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Serum level of IL-37 as a modulator in atherosclerosis, correlating its levels with oxidative stress and disease progression

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Atherosclerosis is a disease where fat, fibrous materials, and calcium build up in the large arteries. This harmful process starts when the inner lining of blood vessels becomes active. This leads to a chain of reactions that cause the blood vessels to narrow and trigger inflammation, eventually resulting in the formation of fatty deposits called atheromatous plaques. Together, these related processes lead to heart problems, which are the main cause of death around the world. The aim of this research is to elucidate the function of IL-37 as a modulator in the pathophysiology of atherosclerosis through an examination of its association with oxidative stress and the advancement of the disease. This case-control investigation endeavors to quantify IL-37 concentrations in individuals diagnosed with atherosclerosis in comparison to healthy control subjects, thereby evaluating its viability as a biomarker indicative of disease severity and its correlation with markers of oxidative stress. This investigation encompassed a cohort of 50 individuals receiving treatment at the Al-Najaf Center for Cardiac Surgery and Catheter Intervention located in Al-Najaf Province, Iraq. A volume of 5 mL of venous blood was procured from each participant, with serum being promptly isolated and subsequently preserved at –80 °C. The concentrations of serum IL37 and TNF-α were quantified employing a human IL37 & TNF-α ELISA kit. The findings demonstrated that, in comparison to control, atherosclerosis patients had significantly higher levels of biochemical variables such as CK-MB, Trop I, MDA, Ox-LDL, and hs-CRP. IL37 and TNF-α mean values showed that patients' levels of IL37 were significantly lower than those of the control group, while TNF-α levels were significantly higher. According to Pearson correlation, there was a significant negative connection between IL37 and TNF-a, MDA, Ox-LDL, RBS, TC, LDL, urea, CK-MB, TropI, and hs-CRP, whereas there was a negative nonsignificant correlation between IL37 and TG and creatinine. In conclusion, research on the function of IL-37 as a modulator in atherosclerosis has shown significant relationships between oxidative stress, IL-37 levels, and the development of the disease.

Keywords: atherosclerosis; IL37; TNF-a; oxidative stress.

Introduction

Atherosclerosis is a chronic inflammatory condition that causes atherosclerotic plaques to develop in the major arteries due to the accumulation of fibrous and lipid-based components (Jebari-Benslaiman et al., 2022). A complex interplay between immunological reactions, oxidative damage, and inflammatory substances characterizes the progression of atherosclerosis (Naseem et al., 2024). Considered a member of the interleukin-1 family, interleukin-37 (IL-37) has attracted a lot of attention because of its strong anti-inflammatory and immunosuppressive properties (Li et al., 2022). Compared to other pro-inflammatory cytokines, interleukin-37 functions as an intrinsic immune-suppressive agent, making it a potential regulator of chronic inflammatory diseases like atherosclerosis (Cruz-Gregorio et al., 2024). IL-37 is produced by many immune and non-immune cells, including macrophages, dendritic cells, and epithelial cells (Rudloff et al., 2017). It is crucial for downregulating inflammatory cytokines like IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α), as well as for preventing the triggering of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, which are vital to the inflammatory reactions associated with atherosclerosis (Nold-Petry et al., 2015). In addition, hydroxytyrosol and oleuropein, two components of olive oil, may prevent LDL cholesterol, which is a major cause of atherosclerosis, stroke, and heart attacks (Neamah et al., 2024). Such anti-inflammatory characteristics suggest that IL-37 might prevent atherosclerosis by lowering vascular inflammation, which is a key contributor to the formation of plaque and the progression of the condition. Oxidative damage is another essential aspect of the pathogenesis of atherosclerosis, resulting in lipid peroxidation, endothelial dysfunction, and the start of inflammatory pathways (Salekeen et al., 2022). An imbalance between antioxidant defenses and reactive oxygen species (ROS) formation leads to oxidative damage to cellular components and intensifies the inflammatory response in atherosclerotic lesions (Aranda-Rivera et al., 2022). Interestingly, it has been shown that IL-37 reduces oxidative stress by increasing the amount of antioxidant enzymes such as catalase and superoxide dismutase (SOD) and lowering ROS production (Faris et al., 2019; Jomova et al., 2023). In light of its dual function in lowering inflammation and oxidative stress, IL-37 is an essential regulator of atherosclerosis progression (Su & Tao, 2021). Numerous studies have demonstrated a negative correlation between the severity of atherosclerosis and IL-37 levels, suggesting that higher IL-37 levels may provide defense against the disease. For instance, those who have chronic atherosclerosis were found to possess lower amounts of blood IL-37, which is linked to a larger plaque burden and more oxidative stress (Al-Gazally et al., 2016; Law et al., 2021). These findings suggest IL-37 as a potential biomarker for oxidative stress and atherosclerosis progression, providing a novel therapeutic target.

Materials and methods

The study comprised 50 individuals from the Al-Najaf Center for Cardiac Surgery and Catheter Intervention in the Al-Najaf Province of Iraq. Additionally, blood from patients who were hospitalized to the private cardiac clinics and who had received a diagnosis from a cardiologist was obtained during September and January 2025. The patient choice process was guided by the finding of a cardiologist based on angiography. 50 healthy controls were additionally enrolled in this study. Additionally, anthropometric data such as height, weight, body mass index (BMI), diastolic blood pressure (DBP), and

systolic blood pressure (SBP) were recorded. The BMI was computed using weight/height^2 (kg/m^2). Following fifteen minutes of sitting, blood pressure was taken according with standard protocol.

The serum was immediately separated and stored at –80 °C after 5 mL of venous blood was extracted from each subject. Using the Beckman Coulter (AU400), a fully automated chemical analyzer (Beckman Coulter, USA), the following biochemical markers were measured; blood glucose (BG), urea, creatinine, triglycerides (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C). A completely automated analyzer (Biorex Diagnostics, UK) was used to measure the levels of troponin I and creatine kinase-myocardial band. An ELISA kit from (Elabscience, USA) was used to determine the levels of Ox-LDL, MDA, and hs-CRP. The sensitivity and accuracy of this method were greater (Catalog No.: E-EL-H6021, E-EL-0060, and E-EL-H5134, separately). The procedure to acquire these sections is detailed in research (Ranin & Ekhlas, 2024).

The blood IL37 level was measured using a human IL37 ELISA kit (Cat. No.: E-EL-H2571, Elabscience, USA). According to the instructions included with the product, the kit's sensitivity was 9.38 pg/mL and its detection range was 15.63–1000 pg/mL. A Biotex (USA) ELISA reader was used to measure the absorbance at 450 nm. The Human TNF-a ELISA kit (Catalog No: E-EL-H0109, Elabscience, USA) was used to measure TNF-α levels in the blood.

Data from participants with and without atherosclerosis were entered, arranged, and examined using IBM's 2017 SPSS version 25 software for Windows. Prior to analysis, every variable was examined for errors and discrepancies. The significance of differences in categorical variable frequencies across study groups was assessed using the chi-square test. The study evaluated the averages of creatinine, HDL, LDL, urea, BMI, SBP, DBP, glucose, TC, TG, and BMI using an independent t-test. A t-test was also used to compare the patient and control groups' levels of IL37, TNF-α, CK-MB, Troponin-I, MDA, ox-LDL, and hsCRP parameters. Additionally, we computed the Pearson correlation between the variables being examined. P-values were considered significant if they were 0.05 or less.

Results

The results in Table 1 demonstrated that the mean of the study variables, including age, BMI, SBP, DBP, glucose, TC, TG, LDL, urea, and creatinine, were significantly ($P < 0.001$) different in atherosclerosis patients than in the control group. In contrast, the mean HDL levels of the patients were considerably lower than those of the control group. Furthermore, the findings demonstrated a significant difference between the male and female patients relative to the control group, with 34 (68.0%) and 16 (32.0%), accordingly.

Table 1
Features of study population (mean ± SD, n = 50)

Variables		Patients	Control	Statistical test	P
Age, years		63.6 ± 10.7	58.6 ± 8.9	t = 11.02	<0.001†
BMI, kg/m^2		27.5 ± 2.3	25.6 ± 1.9	t = 4.87	<0.001†
Sex	Male, *n* (%)	34 (68.0%)	36 (72.0%)	$\chi^2 = 5.37$	<0.001
	Female, *n* (%)	16 (32.0%)	14 (28.0%)		
SBP, mm/Hg		127.7 ± 14.3	123.2 ± 11.3	t = 3.54	<0.001†
DBP, mm/Hg		78.0 ± 13.6	75.2 ± 9.1	t = 4.88	<0.001†
Glucose, mg/dL		150.2 ± 37.4	94.5 ± 7.8	t = 10.29	<0.001†
Cholesterol, mg/dL		184.5 ± 30.4	139.7 ± 13.5	t = 9.51	<0.001†
TG, mg/dL		164.4 ± 54.9	130.4 ± 35.4	t = 3.68	<0.001†
HDL, mg/dL		39.7 ± 7.5	45.5 ± 7.4	t = 3.88	<0.001†
LDL, mg/dL		80.53 ± 13.5	52.1 ± 8.6	t = 8.13	<0.001†
Urea, mg/dL		32.77 ± 9.9	21.8 ± 4.7	t = 7.04	<0.001†
Creatinine, mg/dL		1.17 ± 0.97	0.88 ± 0.12	t = 1.62	0.107

Notes: SD – standard deviation; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; TG – triglyceride; HDL – high density lipoprotein; LDL – low density lipoprotein; t – independent test; ¥ – chi-square test; P < 0.05 considered statistically significant.

Biochemical variables, including CK-MB, Trop I, MDA, Ox-LDL, and hs-CRP, were considerably greater in the atherosclerosis patients than in the control, as indicated by Table 2.

Table 2
Serum level of biochemical variables among patients and control groups (mean ± SD)

Biochemical variables	Control	Patients	Statistical evaluation	
			t	P
CK-MB, IU/L	6.01 ± 0.71	20.4 ± 5.3	18.93	<0.001†
Troponin, ng/L	70.6 ± 18.7	118.4 ± 52.5	6.05	<0.001†
MDA, µmol/L	3.34 ± 0.41	5.96 ± 0.78	20.96	<0.001†
Ox-LDL, pg/mL	1.73 ± 1.04	6.93 ± 2.30	14.10	<0.001†
hs-CRP, mg/L	2.03 ± 0.93	8.01 ± 3.06	12.95	<0.001†

Notes: SD – standard deviation; CK-MB – creatine kinase-myocardial band; MDA – malondialdehyde; ox-LDL – oxidized low-density lipoprotein; hsCRP – high sensitive C-reactive protein; t – independent test; P < 0.05 considered statistically significant.

The average levels of TNF-α and IL37 are displayed in Table 3, which also demonstrates that while IL37 levels were dramatically lowered in comparison to control, TNF-α levels in patients markedly rose. Figures 1 and 2 also illustrate same outcomes.

TNF-a, MDA, Ox-LDL, RBS, TC, LDL, urea, CK-MB, TropI, and hs-CRP were all significantly correlated negatively with IL37, but TG and creatinine were negatively correlated but not significantly correlated with IL37 (Table 4). A Pearson correlation analysis was used to assess the relationship between the factors being examined. TNF-a showed a strong positive connection with MDA and ox-LDL.

Table 3
Concentration of IL37 and TNF-α among atherosclerosis patients in comparison with healthy control (mean ± SD)

Inflammatory markers	Control	Patients	Statistical evaluation	
			t	P
IL37, pg/mL	108.8 ± 39.6	78.5 ± 14.7	5.059	<0.001†
TNF-α, pg/mL	22.6 ± 4.0	80.5 ± 16.1	24.73	<0.001†

Notes: SD – standard deviation; IL37 – interleukin-37; TNF-α – tumor necrosis factor-alpha; t – independent test; P < 0.05 considered statistically significant.

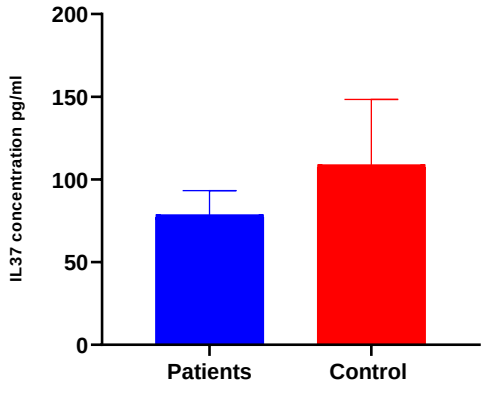

Fig. 1. Level of IL37 among atherosclerosis patients in comparison with control

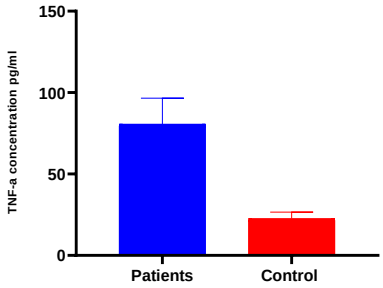

Fig. 2. Level of TNF-α among atherosclerosis patients in comparison with control

Table 4
Correlation between study variables

Variables	IL37		TNF-α		MDA		ox-LDL	
	R	P	R	P	R	P	R	P
IL37	1	0	–0.433	0.001	–0.471	0.001	–0.429	0.001
TNF-α	–0.433	0.001	1	0	0.827	0.001	0.763	0.001
MDA	–0.471	0.001	0.827	0.001	1	0	0.729	0.001
ox-LDL	–0.429	0.001	0.763	0.001	0.729	0.001	1	0
Glucose	–0.282	0.005	0.662	0.001	0.616	0.001	0.599	0.001
TC	–0.386	0.002	0.554	0.001	0.643	0.001	0.589	0.001
TG	–0.082	0.420	0.299	0.003	0.312	0.002	0.380	0.001
HDL	0.210	0.036	–0.321	0.001	–0.322	0.001	–0.318	0.001
LDL	–0.365	0.001	0.600	0.001	0.553	0.001	0.555	0.001
Urea	–0.285	0.004	0.462	0.001	0.577	0.001	0.477	0.001
Creatinine	–0.091	0.367	0.188	0.061	0.141	0.161	0.194	0.053
CK-MB	–0.409	0.001	0.849	0.001	0.768	0.001	0.787	0.001
Troponin	–0.246	0.014	0.565	0.001	0.463	0.001	0.334	0.001
hs-CRP	–0.348	0.001	0.732	0.001	0.696	0.001	0.623	0.001

Notes: R – Pearson correlation; correlation is significant at the $P < 0.05$ level (2-tailed); correlation is highly significant at the $P < 0.001$ level (2-tailed).

Discussion

Formation of plaque in arterial walls is a symptom of atherosclerosis, a condition whose severity and progression are significantly impacted by age. Numerous age-related biochemical changes increase the risk of cardiovascular diseases in older adults, according to research. Increased oxidative stress, inflammation, and altered immunological function are some of the alterations that promote the establishment of atherosclerosis (Tyrrell & Goldstein, 2021). Atherosclerosis develops because of increased oxidative stress and inflammation, both of which are associated with the elderly (Poznyak et al., 2024). The aging process causes abdominal fat to become more inflamed, which increases the production of inflammatory molecules that promote plaque formation and monocyte chemotaxis, accelerating atherosclerosis (Song et al., 2023). Compared to the controls, the mean BMI of the patients in this study was significantly elevated. The complex and multifaceted relationship between atherosclerosis and body mass index (BMI) has varying impacts on cardiovascular health. Growth and development can increase the rate and the chance of survival even after puberty .According to studies, elevated body mass index (BMI) is often associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD), even though lifestyle and metabolic health are also significant factors of this risk (Held et al., 2022). A cohort study found that those with a BMI of greater than 30 kg/m² had a much reduced prevalence of significant coronary artery plaque (Venuraju et al., 2022). Patients with atherosclerosis had higher blood levels of glucose and lipids than healthy controls ($P < 0.001$). There is a favorable correlation between the risk of atherosclerosis and elevated blood glucose, cholesterol, and BMI (Jin et al., 2024). Therefore, managing metabolic parameters may be more crucial than focusing just on weight. Raised TC and LDL values are strongly associated with an increased risk of atherosclerosis. The mean TC levels were 174.2 mg/dL in healthy people and 254.23 mg/dL in CAD patients (Verma et al., 2016). The necessity of maintaining a balanced lipid profile is highlighted by the negative correlation between low HDL levels and the risk of atherosclerosis (Gaggini et al., 2022). The level of cardiac enzyme CK-MB rises when myocardial injury occurs. Studies showed that compared to healthy controls, CK-MB levels were significantly greater in individuals with acute coronary syndrome (ACS). Moreover, troponin I is an extremely accurate marker of heart injury. Research indicates significant differences in levels between controls and patients who have experienced an acute myocardial infarction (AMI), with AMI cases often having elevated levels (Biasillo et al., 2016). The systemic index of inflammation, hs-CRP, was significantly greater in CAD patients than in controls (Rathore et al., 2016). Due to their association with the progression of coronary artery disease (CAD), malondialdehyde (MDA) and oxidized low-density lipoprotein (ox-LDL) levels are strongly associated in people with atherosclerosis (Hou et al.,2020). In individuals with CAD, elevated MDA levels, a byproduct of lipid peroxidation, are linked to cardiovascular events and hardened arteries (Hung et al., 2023). Additionally, it is well recognized that Ox-LDL speeds up the development of plaque and inflammation, two processes that are crucial in the development of atherosclerosis (Poznyak et al., 2021). As indicators for assessing cardiovascular risk and disease progression, MDA and ox-LDL may be helpful in clinical settings for assessing atherosclerosis (Khaki-Khatibi & Mahmoodi, 2016). The results showed that the mean IL37 levels in the atherosclerosis patients were decreased compared with those in the matched control group. According to research, CAD patients' blood IL-37 levels were much lower than those of healthy controls, this might indicate a protective impact towards inflammatory processes (Rafiei et al., 2022). Conversely, elevated IL-37 levels have been associated with the development of substantial coronary artery calcification, indicating a complex role in inflammation and the progression of the disease (Chai et al., 2017). Higher TNF-α levels are typically seen in atherosclerosis, which exacerbates the inflammatory environment. In individuals with CAD, TNF-α levels are closely linked to the degree of pollution and inflammatory responses (Li et al., 2020). Through its control of macrophage division, which decreases TNF-α expression and promotes an anti-inflammatory environment, IL-37 may impede the prevention of atherosclerosis (Huang et al., 2016). Our results confirmed that lower levels of IL-37 attention and better blood levels of total cholesterol, TG, LDL-C, hs-CRP, ox-LDL, and MDA were associated with atherosclerotic patients. Important information about the inflammatory pathways behind atherosclerosis can be obtained from the association between oxidative stress and IL-37 levels in patients (Marza et al., 2020). According to studies, those with coronary artery disease (CAD), a common indicator of atherosclerosis, had lower blood levels of IL-37 than healthy controls. Malondialdehyde and ox-LDL, two inflammatory markers, and oxidative pressure are adversely connected with this decrease, suggesting that IL-37 may also protect against oxidative damage in atherosclerosis (Rafiei et al., 2022). The production of GPX4 and enhanced antioxidant responses by IL-37 have been demonstrated to be essential for lowering oxidative stress in macrophages (Xu et al., 2023). The protective role of interleukin-37 (IL-37) against atherosclerosis has become increasingly recognized, particularly because of its anti-inflammatory and immunoregulatory properties. The capacity of IL-37 to suppress macrophage ferroptosis, reduce plaque formation, and improve plaque stability makes it a potential therapeutic target for atherosclerotic diseases (Cruz-Gregorio et al., 2024).

Conclusion

The findings of the study on the modulation role of IL-37 in atherosclerosis indicate that oxidative stress, IL-37 levels, and the progression of the disease are significantly correlated. The prospect of IL-37 as a biomarker for the severity of atherosclerosis and prospective therapeutic possibilities is demonstrated by this study. More research is needed to fully comprehend the role of IL-37 in atherosclerotic processes and determine whether it might be a target for novel treatment strategies. Understanding the relationship between oxidative stress, IL-37, and the appearance of atherosclerosis should lead to improved diagnostic techniques and more effective therapies for this prevalent cardiovascular disease.

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