Original Article

Is Ferroptosis and Oxidative Stress Involved in NSTEMI Patient's?

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Highlights

- Ferroptosis (iron-dependent lipid peroxidation–driven cell death) is implicated in ischemic injury.
- NSTEMI patients showed significantly higher oxidative stress (↑LPO) and iron overload (↑iron, ↑ferritin) vs controls.
- Antioxidant defenses were reduced in NSTEMI (↓TAC, ↓TTG, ↓SOD, ↓GPx activity).
- This biomarker pattern supports ferroptosis activation contributing to myocardial injury in NSTEMI.

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ABSTRACT

Background: Ischemic heart disease is the leading cause of death worldwide. Oxidative stress plays a key role in myocardial infarction (MI). Ferroptosis, a type of iron-dependent regulated cell death caused by lipid peroxide accumulation, has been identified as a key mechanism in ischemic injury. This study aimed to investigate the association between oxidative stress and ferroptosis in patients with non–ST-segment-elevation myocardial infarction (NSTEMI).

Methods: In this case-control study, 25 patients with NSTEMI and 25 controls were included. In serum samples, cardiac markers (troponin I and CK-MB), oxidative stress biomarkers including lipid peroxidation (LPO), total antioxidant capacity (TAC), total thiol groups (TTG), superoxide dismutase (SOD) activity, glutathione peroxidase (GPx) activity, and iron and ferritin levels were measured.

Results: In patients with NSTEMI, serum levels of cardiac markers (troponin I and CK-MB), LPO, iron, and ferritin were significantly higher than in controls. In contrast, TAC, TTG, and SOD and GPx activities were significantly lower in patients with NSTEMI.

Conclusion: This study demonstrated a possible role of oxidative stress in the pathophysiology of NSTEMI. Elevated iron and LPO levels and reduced GPx activity may contribute to cardiac cell death through ferroptosis.

Keywords: Non–ST-Segment Elevation Myocardial Infarction; Oxidative Stress; Ferroptosis

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Introduction

Cardiovascular diseases are considered one of the most potent noncommunicable diseases in the modern world, imposing considerable strains on health care systems and economies. The most severe and potentially fatal manifestation of ischemic heart disease is myocardial infarction (MI), which occurs due to the abrupt cessation of blood supply to an area of the myocardium.[1]

One of the most important pathophysiologic events in ischemic injury is oxidative stress.[2] Oxidative stress is a state of disequilibrium between the rate at which reactive oxygen species (ROS) are generated and the capacity of the cell's antioxidant defense system to detoxify them.[3] The release of ROS initiates a cascade of injurious processes in cardiomyocytes.[4] Oxidative stress also leads to oxidation and conformational changes in essential lipids, resulting in cell death.[5]

Cardiomyocyte death is the terminal event and determines the extent of damage from MI.[6] The past decade has witnessed remarkable advances in elucidating mechanisms of regulated cell death (RCD) that reveal the concept of cell death to be more extensive than the traditional apoptosis/necrosis dichotomy. Among the newly discovered RCD mechanisms, ferroptosis has garnered notable interest because of its implication in a variety of diseases, including ischemic injury.[7] Ferroptosis is an iron-dependent form of cell death biochemically characterized by the detrimental accumulation of lipid peroxides in cell membranes. The process differs genetically, biochemically, and morphologically from apoptosis, necrosis, and other forms of RCD, such as pyroptosis and necroptosis. Unlike apoptosis, in which caspase activation is typical, ferroptosis is completely caspase independent.[8]

The molecular mechanism of ferroptosis is centered on three major pathways: iron homeostasis, lipid homeostasis, and antioxidant defense.[8-10]

Oxidative stress can serve as a primary inducer of ferroptosis through various mechanisms.[11] At the structural level, ultrastructural modifications characteristic of ferroptosis (ie, diminished mitochondrial size and augmented mitochondrial membrane density) have been seen in cardiomyocytes subjected to myocardial ischemia conditions.[12] More importantly, administration of ferroptosis inhibitors (eg, ferrostatin-1) in these animal models has led to reduced infarct size and improved cardiac function.[13,14]

Accordingly, this study aimed to investigate the relationship between oxidative stress and ferroptosis in patients with non–ST-segment elevation myocardial infarction (NSTEMI).

Methods

Study Population and Sample Collection

Patient Group: A total of 25 patients with a confirmed diagnosis of NSTEMI were enrolled. The diagnosis was established based on relevant clinical symptoms (chest pain lasting≥30 min), elevated cardiac troponin levels, and absence of major ST-segment elevation on electro-cardiography, defined as less than 0.2 mV in men or less than 0.15 mV in women in leads V_2–V_3 and/or less than 0.1 mV in the other leads. The diagnosis was confirmed by a cardiologist and coronary angiography demonstrating a minimum of 50% stenosis in at least one major epicardial coronary artery.

Control Group: A total of 25 healthy sex-matched volunteers without underlying disease were recruited as controls.

From all participants in both groups, a 10-mL baseline venous blood sample was collected in tubes containing ethylene- diaminetetraacetic acid (EDTA) as an anticoagulant. Samples were transported promptly to the Toxicology Laboratory, Faculty of Pharmacy. Blood samples were centrifuged at 3000 rpm for 10 minutes at 4 °C to obtain serum. Serum aliquots were transferred to microtubes and stored at −70 °C until completion of sample collection for batch analysis.

Total Antioxidant Capacity (TAC)

TAC was measured using the ferric reducing antioxidant power colorimetric method. This method is based on the reduction of ferric iron to ferrous iron complexed with tripyridyl-S-triazine in an acidic medium, producing a blue color measured at 593 nm. Results were expressed as mmol/L.

Lipid Peroxidation (LPO)

Unsaturated fatty acids undergo peroxidation in reactions with reactive oxygen species, producing electrophilic aldehydes such as malondialdehyde, which serve as markers of cellular redox status. LPO was determined using the thiobarbituric acid reactive substances (TBARS) assay, based on the formation of a molecular adduct measured at 532 nm. Results were expressed as µmol/L.

Total Thiol Groups (TTG)

Thiol (sulfhydryl) groups present in peptides and proteins contribute to the stabilization of protein tertiary structure and neutralization of reactive electrophilic and oxidizing species. Serum TTG was measured using Ellman reagent (5,5′-dithiobis [2-nitrobenzoic acid]).

Superoxide Dismutase (SOD) Activity

SOD catalyzes the dismutation of the superoxide anion. Enzyme activity reflects antioxidant status. Serum SOD activity was measured using a commercial colorimetric kit (Kiazist).

Glutathione Peroxidase (GPx) Activity

GPx catalyzes the reduction of hydrogen peroxide to water using glutathione. Serum GPx activity was measured according to the manufacturer's protocol using a commercial kit (Kiazist).

Troponin I and Creatine Kinase-MB (CK-MB)

Serum troponin I and CK-MB concentrations were measured using enzyme-linked immunosorbent assay kits according to the manufacturer's instructions. Colorimetric detection was performed at 450 nm. Concentrations were calculated from standard curves and expressed as ng/mL.

Iron Level

Serum iron concentration was measured using a commercial kit (Pars Azmoun) based on the Ferene photometric method. Iron is released from transferrin and reduced to the ferrous form by ascorbic acid. The ferrous ion reacts with Ferene reagent to form a stable blue complex, the intensity of which is proportional to iron concentration.

According to the manufacturer's protocol, 100 µL of serum was incubated with reagents 1 and 2 at 37 °C. Absorbance was measured at 600 nm against a reagent blank. Iron concentration was calculated using the formula provided and compared with standard absorbance. The assay measurement range was 5 to 500 µg/dL, with a lower detection limit of 5 µg/dL.

Ferritin Concentration

Serum ferritin concentration was determined using a commercial enzyme-linked immunosorbent assay kit (Pishtaz Teb). The assay is based on a sandwich immunoenzymatic method using monoclonal antibodies. Ferritin in the sample binds to an antibody coated on microplate wells and to a second antibody conjugated to horseradish peroxidase. After incubation and addition of tetramethylbenzidine substrate, color development is directly proportional to ferritin concentration. The reaction was terminated with a stop solution, and absorbance was measured at 450 nm with a reference wavelength of 630 nm. The assay detection range was 0.5 to 1000 ng/mL, with an analytical sensitivity of 0.5 ng/mL.

Ethical Considerations

This study was approved by the ethics committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1402.408) and conducted in accordance with the 2013 Declaration of Helsinki. Written informed consent was obtained from all participants or their legal representatives before enrollment, in compliance with ethical guidelines.

Statistical Analysis

All data are presented as mean (SD). The Shapiro-Wilk test was used to assess the normality of the distribution of the continuous variables. Comparisons of clinical and oxidative stress markers between the control and patient groups were analyzed using the unpaired t test or the Mann-Whitney U test, depending on data distribution.

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Linear regression was employed to evaluate the association between myocardial injury biomarkers (troponin I and CK-MB) and redox status indicators (LPO, GPx, SOD, TAC, TTG, iron, and ferritin). A two-sided *P* value of less than 0.05 was considered statistically significant. All tests were performed using STATA, version 14.0 (STATA Corp).

Results

Demographic Analysis

Descriptive findings related to the demographic characteristics of patients with NSTEMI and the control group showed a significant difference in smoking patterns between the two groups. In the control group, 6 participants (24%) were smokers compared with 19 (76%) who were nonsmokers, whereas in the patient group, this pattern reversed, with 16 smokers (64%) and 9 nonsmokers (36%). These data indicate a substantially higher prevalence of smoking in the patient group.

Regarding sex distribution, both groups were predominantly male, with 88% of the control group and 92% of the patient group being male. For age distribution, most participants in both groups were aged 50 years or older, comprising 80% of the control group and 92% of the patient group (Table 1).

Serum Levels of Oxidative Stress Biomarkers and Ferritin and Iron

As shown in (Figure 1), the TAC level in serum was significantly lower in the patient group than in the control group (P<0.05). LPO in serum was significantly higher in the patient group than in the control group (P<0.05). The SOD activity in serum samples was significantly lower in the patient group than in the control group (P<0.05). The GPx activity in serum was significantly lower in the patient group than in the control group (P<0.05). As shown in (Figure 2), the serum ferritin and iron level were also significantly lower in the patient group than in the control group (P<0.05).

Cardiac Factors (Troponin I and CK-MB Levels)

The creatine kinase–MB and troponin I levels in serum samples were significantly higher in the patient group than in the control group (P<0.05) (Figure 3).

Linear Regression Analysis for Antioxidant Biomarkers, Iron, and Ferritin With CK-MB and Troponin I by Group

Linear regression analysis in the patient group showed no statistically significant association between oxidative stress biomarkers, iron, or ferritin and troponin I or CK-MB levels (Table 2).

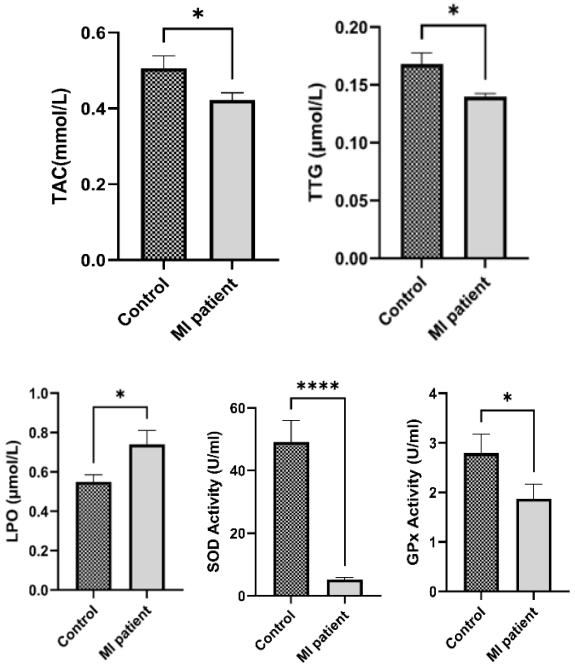

Figure 1. Oxidative stress biomarkers in serum of the patient and control groups

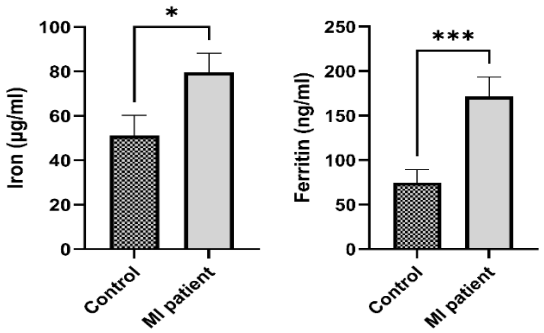

Figure 2. Iron and Ferritin levels in serum of the patient and control groups

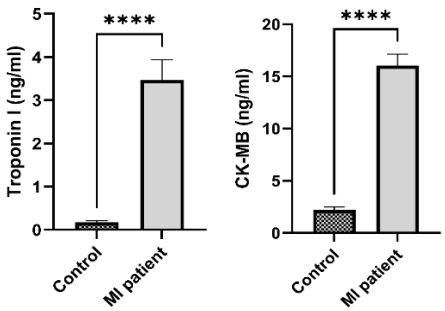

Figure 3. Troponin and CK-MB levels in serum of the patient and control groups

Table 1. Demographic table of MI patient and healthy people

		Control group		Patient group	
		Frequency	Percent	Frequency	Percent
Sex	Male	22	88%	23	92%
	Female	3	12%	2	8%
Age group	≤50 yr	5	20%	2	8%
	>50 yr	20	80%	23	92%
Smoking status	Yes	6	24%	16	36%
	No	19	76%	9	64%

Table 2. Linear regression test results in the patient group

Variable	Coef	P-Value	Significant	(95 % conf. interval)
SOD, Troponin I	-0.1947958	0.489	No	(-0.78, 0.39)
SOD, CK-MB	0.0781314	0.639	No	(-0.27, 0.42)
Gpx, Troponin I	-0.0158455	0.901	No	(-0.27, 0.24)
Gpx, CK-MB	-0.1037269	0.061	No	(-0.21, 0.005)
LPO, Troponin I	0.110812	0.694	No	(-0.04, 0.06)
LPO, CK-MB	-0.0156992	0.192	No	(-0.03, 0.008)
TAC, Troponin I	-0.0310772	0.145	No	(-0.07, 0.01)
TAC. CK-MB	-0.0083607	0.400	No	(-0.02, 0.01)
TTG, Troponin I	0.0007972	0.743	No	(-0.004, 0.005)
TTG, CK-MB	-0.0015911	0.123	No	(-0.003, 0.004)
Iron, Troponin I	-1.172244	0.748	No	(-8.76, 6.41)
Iron, CK-MB	-0.4639609	0.756	No	(-3.56, 2.64)
Ferritin, Troponin I	-6.325728	0.468	No	(-24.61, 11.96)
Ferritin, CK-MB	5.693681	0.255	No	(-4.62, 16.01)

Discussion

Oxidative stress, resulting from increased production of reactive oxygen species or a reduction in the body's antioxidant defense system, ultimately causes cardiac tissue injury. The results of this study showed that oxidative stress is induced in patients with NSTEMI. Furthermore, the findings, confirmed by an acute increase in markers of cardiac injury (troponin I and creatine kinase–MB), endorse the central role of oxidative stress in the pathophysiology of NSTEMI.

One of the principal observations of this research was that in patients with NSTEMI, activity of the antioxidant enzymes superoxide dismutase and glutathione peroxidase was significantly lower than in the control group. Superoxide dismutase is the body's primary defense against the free radical superoxide (O_2•−), which it converts into hydrogen peroxide (H_2O_2).[15,16] This is followed by glutathione peroxidase catalyzing the reduction of potentially harmful hydrogen peroxide to water.[17] The concurrent decrease in the activity of these two enzymes results in increased production of reactive oxygen species and enhanced cellular damage. Previous studies have demonstrated a reduction in enzymatic antioxidant defenses related to cardiovascular diseases.[18,19] In addition, ferroptosis research has found that glutathione peroxidase 4 can prevent ferroptosis by clearing intracellular peroxides and maintaining cell survival; dysfunction of glutathione peroxidase 4 leads to the accumulation of intracellular peroxides, resulting in ferroptosis.[20]

Along with the enzymatic defense system, a notable reduction in transferrin/total iron-binding capacity level was observed. Transferrin/total iron-binding capacity, which mainly comprises proteins and the molecule glutathione, acts as a powerful nonenzymatic antioxidant and directly neutralizes free radicals.[21–23] The decrease in glutathione level indicates oxidative stress during MI.[24,25] Moreover, in this study, the TAC level in serum was significantly lower in the patient group than in the control group. A possible explanation is that

TAC is a general assay that measures the sum of all antioxidants present in serum (including ascorbate, urate, and bilirubin). It is possible that in MI, the levels of some of these molecules decrease considerably, reflecting a disturbance in the normal redox system of the cardiovascular components.[26,27]

The significant increase in the LPO level, an end product of LPO, provides strong and direct evidence of oxidative damage to cell membranes in heart disease.[26,28] This finding suggests that the antioxidant defense system was unable to protect membrane lipids from reactive oxygen species attack.[29,30] This destructive process not only compromises the integrity of the cardiac cell membrane but also contributes to the leakage of intracellular markers such as troponin I and creatine kinase–MB into the bloodstream, indicating myocardial necrosis.[31,32]

An important aspect of this study was investigating the role of iron in patients with NSTEMI. Our results showed a significant increase in serum levels of both free iron and ferritin in patients with NSTEMI. Free iron, through the Fenton reaction, is a very strong catalyst for the production of hydroxyl radicals (•OH), one of the most destructive reactive oxygen species.[33,34] The increase in free iron during ischemia could be due to its release from myoglobin and heme proteins in damaged cardiac cells. Free iron creates a vicious cycle in which initial oxidative stress leads to further iron release and more intense reactive oxygen species production.[35,36] Therefore, increased iron levels may promote ferroptosis pathways.

In addition, increased troponin I and creatine kinase–MB levels in the serum of patients with NSTEMI confirm myocardial damage.[37] Although linear regression analysis showed no statistically significant association between ferroptosis biomarkers (eg, LPO), iron metabolism markers (eg, ferritin, iron), or antioxidant markers (eg, TAC, superoxide dismutase, glutathione peroxidase) and troponin I or CK-MB levels, these pathways may still contribute to cardiac cell damage in patients with NSTEMI. Demographic data analysis revealed significant differences between the patients with NSTEMI and the control group.

The most striking difference was observed in smoking status, with the prevalence of smoking in the patient group (59.3%) being more than three times higher than in the control group (17.1%). This finding emphasizes the key role of smoking as a serious risk factor for MI in patients with ischemic heart disease. Cigarette smoke contains cytotoxic compounds that can induce oxidative stress and inflammation in cardiovascular cells. Extreme cell death, principally ferroptosis driven by reactive oxygen species and iron accumulation, contributes to cardiac damage.[38]

Although both groups were predominantly male, most participants in both groups (more than 80%) were aged 50 years or older, indicating that older age and male sex were prominent characteristics of the patients with NSTEMI. The slight increase in the percentage of women and people older than 50 years in the patient group compared with the control group is consistent with current knowledge about risk factors for MI.[39–42] Remarkably, ferroptosis has been linked to the initiation and progression of many age-related diseases and oxidative stress. Consequently, elucidation of ferroptosis pathways may suggest new therapeutic approaches for treating age-related diseases.[43]

This study has limitations, including the small sample size and the inability to follow up with patients or detect molecular markers related to ferroptosis pathways in blood samples. Further research is needed to better understand the underlying mechanisms of ferroptosis in the onset and progression of cardiovascular disease, particularly in patients with NSTEMI. We anticipate that this will lead to the development of more effective and suitable strategies for clinical treatment and prevention in the near future.

Conclusion

The results of this study suggest that oxidative stress, exacerbated by disrupted iron metabolism and ferroptosis, may play a key role in the pathophysiology of patients with NSTEMI. Our findings demonstrate impairment in both enzymatic and nonenzymatic antioxidant defenses, leading to extensive LPO and subsequent myocardial cell damage via ferroptosis pathways. These biochemical markers could serve as potential targets for new therapies, including antioxidants or iron chelators, aimed at improving cardiac injury in patients with NSTEMI.

Declarations:

Ethical Approval

All participants provided written informed consent prior to study participation, and the study protocol was approved by the ethics committee at Hamadan University of Medical Sciences (IR.UMSHA.REC.1402.408).

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Conflict of Interest

The authors declare that they have no competing interests.

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