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Association Between Circulating Oxidized LDL Cholesterol Levels and Premature Myocardial Infarction: A Case-Control Study

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Abstract

Background: Acute myocardial infarction (MI) occurs less frequently in younger individuals compared to older ones. The development of atherosclerotic plaque is primarily linked to oxidized low-density lipoprotein cholesterol (Ox-LDL).

Objectives: This study aimed to investigate circulating Ox-LDL levels in individuals with premature MI and compare them to controls without a history of ischemic heart disease.

Methods: In this case-control study, 35 patients who experienced a premature MI within 24 hours of symptom onset and met the age criteria (men ≤ 55 years and women ≤ 65 years) were recruited as cases. For comparison, 35 age and sex-matched individuals without a history of ischemic heart disease were selected as controls.

Results: Analysis of circulating Ox-LDL levels revealed a significant elevation in patients with premature MI compared to controls (2.25 ± 1.78 vs. 1.04 ± 1.17 µg/dL; P = 0.002). Elevated Ox-LDL levels were associated with a 1.70-fold increased risk of premature MI compared to healthy individuals (95% CI: 1.16 - 2.49; P = 0.007).

Conclusions: This study demonstrates an association between elevated Ox-LDL levels and premature MI, particularly in younger individuals. Measuring Ox-LDL levels may help predict heart attack risk, and interventions aimed at reducing these levels could potentially prevent atherosclerosis.

Keywords: Oxidized LDL, Myocardial Infarction, Premature, Cardiovascular Disease

1. Background

Acute coronary syndrome (ACS) is a clinical syndrome caused by the sudden onset of myocardial ischemia and is a major cause of morbidity and mortality worldwide (1, 2). In Iran, cardiovascular diseases have been reported to cause a mortality rate of 402.2 per 100,000 population (3). Although acute myocardial infarction (MI) occurs more frequently in older individuals, it can also affect younger populations (4). Several studies have shown varying frequencies of coronary artery disease (CAD) in younger individuals. One study found that the prevalence of CAD in people under 55 was 23.0% (5), while another reported frequencies of 26.3% for men and women under the ages of 55 and 65, respectively (6). The risk factors for premature CAD often differ from those in older adults (4).

Research has shown that Ox-LDL cholesterol (Ox-LDL) is closely linked to the development of atherosclerosis, starting with its role in causing endothelial injury (7). Oxidized low-density lipoprotein cholesterol is a modified form of low-density lipoprotein (LDL) cholesterol, which is responsible for transporting fats through the bloodstream. When LDL cholesterol undergoes oxidative stress, it transforms into Ox-LDL, which plays a pivotal role in the development of

atherosclerosis. The association between Ox-LDL and endothelial damage has been reinforced by findings showing that antioxidant substances can slow the progression of atherosclerosis (8). Oxidized low-density lipoprotein cholesterol triggers several inflammatory processes and contributes to atherosclerotic plaque formation (9). A higher concentration of Ox-LDL increases endothelial damage by promoting lipid infiltration into the arterial walls (10). Numerous studies have emphasized the critical role of Ox-LDL in atherosclerosis (11), ischemic cerebral infarction (12), ACS (13), CAD (14), and premature MI (15). Cheriyan et al. (16) demonstrated a positive association between serum Ox-LDL levels and CAD, showing elevated Ox-LDL levels in ACS patients compared to healthy individuals. Additionally, they found that Ox-LDL levels increased as the number of coronary artery stenoses increased (17). However, Wu et al. suggested through a predictive model that Ox-LDL may not be an independent prognostic factor for CAD (18). Ghosh et al. (19) also found no significant difference in serum Ox-LDL levels between CAD patients and controls.

2. Objectives

This study aims to investigate the association between serum Ox-LDL levels and premature acute myocardial infarction (AMI) in an Iranian population, focusing on whether elevated Ox-LDL levels are significantly associated with premature AMI.

The specific hypotheses include examining whether individuals with premature AMI exhibit higher Ox-LDL concentrations compared to age and sex-matched controls without a history of heart disease.

3. Methods

We conducted a case-control study to investigate the association between premature MI and various risk factors at Peymanieh Hospital's cardiac care unit in Jahrom, Iran. Using G*Power software and Cohen's criteria ($d = 0.7$, $\alpha = 0.05$, power = 0.80), we calculated the necessary sample size to be 35 individuals in each group.

We recruited 35 patients with premature MI as the case group and selected 35 age, sex, and smoking status-matched individuals without a history of heart disease as controls from Peymanieh Hospital. The exclusion criteria included individuals who had received chemotherapy, anti-inflammatory or mutagenic agents, were exposed to radiation, had malignant or inflammatory disorders, or were pregnant.

The diagnostic criteria for MI were based on the guidelines provided by the World Health Organization and were confirmed by a cardiologist. The diagnosis of acute MI was made based on the presence of at least two of the following three criteria: (1) characteristic chest pain lasting more than 30 minutes; (2) ST elevation greater than 0.1 mV in at least two contiguous electrocardiographic leads; (3) and an elevated troponin I level above the upper limit of normal.

Cases were selected to investigate specific risk factors associated with early-onset MI, which may differ from those that occur later in life. Controls were matched to the cases based on age, sex, and smoking status to ensure that any observed differences could be more confidently attributed to factors other than these variables. Matching on these factors minimized confounding, given their known influence on MI risk.

Each case was paired with a control who shared the same age (within a narrow range), sex, and smoking status (smoker or non-smoker). This method aimed to eliminate potential confounding from these factors, allowing for a more accurate assessment of other risk factors associated with premature MI. Controls were selected from the same hospital where the cases were identified, ensuring they were representative of the same population. Each control was screened to confirm the absence of heart disease through a review of their medical history and patient interviews.

Before data collection, participants from both study groups completed a structured questionnaire that gathered information on age, sex, family history of ischemic heart disease, cigarette smoking, and known histories of hypertension, diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia. Hypercholesterolemia was defined as a history of serum total cholesterol levels ≥ 200 mg/dL or the use of lipid-lowering drugs, based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines (20). Hypertriglyceridemia was defined as serum triglyceride levels ≥ 200 mg/dL or the use of lipid-lowering drugs, in line with the American Heart Association (AHA) scientific statement on triglyceride management (21). Diabetes mellitus and hypertension were defined as a history of elevated blood glucose or blood pressure or the use of glucose- or blood pressure-lowering medications.

To measure serum Ox-LDL levels, participants provided 3 mL of venous blood in EDTA tubes. The blood plasma was separated and stored at -70°C until analysis. Oxidized low-density lipoprotein cholesterol levels were measured using an enzyme-linked immunosorbent assay (ELISA) method with a commercial kit (Mercodia, Sweden).

Data were analyzed using SPSS version 16. Qualitative variables were expressed as frequencies and percentages, while quantitative variables were reported as mean ± standard deviation. The chi-square test was used to compare qualitative variables between groups, while independent Student's *t*-test, Fisher's exact test, and Mann-Whitney U-test were used for quantitative variables. Conditional logistic regression analysis was performed to assess the association between Ox-LDL levels and premature MI, with a P-value of less than 0.05 considered statistically significant. Missing data were handled using multiple imputation techniques.

The study adhered to ethical guidelines, including obtaining written informed consent from all participants. They were informed about the purpose of the study, potential risks and benefits, their right to withdraw at any time without penalty, and their right to access the study results. The study protocol was approved by the ethics committee at Jahrom University of Medical Sciences (IR.JUMS.REC.1390.015).

4. Results

Table 1 presents a comprehensive comparison of various variables between the premature MI cases and the control group. Demographic characteristics, such as age and sex, were comparable between the two groups, with mean ages of 46.29 years (SD 5.20) in premature MI cases and 47.23 years (SD 3.79) in controls. The distribution of sex was also similar, with 68.8% males in the premature MI group and 68.6% in the control group. No significant differences were observed in smoking status, family history of ischemic heart disease, or history of hypertriglyceridemia (P > 0.05).

Although the percentages of hypertension were higher in the premature MI group compared to the controls (22.9% vs. 11.4%, P = 0.205), and the prevalence of diabetes mellitus was greater in the premature MI group compared to controls (31.4% vs. 17.1%, P = 0.163), these differences were not statistically significant. The frequency of hypercholesterolemia was lower in the premature MI group than in controls, but the difference was not statistically significant. A notable finding was the significantly higher levels of circulating Ox-LDL in patients with premature MI compared to controls, showing a substantial difference of approximately 1.21 μg/mL (P = 0.002) (Table 1).

Conditional logistic regression analysis was conducted to evaluate the risk factors predicting premature MI (Table 2). The results indicated that family history of ischemic heart disease (adjusted odds ratio [OR] = 0.95; 95% confidence interval [CI] = 0.30 - 3.01; P = 0.943) and history of diabetes mellitus (adjusted OR = 3.11; CI = 0.55-17.50; P = 0.198) were not significantly associated with the occurrence of premature MI. Similarly, a history of hypertension (adjusted OR = 1.82; CI = 0.37 - 8.99; P = 0.461), hypertriglyceridemia (adjusted OR = 1.70; CI = 0.34-8.48; P = 0.517), hypercholesterolemia (adjusted OR = 1.24; CI = 0.25 - 6.11; P = 0.791), and past medical history (adjusted OR = 1.65; CI = 0.24 - 11.42; P = 0.609) were not significantly associated with premature MI. On the other hand, oxidized LDL levels were identified as the only significant variable associated with premature MI (adjusted OR = 1.70; CI = 1.16 - 2.49; P = 0.007) (Table 2).

5. Discussion

The results of this study indicate that smoking, family history of ischemic heart disease, diabetes mellitus, hypertension, hypertriglyceridemia, hypercholesterolemia, and past medical history did not significantly differ between the premature MI and control groups. However, elevated levels of Ox-LDL were identified in patients with premature MI compared to control subjects without heart disease. The serum level of Ox-LDL emerged as a crucial factor in the development of early MI.

Goliasch et al. found that higher levels of total cholesterol and triglycerides were associated with an increased risk of premature MI in individuals aged 40 or younger (22). Similarly, a study of patients with acute MI under 45 showed significantly higher serum triglyceride levels than healthy controls, while the total cholesterol levels were similar between the two groups (23). Furthermore, dyslipidemia was identified as a risk factor for premature MI in another study (24).

This study has highlighted a notable correlation between circulating levels of Ox-LDL and premature MI. This finding is consistent with research conducted by Sartore et al., which revealed significantly higher levels

Table 1. Comparative Analysis of Variables Between the Patient and Control Groups in the Study [a, b, c, d]

Study Groups and Category	Premature MI	Controls	P-Value
Age (y)			0.389 [b]
NA	46.29 ± 5.20	47.23 ± 3.79	
Gender			0.999 [c]
Male	24 (68.8)	24 (68.6)	
Female	11 (31.4)	11 (31.4)	
Family history CAD			0.631 [c]
Yes	20 (57.1)	18 (51.4)	
No	15 (42.9)	17 (48.6)	
Smoking			0.999 [c]
Yes	14 (40.0)	14 (40.0)	
No	21 (60)	21 (60)	
Hypertension			0.205 [c]
Yes	8 (22.9)	4 (11.4)	
No	27 (77.1)	31 (88.6)	
Diabetes mellitus			0.163 [c]
Yes	11 (31.4)	6 (17.1)	
No	24 (68.6)	29 (82.9)	
Hypertriglyceridemia			0.788 [c]
Yes	10 (28.6)	9 (25.7)	
No	25 (71.4)	26 (74.3)	
Hypercholesterolemia			0.420 [c]
Yes	8 (22.9)	11 (31.4)	
No	27 (77.1)	24 (68.6)	
Past Medical history			0.569 [c]
Yes	28 (80)	26 (74.3)	
No	7 (20)	9 (25.7)	
Number of diseases			0.723 [c]
No	7 (20.0)	9 (25.7)	
One	22 (62.9)	22 (62.9)	
>1	6 (17.1)	4 (11.4)	
Oxidized LDL, μg/mL			0.002 [d]
NA	2.25 ± 1.78	1.04 ± 1.17	

Abbreviations: CAD, coronary artery disease; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; SD, standard deviation; NA, not applicable.

[a] Values are expressed as No. (%) or mean ± SD.

[b] Independent *t*-test.

[c] Chi-square test.

[d] Mann-Whitney U-test, significance level < 0.05.

of serum oxidized Apo-lipoprotein AI in premature MI patients compared to controls (23). Cheriyan et al. also demonstrated elevated serum Ox-LDL levels in patients with ACS compared to healthy controls (16). Several studies have established a strong positive association between circulating Ox-LDL levels and the extent of coronary artery involvement, particularly in individuals aged 60 years or younger (17, 25). These findings suggest that the number of coronary artery involvements is correlated with elevated Ox-LDL levels. However, Ghosh et al. (19) reported a non-significant difference in circulating Ox-LDL levels between CAD cases and controls.

In addition to Ox-LDL, several other factors have been linked to premature MI, including fibrinogen (26), metabolic syndrome (27), remnant cholesterol (22), and

Table 2. Conditional Logistic Regression Analysis of Risk Factors Predicting Premature Myocardial Infarction

Variables	Univariate Conditional Logistic Regression		Multiple Conditional Logistic Regression	
	Crude Odds Ratio (OR)	P-Value	Adjusted OR (95%CI)	P-Value
Family history of ischemic heart disease/ yes vs. no	1.29 (0.41 - 3.14)	0.541	0.95 (0.30 - 3.01)	0.943
History of diabetes mellitus/ yes vs. no	2.21 (0.71 - 6.87)	0.171	3.11 (0.55 - 17.50)	0.198
History of hypertension/ yes vs. no	2.37 (0.62 - 8.48)	0.212	1.82 (0.37 - 8.99)	0.461
History of Hypertriglyceridemia/ yes vs. no	1. 17 (0.37 - 3.21)	0.788	1.70 (0.34 - 8.48)	0.517
History of hypercholesterolemia/ yes vs. no	0.64 (0.22 - 1.87)	0.422	1.24 (0.25 - 6.11)	0.791
History of past medical history/ yes vs. no	1.38 (0.45 - 4.25)	0.570	1.65 (0.24 - 11.42)	0.609
Ox-LDL	1.73 (1.19 - 2.51)	0.003	1.70 (1.16 - 2.49)	0.007

Abbreviations: CI, Confidence Interval; OR, Odds Ratio; MI, myocardial infarction; Ox-LDL, oxidized low-density lipoprotein cholesterol.

Apo A1 (23). The multifaceted nature of these associations underscores the complex interplay of various factors in the pathogenesis of premature MI. Further research is warranted to explore these complex relationships and the role of Ox-LDL and other contributing factors in premature MI.

One study has shown that apolipoprotein A-1 (Apo A-1), the major protein component of high-density lipoprotein (HDL), plays a crucial role in inhibiting low-density lipoprotein (LDL) oxidation (28). Therefore, low levels of HDL cholesterol combined with low levels of Apo A-1 may increase susceptibility to LDL oxidation. These findings further suggest that low levels of HDL cholesterol and Apo A-1 may be associated with an increased risk of CAD. Furthermore, Ox-LDL has been found to induce the activation and production of various factors, including macrophages and prostaglandins, which contribute to the destruction of fibrous plaques. In endothelial cells, Ox-LDL uptake by macrophages leads to the formation of foam cells, which contribute to the development of atherosclerotic plaques. Damage to the vascular endothelium by Ox-LDL is a key mechanism in the development of atherosclerosis.

This study has several limitations that must be considered when interpreting the results. Firstly, the sample size was relatively small, which may limit the generalizability of the findings to other populations. Secondly, the study exclusively measured Ox-LDL levels at a single point in time, which might not fully capture the dynamic changes in Ox-LDL levels over an extended period. Ox-LDL levels can be influenced by various factors, and a single measurement may not reflect the fluctuations that could occur over time. This limitation underscores the need for future studies with larger and more diverse samples, as well as longitudinal designs, to provide a more comprehensive understanding of the relationship between Ox-LDL levels and the risk of premature MI.

In conclusion, this study has established a meaningful association between Ox-LDL levels and premature MI, indicating that assessing circulating Ox-LDL levels could potentially serve as a promising biomarker for identifying young patients at an elevated risk of experiencing premature MI. These findings hold significant implications for clinical practice, offering a potential avenue for early risk stratification in young individuals. Implementing such biomarker assessments could lead to improved patient outcomes by enabling timely interventions and preventive measures, ultimately contributing to the reduction of the cardiovascular disease burden in younger populations.

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Footnotes

Authors' Contribution: K. R. contributed to this work in various ways. V. R. and M. Sh. designed and conducted the study, collected and analyzed the data, and wrote the initial draft of the manuscript. V. R. and F. H. were

responsible for the literature search and screening. V. R. and K. R. contributed to the interpretation and reviewed and edited the manuscript. N. S. H. and M. Sh. helped with data collection and reviewed the manuscript. All authors have read and approved the final version of the manuscript.

Conflict of Interests Statement: The authors state that they have no conflicts of interest.

Data Availability: The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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