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MicroRNA-146a as a Potential Diagnostic Biomarker for Myocardial Infarction: Association with Inflammatory Response via TNF-α and NF-κB Regulation

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ABSTRACT

Among cardiovascular disorders, the leading cause of death and disability worldwide is still myocardial infarction (MI). The most common cause of MI is thrombotic blockage of a coronary artery, which happens when a susceptible plaque ruptures. Numerous miRNAs have been demonstrated to regulate significant mechanisms that lead to the pathophysiological effects of acute MI. Small noncoding RNAs known as microRNAs control gene expression by translation suppression or destruction of messenger RNAs. This research aims to determine if miRNA-146a expression levels might serve as a potential diagnostic biomarker for MI and to investigate their correlation with the inflammatory response. In this case-control study, 100 MI patients and 50 healthy subjects participated. MiRNA-146a expression levels in whole blood, NF-κB, and TNF-α in serum were identified by (qRT-PCR) and ELISA, respectively. The findings showed that miRNA-146a was significantly upregulated in MI patients compared to healthy subjects (P=0.002). Besides, mean TNF-α levels were elevated in MI cases; however, there was no significant difference between the control group's TNF-α levels and those of the MI patients (P=0.606). Furthermore, a statistically significant decrease (P<0.001) in the level of NF-κB was observed in MI patients compared to normal participants. Additionally, there was a negative correlation between miRNA-146a and (NF-kB and TNF-α), but the correlations were not statistically significant. The results indicate that microRNA-146a acts as a crucial molecular regulator of inflammatory signaling in MI. It functions as a negative feedback modulator that controls excessive inflammation mediated by the NF-κB pathway.

1.Introduction

Acute myocardial infarction (AMI) is a major cardiovascular condition caused by a sudden interruption of coronary blood flow, leading to ischemic necrosis of cardiac muscle tissue. It is a primary contributor to mortality and disability globally (Sathvik *et al*., 2023). A wide range of cardiometabolic and environmental risk factors, such as obesity, hypertension, diabetes, dyslipidemia, smoking, excessive alcohol intake, unhealthy diet, genetic and epigenetic determinants, and physical inactivity, contribute to endothelial dysfunction, initiating and accelerating atherosclerotic processes (Abdulfattaha, 2019) (Mahdavi et al., 2022).

MicroRNAs (miRNAs) are a class of endogenous non-coding RNA molecules, which are single-stranded and relatively small (18-22 nucleotides) and control the expression of genes post-transcriptionally. They accomplish this by the attachment of specific messenger RNA, which may lead to the destruction of the mRNA or translational suppression (Abdulfattaha, 2019). At least 60% of human genes are believed to be regulated by miRNA and make up as much as 1% of the human geno me (O'Connell *et al.*, 2012). With advances in genetic technologies, miRNA has gradually gained attention. Due to their high stability in the bloodstream, miRNAs have significant potential as biomarkers for disease detection. miRNAs are key regulators of the onset and progression of cardiovascular pathology following myocardial infarction (Gilyazova *et al.*, 2023). Many studies have shown that miRNAs participate in a wide range of cardiovascular disorders, including coronary atherosclerosis, AMI, cardiac remodeling, myocardial fibrosis after infarction, and other cardiovascular diseases. (Xiao *et al.*, 2021).

MicroRNA-146a is an established factor implicated in inflammation and contributes to the occurrence and advancement of atherosclerosis (Xie *et al.*, 2020). Furthermore, by regulating multiple target genes, miRNAs have been shown to influence the progression of carotid atherosclerosis (Abdulfattaha, 2019). Several genes in the Toll-like receptor 4 (TLR4)/ Nuclear Factor Kappa B (NF-κB) pathway, a crucial immunological and inflammatory response system, are targeted by miRNA-146a. Additionally, miRNA-146a targets TLR signaling to modify infection, neoplasia, and innate immunity (Huang, 2023).

The mechanism underlying the role of miRNA-146a as an important molecular brake of inflammation comprises targeting the TLR signaling pathway (Chu *et al.*, 2022). Binding of oxidized LDL to Toll-like receptors (TLRs) activates the myeloid differentiation primary response protein 88 (MyD88) signaling pathway. MyD88's death domain attaches to interleukin-1 receptor-associated kinase 1 (IRAK1) and triggers TNF receptor-associated factor 6 (TRAF6). Eventually, TRAF6 activation triggers NF-κB activation, leading to the generation of cytokines that promote inflammation, including TNF-α, macrophage apoptosis, and atherosclerosis progression (Gissler *et al.*, 2022). miRNA-146a suppresses innate inflammation in atherosclerosis by targeting IRAK and TRAF6 (Chu *et al.*, 2022). Additionally, miRNA-146a contributes to the prevention of endothelial dysfunction by reducing endothelial activation through the NADPH Oxidase 4 (NOX4) pathway, which increases endothelial nitric oxide synthase (eNOS) production and inhibits reactive oxygen species (ROS) (L. Xiao *et al.*, 2021).

An essential factor in several inflammatory processes is miRNA-146. Research indicates that miRNA-146a treatment *in vitro* may stimulate the production of proinflammatory proteins, for instance, Tumor necrosis factor alpha (TNF-α) and a crucial transcription factor (NF-κB), which play roles in atherosclerosis (Bannazadeh Baghi *et al.*, 2024). In several heart disorders, inflammation leads to cardiomyocyte apoptosis and diminished cardiac contractility. Under these circumstances, miRNA-146 is upregulated at the tissue level to inhibit inflammation by negative autoregulation. According to these principles, many investigations were conducted to assess the diagnostic capabilities of these biomarkers (Bacmeister *et al.*, 2024). There is evidence that atherosclerosis can be regulated by modulating miRNAs, which reduce innate inflammation.

Specifically, reduced levels of inflammatory markers and more stable plaques are linked to miRNA-146a expression (Ardinal *et al*., 2024). One effective proinflammatory mediator that promotes atherogenesis is TNF-α (Rolski and Błyszczuk, 2020). Furthermore, a greater risk of ischemic events is linked to higher levels of TNF-α, and it is intimately linked to cardiovascular prognosis. Consequently, in individuals with established atherosclerosis, the possibility of targeting TNF-α as a therapeutic agent has been explored (Ridker *et al*., 2019). Several investigations have demonstrated that TLRs in macrophages and monocytes trigger NF-κB signaling, which performs an important function in both acute and chronic inflammation, including atherosclerosis. The stimulation of NF-κB in monocytes and macrophages is restricted by a variety of regulatory mechanisms. Of these, one of the most important negative regulators of NF-κB is miRNA-146a (Li *et al*., 2015). The current investigation aims to analyze the abundance of miRNA-146a gene expression in the pathogenesis of MI and investigate the potential linkage between NF-kB, TNF-α levels, and the occurrence of this disease, and explore their relationship with miRNA-146a expression.

2.Materials and methods

2.1 Study Population

The current research was conducted in Hawler Medical University- College of Medicine at the Clinical Biochemistry Department, from June 2024 to January 2025. 50 healthy participants constituted the control group, and 100 patients diagnosed with Myocardial Infarction from the Erbil Cardiac Centre were included in this research to assess TNF-α and NF-κB. Among them, the first 50 MI patients and the first 25 controls were used for the analysis of miRNA-146a gene expression.

2.2 Collection of blood samples

Venous blood samples were collected from participants in both groups upon admission, with 5 mL drawn and placed into two separate vacutainer tubes, one containing anticoagulant and the other plain. For miRNA-146a analysis, 2 mL of whole blood was collected into EDTA-containing tubes and stored at −80 °C until further processing. Blood in the plain tube was allowed to clot for 20 minutes, followed by centrifugation at 3,000 rpm for 10 minutes to isolate serum. The serum samples were then used for NF-κB and TNF-α assays and subsequently stored at −80 °C.

2.3 Inclusion Criteria

The case group was selected based on four criteria: (1) individuals with clear clinical signs of myocardial ischemia, for instance, shortness of breath, chest discomfort, or chest tightness; (2) myocardial enzyme increase (CK-MB and Troponin); (3) ECG abnormalities; and (4) coronary angiography-verified target vessel stenosis.

2.4 Exclusion Criteria

Patients with all types of cardiac disease except those with myocardial infarction, as well as those who received anti-arrhythmic drugs such as Cordarone and blood-thinning medications like heparin.

2.5 Molecular analysis

2.5.1Detection of miRNA-146a relative expression by Quantitative Reverse Transcription polymerase chain reaction (qRT-PCR)

MicroRNA-146a and Total RNA were extracted separately from the whole blood of 50 cases and 25 controls using the Total RNA isolation kit (Cat number: 10119, add bio kit, Korea) and the miRNA isolation kit (Cat number: FAMIK 002, Favorgen, Taiwan) as per the protocol. Subsequently, a complementary DNA (cDNA) synthesis kit (Cat number: 22701, add bio kit, Korea) was used to reverse isolate miRNA-146a and Total RNA into first-strand cDNA. The PCR reaction was performed using a Stem-loop primer sequence for miRNA-146a (GCGGGGGATTTAAAATAGTGACACTTTTCAA ACGCCCCCCCCATGGAA). We used the qRT-PCR technique to measure miRNA-146a expression following the instructions from the manufacturer. Specific primers were designed by (Cat number: 44001, Humanizing Genomics MacroGen, Ligo, Korea).

The forward primer: 5′- CCTGAGAAGTGAATTCCATG -3′ and the reverse primer: 5′- TGACACTTTTCAAACGCCC -3′. cDNA product and primers were mixed with master mix SYBR GREEN (Cat number:

A323402, AMPLIQON, Denmark). Applied Biosystems-7500 Real-Time PCR system, USA, was used for the qRT-PCR, and its 96 wells were filled with the reaction mixture; for every sample, three separate wells were used. The amplification protocol included an initial denaturation at 95°C for 2 min, followed by 35 PCR cycles including denaturation at 95°C for 20 s, annealing at 58°C for 30 s, and extension at 72°C for 40 s. An endogenous control that was used to normalize expression levels was the measurement of U6 snRNA (Forward primer: CTCGCTTCGGCAGCACAT and Reverse primer: AACGCTTCACGAATTTGCGT) (Huang *et al.*, 2020).

2.6 Detection of TNF-α and NF-kB by Enzyme-linked immunosorbent assay (ELISA)

ELISA was utilized to measure the concentration of NF-kB and TNF-α in the serum of MI patients and controls (Cat number: ELK 9589, ELK 1190, ELK Biotechnology kit-USA).

2.7 Statistical analysis

To analyze the results statistically, the Statistical Package for Social Sciences (SPSS) version 27 software was used. Results were presented as mean ± SE, and the significance of differences was assessed using an independent t-test. The levels of NF-kB and TNF-α in healthy participants and MI patients were compared, and correlations between continuous variables were tested using Pearson's correlation (Pereira-da-Silva *et al.*, 2021). GraphPad Prism statistical software (version 10) was used for the statistical tests for miRNA-146a gene expression, NF-kB, and TNF-α. Statistical significance was established using a $P<0.05$. The $2^{-\Delta\Delta Ct}$ method was used to assess the relative quantity of miRNA-146a (Kim *et al.*, 2021).

2.8 Ethics approval

The Scientific Research and Ethics Committee of the College of Medicine - Hawler Medical University reviewed and approved the study protocol in accordance with the Declaration of Helsinki (Paper code: 11, 27 May 2024). Following an explanation of the study's purpose, procedures, and advantages, verbal consent was obtained from each participant, and an agreement letter was provided to the administration department of the Erbil Cardiac Center before starting to collect data.

3.Results

3.1 Characteristics of the study population

This research was conducted on 150 participants, from which 100 Myocardial Infarction patients (62 ST-elevation MI and 38 non-ST-elevation MI), which include 75 males and 25 females with a mean age of 59 years, the age range was 25 to 85 years, and 50 healthy controls, there were 28 males and 22 females with a mean age of 57 years, the age range was 40 to 70 years (P=0.292) (Table 1).

Table 1: Comparative evaluation of Age distribution between Myocardial Infarction patients and Healthy Controls.

Groups	No. of participants	Age (year)		Statistical evaluation *Pb
		Mean±SE	Range	P=0.292
Group I (Healthy controls)	50	57±1.7	40-70	
Group II (Myocardial Infarction patients)	100	59±1.2	25-85	

*Pb statistics obtained by Student's t-test.

3.2 The miRNA-146a gene expression

MiRNA-146a expression level in whole blood was detected by qRT-PCR**.** The mean±SE values for miRNA-146a were (2.16±0.46) and (7.6±1.22), and the range of variation was (0.1-6.4) and (0.1-28.8) in healthy controls and Myocardial Infarction patients, respectively (Table 2). The present study demonstrated that miRNA-146a was significantly overexpressed in myocardial infarction (MI) patients compared to healthy controls, with the difference reaching statistical significance (P = 0.002) (Figure 1).

3.3 The inflammatory cytokine estimation

Group I (Healthy controls)

The laboratory parameters of this study are detailed in Table 2. The mean±SE value for TNF-α was 166 ± 5.3 pg/mL, with a variation range of 126 to 222 pg/mL. The mean±S.E value for NF-kB was (3.9±0.09) ng/mL with a range of

variation (3.22-5.31).

3.4Group II (Myocardial Infarction Patients)

The results of the inflammatory cytokine comparison between healthy controls and MI patients are presented as mean ± SE and illustrated in Table 2. The mean ± S.E. value for TNF-α was (172 ± 6.0) pg/mL, with a variation range of (121-339). Although the mean TNF-α concentrations were increased, the amounts of this protein were not significantly different between the control group and patients suffering from myocardial infarction (P=0.606) (Figure 1). The mean ± SE value for NF-kB was 3.1 ± 0.06 ng/mL, with a variation range of 2.31 to 3.98 ng/mL. The findings of the present research showed that the levels of NF-kB were significantly reduced (P<0.001) when comparing the control group to patients with Myocardial Infarction (Figure 1).

Table 2: Comparison of miRNA-146a, TNF-α, and NF-kB between Myocardial Infarction patients and Healthy Controls.

Parameters	Group I (Healthy controls)			Group II (Myocardial Infarction patients)			Statistical evaluation *Pb
	Mean±SE	Range	No.	Mean±SE	Range	No.	
miRNA-146a	2.16±0.46	0.1-6.4	25	7.6±1.22	0.1-28.8	50	*P=0.002
TNF-α, (pg/mL)	166±5.3	126-222	50	172±6.0	121-339	100	P=0.606
NF-kB, (ng/mL)	3.9±0.09	3.22-5.31	50	3.1±0.06	2.31-3.98	100	*P<0.001

*Pb statistics obtained by Student's t-test.

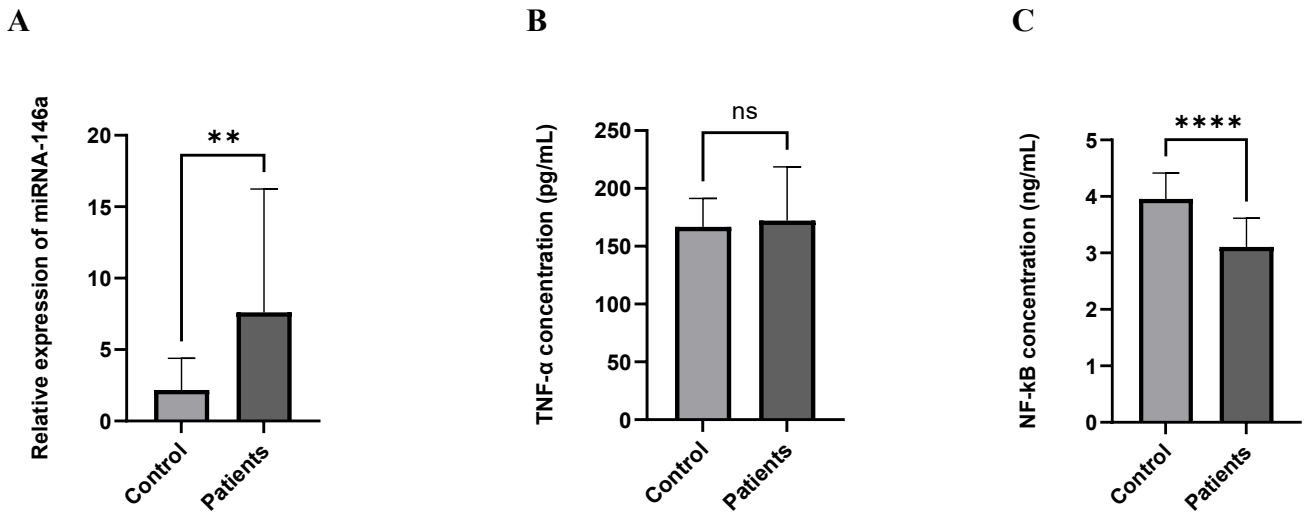

Figure 1: The expression levels of miRNA-146a, TNF-α, and NF-kB in patients with myocardial infarction and control group. (A) miRNA-146a; (B) TNF-α; (C) NF-kB. **P<0.01, ****P<0.0001, ns= not significant. miRNA-146a, microRNA-146a; TNF-α, tumor necrosis factor-alpha; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells. The relative expression of miRNA-146a was calculated using the $2^{-\Delta\Delta Ct}$ method.

3.5 Correlation between miRNA-146a and TNF-α, and NF-kB

Both TNF-α and NF-kB were shown to be negatively correlated with miRNA-146a; however, none of these correlations was statistically significant (r = -0.156, P =0.604 and r = -0.103, P =0.617), respectively (Figure 2).

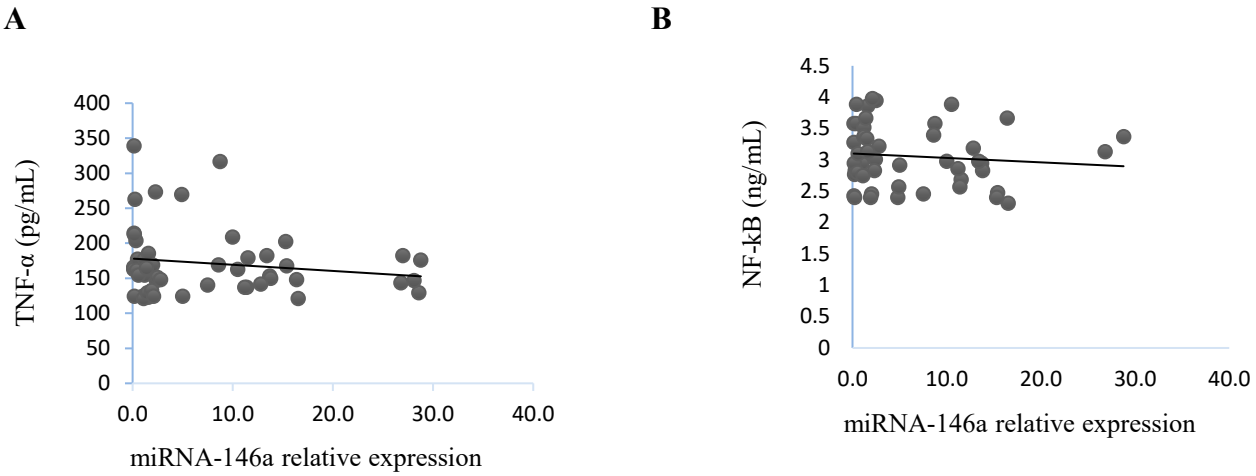

Figure 2: Correlation analysis between microRNA-146a relative expression and the potential factors in MI patients. (A) correlation of the miRNA-146a with TNF-α. (B) correlation of the miRNA-146a with NF-kB. miRNA-146a represents the X-axis, TNF-α and NF-kB represent the Y-axis. miRNA-146a, microRNA-146a; TNF-α, tumor necrosis factor-alpha; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells.

4.Discussion

One miRNA that has been shown to have anti-inflammatory properties is miRNA-146a; it regulates pro-inflammatory immunological responses by limiting overstimulation, thereby preserving the homeostasis state of the immune system. By affecting the TRAF6, it negatively modulates the inflammatory response via reducing levels of NF-kB, which is one of the primary immunological transcription factors (Gilyazova *et al.*, 2023). This study investigates the expression levels of miRNA-146a in MI patients and their association with TNF-α and NF-kB. The findings indicated that miRNA-146a was significantly overexpressed in MI patients in comparison to the control subjects. A notable reduction in NF-kB levels was observed in MI patients. Furthermore, TNF-α levels in patients with MI showed an increase, although this was not statistically significant. Additionally, there was a negative correlation between miRNA-146a and (NF-kB and TNF-α), but the correlations were not statistically significant.

This finding is in agreement with the results of research conducted on 50 patients in Romania (Scărlătescu *et al.*, 2022), who worked on every single miRNA that has been linked to cardiovascular disease, found that patients with STEMI had significantly upregulated miRNA-146a. Whereas in a study on 63 patients in China, miRNA-146a was elevated in the serum exosomes of patients with acute coronary syndrome (ACS) (Li *et al.*, 2021). (Xiao *et al.*, 2021) found that compared to healthy controls, STEMI patients had higher expression of miRNA-146a in their 256 research participants. In China, in a study done by Huang *et al.* (2020) on 180 Carotid atherosclerosis (CAS) patients, in comparison to the normal group, the peripheral blood miRNA-146a and TNF-α levels were raised in the CAS group, which is similar to our findings. Furthermore, significantly increased miRNA-146a gene expression was observed according to a study done on 100 atherosclerotic coronary artery disease (ACAD) patients in Iraq (Abdulfattaha, 2019). (Xue *et al.*, 2019) discovered that the expression levels of plasma miRNA-146a of 31 Acute MI patients in China were significantly increased. In the research done by Pereira-da-Silva *et al.* (2021), there was

a negative association between the levels of miRNA-146a and TNF-α levels; on the other hand, a higher severity of coronary artery disease was linked to lower levels of miRNA-146a, which contrasts with our findings.

In the past few years, miRNAs have emerged as potential diagnostic and prognostic biomarkers implicated in the pathophysiology of cardiovascular disorders, and they have a role in myocardial contraction, electrical signal conduction, cardiac development, and morphogenesis (Yu *et al*. 2019). The damage caused by cardiac ischemia/reperfusion is reduced when miRNA-146a is upregulated. The prediction of left ventricular remodeling after MI is based on elevated levels of miRNA-146a in the blood (An *et al*. 2018). miRNA-146a may inhibit apoptosis in cardiomyocytes caused by ischemia or sepsis by targeting (IRAK1) and (TRAF6), two proteins involved in this process (He *et al*. 2021).

When a myocardial infarction occurs, the first inflammatory reaction triggers NF-κB, which raises the production of TNF-α and miRNA-146a. miRNA-146a, which is activated by NF-κB, behaves as a negative feedback regulator that targets important signaling molecules, including IRAK1 and TRAF6, causing NF-κB activity to decrease over time. TNF-α levels continue to rise despite this inhibition because of persistent tissue damage and other inflammatory pathways, including mitogen-activated protein kinase (MAPK) signaling. As the inflammatory response shifts into a reparative phase, miR-146a and TNF-α continue to influence immune responses and support tissue repair, but NF-κB activity declines to minimize excessive inflammation. This explains why NF-κB is reduced in MI patients while miRNA-146a and TNF-α are elevated (Wang, 2022).It is well established that TNF-α causes blood vessels to produce less nitric oxide and more reactive oxygen species (ROS), which can result in endothelial dysfunction: an early stage of atherogenesis (Lee *et al.*, 2017). The creation of ROS caused by TNF-α in this process needs NADH oxidase to be activated. By increasing LDL transcytosis in endothelial cells, controlling the function of macrophage scavenger receptors, and promoting the generation of foam cells, TNF-α is also involved in the formation of atherosclerotic plaques (Nicolaou *et al.*, 2017).

5.Conclusion

The study's findings showed that both miRNA-146a and NF-kB were significantly linked to myocardial infarction, with miRNA-146a being overexpressed and NF-kB being decreased in MI patients. On the other hand, no significant association between TNF-α and myocardial infarction was found in this investigation. Furthermore, there was a negative correlation between miRNA-146a and (TNF-α and NF-kB), but the correlation was not statistically significant. According to these results, miRNA-146a and NF-kB could be potential biomarkers or therapeutic targets for myocardial infarction.

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