.; Rosiak, M.; Cudna, A.; Kapłon-Cieślicka, A.; Opolski, G.; Filipiak, K.J.; Kosior, D.A.; Mirowska-Guzel, D.; Postula, M. Serum Brain-Derived Neurotrophic Factor is Related to Platelet Reactivity but not to Genetic Polymorphisms within BDNF Encoding Gene in Patients with Type 2 Diabetes. *Med. Sci. Monit.,* **2016**, *22*, 69-76. http://dx.doi.org/10.12659/MSM.895607 PMID: 26739449

[50] Fujimura, H.; Chen, R.; Nakamura, T.; Nakahashi, T.; Kambayashi, J.; Sun, B.; Altar, C.; Tandon, N. Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. *Thromb. Haemost.,* **2002**, *87*(4), 728-734. http://dx.doi.org/10.1055/s-0037-1613072 PMID: 12008958

[51] Walsh, J.J.; Bentley, R.F.; Gurd, B.J.; Tschakovsky, M.E. Short-Duration Maximal and Long-Duration Submaximal Effort Forearm Exercise Achieve Elevations in Serum Brain-Derived Neurotrophic Factor. *Front. Physiol.,* **2017**, *8*, 746. http://dx.doi.org/10.3389/fphys.2017.00746 PMID: 29056915

[52] Zhang, Y.; Xun, P.; Wang, R.; Mao, L.; He, K. Can Magnesium Enhance Exercise Performance? *Nutrients,* **2017**, *9*(9), 946. http://dx.doi.org/10.3390/nu9090946 PMID: 28846654

[53] Pietrangelo, T.; Di Filippo, E.S.; Locatelli, M.; Piacenza, F.; Farina, M.; Pavoni, E.; Di Donato, A.; Innosa, D.; Provinciali, M.; Fulle, S. Extracellular Guanosine 5′-Triphosphate Induces Human Muscle Satellite Cells to Release Exosomes Stuffed With Guanosine. *Front. Pharmacol.,* **2018**, *9*, 152. http://dx.doi.org/10.3389/fphar.2018.00152 PMID: 29615899

[54] Zilahi, E.; Adamecz, Z.; Bodoki, L.; Griger, Z.; Póliska, S.; Nagy-Vincze, M.; Dankó, K. Dysregulated expression profile of myomiRs in the skeletal muscle of patients with polymyositis. *EJIFCC,* **2019**, *30*(2), 237-245. PMID: 31372109

[55] Ramos, A.E.; Lo, C.; Estephan, L.E.; Tai, Y.Y.; Tang, Y.; Zhao, J.; Sugahara, M.; Gorcsan, J., III; Brown, M.G.; Lieberman, D.E.; Chan, S.Y.; Baggish, A.L. Specific circulating microRNAs display dose-dependent responses to variable intensity and duration of endurance exercise. *Am. J. Physiol. Heart Circ. Physiol.,* **2018**, *315*(2), H273-H283. http://dx.doi.org/10.1152/ajpheart.00741.2017 PMID: 29600898

[56] Clauss, S.; Wakili, R.; Hildebrand, B.; Kääb, S.; Hoster, E.; Klier, I.; Martens, E.; Hanley, A.; Hanssen, H.; Halle, M.; Nickel, T. MicroRNAs as Biomarkers for Acute Atrial Remodeling in Marathon Runners (The miRathon Study – A Sub-Study of the Munich Marathon Study). *PLoS One,* **2016**, *11*(2), e0148599. http://dx.doi.org/10.1371/journal.pone.0148599 PMID: 26859843

[57] Nielsen, S.; Åkerström, T.; Rinnov, A.; Yfanti, C.; Scheele, C.; Pedersen, B.K.; Laye, M.J. The miRNA plasma signature in response to acute aerobic exercise and endurance training. *PLoS One,* **2014**, *9*(2), e87308. http://dx.doi.org/10.1371/journal.pone.0087308 PMID: 24586268

[58] Soplinska, A.; Zareba, L.; Wicik, Z.; Eyileten, C.; Jakubik, D.; Siller-Matula, J.M.; De Rosa, S.; Malek, L.A.; Postula, M. MicroRNAs as biomarkers of systemic changes in response to endurance exercise-A comprehensive review. *Diagnostics,* **2020**, *10*(10), 813.

[59] Yin, X.; Cui, S.; Li, X.; Li, W.; Lu, Q.; Jiang, X.; Wang, H.; Chen, X.; Ma, J. Regulation of Circulatory Muscle-specific MicroRNA during 8 km Run. *Int. J. Sports Med.,* **2020**, *41*(9), 582-588. http://dx.doi.org/10.1055/a-1145-3595 PMID: 32353882

[60] Kasapis, C.; Thompson, P.D. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. *J. Am. Coll. Cardiol.,* **2005**, *45*(10), 1563-1569. http://dx.doi.org/10.1016/j.jacc.2004.12.077 PMID: 15893167

[61] Barros, E.S.; Nascimento, D.C.; Prestes, J.; Nóbrega, O.T.; Córdova, C.; Sousa, F.; Boullosa, D.A. Acute and Chronic Effects of Endurance Running on Inflammatory Markers: A Systematic Review. *Front. Physiol.,* **2017**, *8*, 779. http://dx.doi.org/10.3389/fphys.2017.00779 PMID: 29089897

[62] Kłapcińska, B.; Waśkiewicz, Z.; Chrapusta, S.J.; Sadowska-Krępa, E.; Czuba, M.; Langfort, J. Metabolic responses to a 48-h ultra-marathon run in middle-aged male amateur runners. *Eur. J. Appl. Physiol.,* **2013**, *113*(11), 2781-2793. http://dx.doi.org/10.1007/s00421-013-2714-8 PMID: 24002469

[63] Wu, J.; Sun, C.; Wang, R.; Li, J.; Zhou, M.; Yan, M.; Xue, X.; Wang, C. Cardioprotective effect of paeonol against epirubicin-induced heart injury *via* regulating miR-1 and PI3K/AKT pathway. *Chem. Biol. Interact.,* **2018**, *286*, 17-25. http://dx.doi.org/10.1016/j.cbi.2018.02.035 PMID: 29505745

[64] Wade, S.M.; Ohnesorge, N.; McLoughlin, H.; Biniecka, M.; Carter, S.P.; Trenkman, M.; Cunningham, C.C.; McGarry, T.; Canavan, M.; Kennedy, B.N.; Veale, D.J.; Fearon, U. Dysregulated miR-125a promotes angiogenesis through enhanced glycolysis. *EBioMedicine,* **2019**, *47*, 402-413. http://dx.doi.org/10.1016/j.ebiom.2019.08.043 PMID: 31466915

[65] Boštjančič, E.; Zidar, N.; Glavač, D. MicroRNAs and cardiac sarcoplasmic reticulum calcium ATPase-2 in human myocardial infarction: expression and bioinformatic analysis. *BMC Genomics,* **2012**, *13*(1), 552. http://dx.doi.org/10.1186/1471-2164-13-552 PMID: 23066896

[66] Menezes Junior, A.S.; Ferreira, L.C.; Barbosa, L.J.V.; Silva, D.M.; Saddi, V.A.; Silva, A.M.T.C. Circulating MicroRNAs as Specific Biomarkers in Atrial Fibrillation: A Meta-Analysis. *Noncoding RNA,* **2023**, *9*(1), 13. http://dx.doi.org/10.3390/ncrna9010013 PMID: 36827546

[67] Yuan, N.; Scherzer, R.; Tanriverdi, K.; Martin, J.; Rahalkar, S.; Hsue, P. MicroRNA biomarkers associated with type 1 myocardial infarction in HIV-positive individuals. *AIDS,* **2019**, *33*(15), 2351-2361. http://dx.doi.org/10.1097/QAD.0000000000002368 PMID: 31764100

[68] Niculescu, L.S.; Simionescu, N.; Sanda, G.M.; Carnuta, M.G.; Stancu, C.S.; Popescu, A.C.; Popescu, M.R.; Vlad, A.; Dimulescu, D.R.; Simionescu, M.; Sima, A.V. MiR-486 and miR-92a Identified in Circulating HDL Discriminate between Stable and Vulnerable Coronary Artery Disease Patients. *PLoS One,* **2015**, *10*(10), e0140958. http://dx.doi.org/10.1371/journal.pone.0140958 PMID: 26485305

[69] Schmitz, B.; Breulmann, F.L.; Jubran, B.; Rolfes, F.; Thorwesten, L.; Krüger, M.; Klose, A.; Schnittler, H.J.; Brand, S.M. A three-step approach identifies novel shear stress-sensitive endothelial microRNAs involved in vasculoprotective effects of high-intensity interval training (HIIT). *Oncotarget,* **2019**, *10*(38), 3625-3640. http://dx.doi.org/10.18632/oncotarget.26944 PMID: 31217898

[70] Sapp, R.M.; Chesney, C.A.; Eagan, L.E.; Evans, W.S.; Zietowski, E.M.; Prior, S.J.; Hagberg, J.M.; Ranadive, S.M. Changes in circulating microRNA and arterial stiffness following high-intensity interval and moderate intensity continuous exercise. *Physiol. Rep.,* **2020**, *8*(9), e14431. http://dx.doi.org/10.14814/phy2.14431 PMID: 32358919

[71] di Prampero, P.E.; Atchou, G.; Brückner, J.C.; Moia, C. The energetics of endurance running. *Eur. J. Appl. Physiol. Occup. Physiol.,* **1986**, *55*(3), 259-266. http://dx.doi.org/10.1007/BF02343797 PMID: 3732253

[72] Costill, D.L.; Fink, W.J.; Pollock, M.L. Muscle fiber composition and enzyme activities of elite distance runners. *Med. Sci. Sports Exerc.,* **1976**, *8*(2), 96-100. http://dx.doi.org/10.1249/00005768-197600820-00015 PMID: 957938

[73] Rhodes, E.C.; McKenzie, D.C. Predicting Marathon Time From Anaerobic Threshold Measurements. *Phys. Sportsmed.,* **1984**, *12*(1), 95-98. http://dx.doi.org/10.1080/00913847.1984.11701745

[74] Tanaka, K.; Matsuura, Y. Marathon performance, anaerobic threshold, and onset of blood lactate accumulation. *J. Appl. Physiol.,* **1984**, *57*(3), 640-643. http://dx.doi.org/10.1152/jappl.1984.57.3.640 PMID: 6490453

[75] Sjödin, B.; Jacobs, I. Onset of blood lactate accumulation and marathon running performance. *Int. J. Sports Med.,* **1981**, *2*(1), 23-26. http://dx.doi.org/10.1055/s-2008-1034579 PMID: 7333732

[76] Pollock, M.L. Submaximal and maximal working capacity of elite distance runners. Part I: Cardiorespiratory aspects. *Ann. N. Y. Acad. Sci.,* **1977**, *301*(1), 310-322. http://dx.doi.org/10.1111/j.1749-6632.1977.tb38209.x PMID: 270924

[77] Saltin, B.; Larsen, H.; Terrados, N.; Bangsbo, J.; Bak, T.; Kim, C.K.; Svedenhag, J.; Rolf, C.J. Aerobic exercise capacity at sea level and at altitude in Kenyan boys, junior and senior runners compared with Scandinavian runners. *Scand. J. Med. Sci. Sports,* **1995**, *5*(4), 209-221. http://dx.doi.org/10.1111/j.1600-0838.1995.tb00037.x PMID: 7552766

[78] Huang, P.; Mao, L.F.; Zhang, Z.P.; Lv, W.W.; Feng, X.P.; Liao, H.J.; Dong, C.; Kaluba, B.; Tang, X.F.; Chang, S. Down-regulated miR-125a-5p promotes the reprogramming of glucose metabolism and cell malignancy by increasing levels of CD147 in thyroid cancer. *Thyroid,* **2018**, *28*, 613-623.

[79] Jin, F.; Wang, Y.; Zhu, Y.; Li, S.; Liu, Y.; Chen, C.; Wang, X.; Zen, K.; Li, L. The miR-125a/HK2 axis regulates cancer cell energy metabolism reprogramming in hepatocellular carcinoma. *Sci. Rep.,* **2017**, *7*(1), 3089. http://dx.doi.org/10.1038/s41598-017-03407-3 PMID: 28596599

[80] Luo, L.; Xiao, L.; Lian, G.; Wang, H.; Xie, L. miR-125a-5p inhibits glycolysis by targeting hexokinase-II to improve pulmonary arterial hypertension. *Aging (Albany NY),* **2020**, *12*(10), 9014-9030. http://dx.doi.org/10.18632/aging.103163 PMID: 32427576

[81] Sun, Z.; Zhang, W.; Li, Q. miR-125a suppresses viability and glycolysis and induces apoptosis by targeting Hexokinase 2 in laryngeal squamous cell carcinoma. *Cell Biosci.,* **2017**, *7*(1), 51. http://dx.doi.org/10.1186/s13578-017-0178-y PMID: 29043013

[82] Perdiz, D.; Lorin, S.; Leroy-Gori, I.; Poüs, C. Stress-induced hyperacetylation of microtubule enhances mitochondrial fission and modulates the phosphorylation of Drp1 at $^{616}$Ser. *Cell. Signal.,* **2017**, *39*, 32-43. http://dx.doi.org/10.1016/j.cellsig.2017.07.020 PMID: 28757354

[83] Chen, D.; Huang, X.; Lu, S.; Deng, H.; Gan, H.; Huang, R.; Zhang, B. miRNA-125a modulates autophagy of thyroiditis through PI3K/Akt/mTOR signaling pathway. *Exp. Ther. Med.,* **2019**, *17*(4), 2465-2472. http://dx.doi.org/10.3892/etm.2019.7256 PMID: 30906434

[84] Xie, Y.; Shi, X.; Sheng, K.; Han, G.; Li, W.; Zhao, Q.; Jiang, B.; Feng, J.; Li, J.; Gu, Y. PI3K/Akt signaling transduction pathway, erythropoiesis and glycolysis in hypoxia. *Mol. Med. Rep.,* **2019**, *19*(2), 783-791. PMID: 30535469

[85] Tang, F.; Yang, T.L. MicroRNA-126 alleviates endothelial cells injury in atherosclerosis by restoring autophagic flux *via* inhibiting of PI3K/Akt/mTOR pathway. *Biochem. Biophys. Res. Commun.,* **2018**, *495*(1), 1482-1489. http://dx.doi.org/10.1016/j.bbrc.2017.12.001 PMID: 29203244

[86] Małek, Ł. Deformation parameters of the heart in endurance athletes and in patients with dilated cardiomyopathy-A cardiac magnetic resonance study. *Diagnostics,* **2021**, *11*(2), 374.

[87] Chakraborty, C.; Doss, C.G.P.; Bandyopadhyay, S.; Agoramoorthy, G. Influence of miRNA in insulin signaling pathway and insulin resistance: micro-molecules with a major role in type-2 diabetes. *Wiley Interdiscip. Rev. RNA,* **2014**, *5*(5), 697-712. http://dx.doi.org/10.1002/wrna.1240 PMID: 24944010

[88] Jiménez-Lucena, R.; Rangel-Zúñiga, O.A.; Alcalá-Díaz, J.F.; López-Moreno, J.; Roncero-Ramos, I.; Molina-Abril, H.; Yubero-Serrano, E.M.; Caballero-Villarraso, J.; Delgado-Lista, J.; Castaño, J.P.; Ordovás, J.M.; Pérez-Martinez, P.; Camargo, A.; López-Miranda, J. Circulating miRNAs as Predictive Biomarkers of Type 2 Diabetes Mellitus Development in Coronary Heart Disease Patients from the CORDIOPREV Study. *Mol. Ther. Nucleic Acids,* **2018**, *12*, 146-157. http://dx.doi.org/10.1016/j.omtn.2018.05.002 PMID: 30195754

[89] Pordzik, J.; Jakubik, D.; Jarosz-Popek, J.; Wicik, Z.; Eyileten, C.; De Rosa, S.; Indolfi, C.; Siller-Matula, J.M.; Czajka, P.; Postula, M. Significance of circulating microRNAs in diabetes mellitus type 2 and platelet reactivity: bioinformatic analysis and review. *Cardiovasc. Diabetol.,* **2019**, *18*(1), 113. http://dx.doi.org/10.1186/s12933-019-0918-x PMID: 31470851

[90] Armstrong, R.B. Muscle damage and endurance events. *Sports Med.,* **1986**, *3*(5), 370-381. http://dx.doi.org/10.2165/00007256-198603050-00006 PMID: 3529285

[91] Kaufmann, C.C.; Wegberger, C.; Tscharre, M.; Haller, P.M.; Piackova, E.; Vujasin, I.; Kassem, M.; Tentzeris, I.; Freynhofer, M.K.; Jäger, B.; Wojta, J.; Huber, K. Effect of marathon and ultra-marathon on inflammation and iron homeostasis. *Scand. J. Med. Sci. Sports,* **2021**, *31*(3), 542-552. http://dx.doi.org/10.1111/sms.13869 PMID: 33140866

[92] Patil, H.R.; O'Keefe, J.H.; Lavie, C.J.; Magalski, A.; Vogel, R.A.; McCullough, P.A. Cardiovascular damage resulting from chronic excessive endurance exercise. *Mo. Med.,* **2012**, *109*(4), 312-321. PMID: 22953596

[93] Taïbi, F.; Metzinger-Le Meuth, V.; Massy, Z.A.; Metzinger, L. miR-223: An inflammatory oncomiR enters the cardiovascular field. *Biochim. Biophys. Acta Mol. Basis Dis.,* **2014**, *1842*(7), 1001-1009. http://dx.doi.org/10.1016/j.bbadis.2014.03.005 PMID: 24657505

[94] Greco, S.; De Simone, M.; Colussi, C.; Zaccagnini, G.; Fasanaro, P.; Pescatori, M.; Cardani, R.; Perbellini, R.; Isaia, E.; Sale, P.; Meola, G.; Capogrossi, M.C.; Gaetano, C.; Martelli, F. Common micro-RNA signature in skeletal muscle damage and regeneration induced by Duchenne muscular dystrophy and acute ischemia.

*FASEB J.,* **2009**, *23*(10), 3335-3346. http://dx.doi.org/10.1096/fj.08-128579 PMID: 19528256

[95] Rangrez, A.Y.; M'Baya-Moutoula, E.; Metzinger-Le Meuth, V.; Hénaut, L.; Djelouat, M.S.I.; Benchitrit, J.; Massy, Z.A.; Metzinger, L. Inorganic phosphate accelerates the migration of vascular smooth muscle cells: evidence for the involvement of miR-223. *PLoS One,* **2012**, *7*(10), e47807. http://dx.doi.org/10.1371/journal.pone.0047807 PMID: 23094093

[96] Zhou, H.; Xiao, J.; Wu, N.; Liu, C.; Xu, J.; Liu, F.; Wu, L. MicroRNA-223 Regulates the Differentiation and Function of Intestinal Dendritic Cells and Macrophages by Targeting C/EBPβ. *Cell Rep.,* **2015**, *13*(6), 1149-1160. http://dx.doi.org/10.1016/j.celrep.2015.09.073 PMID: 26526992

[97] Cheng, N.; Liu, C.; Li, Y.; Gao, S.; Han, Y.C.; Wang, X.; Du, J.; Zhang, C. MicroRNA-223-3p promotes skeletal muscle regeneration by regulating inflammation in mice. *J. Biol. Chem.,* **2020**, *295*(30), 10212-10223. http://dx.doi.org/10.1074/jbc.RA119.012263 PMID: 32493731

[98] Danese, E.; Benati, M.; Sanchis-Gomar, F.; Tarperi, C.; Salvagno, G.L.; Paviati, E.; Montagnana, M.; Schena, F.; Lippi, G. Influence of middle-distance running on muscular micro RNAs. *Scand. J. Clin. Lab. Invest.,* **2018**, *78*(3), 165-170. http://dx.doi.org/10.1080/00365513.2018.1426104 PMID: 29325455

[99] Fernández-Sanjurjo, M.; Úbeda, N.; Fernández-García, B.; del Valle, M.; Ramírez de Molina, A.; Crespo, M.C.; Martín-Hernández, R.; Casas-Agustench, P.; Martínez-Camblor, P.; de Gonzalo-Calvo, D.; Díez-Robles, S.; García-González, Á.; Montero, A.; González-González, F.; Rabadán, M.; Díaz-Martínez, Á.E.; Whitham, M.; Iglesias-Gutiérrez, E.; Dávalos, A. Exercise dose affects the circulating microRNA profile in response to acute endurance exercise in male amateur runners. *Scand. J. Med. Sci. Sports,* **2020**, *30*(10), 1896-1907. http://dx.doi.org/10.1111/sms.13759 PMID: 32609897