Kerbala Journal of Pharmaceutical Sciences

ISSN: 2221-7207(Print) / **ISSN**: 3006-7189 (Online)

Study the Correlation of Sirtuin–1 with OX–LDL in Iraqi Men with Atherosclerosis

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Received: 12/02/2026
Accepted: 06/04/2026
Published: 30/06/2026

Keywords: Atherosclerosis, Sirtuin-1, ox-LDL, Cardiac Troponin I, Cardiovascular diseases.

DOI:10.62472/kjps.v17.i28.433-444

Abstract

Background: Atherosclerosis (AS) is a chronic inflammatory disease and one of the leading causes of mortality in Iraq. AS a condition where fatty deposits and cholesterol accumulate on the walls of blood vessels. The main goal of this paper is to determine the link between Sirtuin-1 (SIRT-1) and oxidized low-density lipoprotein (ox-LDL) in AS patients and to determine the bio-roles of Sirtuin-1 and ox-LDL in Iraqi patients with AS.

Patients and methods: The study was performed in Al-Fallujah Teaching Hospital on 42 patients and 42 healthy individuals. Serum levels of sirtuin-1 and ox-LDL were estimated by enzyme linked immune sorbent assay (ELISA), while other parameters were determined by colorimetric enzymatic methods.

Results: The data of the present paper showed a significant decrease in serum SIRT-1 levels in AS patients compared to healthy individuals', but serum ox-LDL levels showed a significant increase in AS patients compared to healthy group in ($p<0.0001$), the study showed good correlation of SIRT–1 with OX–LDL and cTnI ($r = -0.497$, $p< 0.0001$ and $r= -0.451$ $p < 0.0001$) respectively, also, the results showed a weak association of SIRT-1with BMI ($r = -0.253$, $p = 0.020$). There is no noticeable effect of SIRT-1 on age ($r = -0.094$, $p = 0.395$). Receiver operator characteristic (ROC) curve showing the following results of SIRT-1 and ox-LDL (AUC=0.879, COF=>85.10, SEN٪= 80.95, SPES٪=78.57) and (AUC=0.957, COF=<156.9, SEN٪=90.48, SPES٪=88.10) respectively. This study concluded that high serum ox-LDL levels and low serum SIRT-1 levels may lead to AS disease in Iraqi men; serum levels of ox-LDL may serve as an excellent biomarker to predict a diagnosis of AS disease.

Conclusion: Atherosclerosis patients show higher serum ox-LDL levels and lower SIRT1 levels than HCs. The negative relationship between ox-LDL and SIRT1 suggests a new bio-role for SIRT1 as an acetyl group scavenger from LDL, which reduces AS development and prognosis in Iraqi men. SIRT1 Serum levels may serve as excellent parameters in predicting and diagnosing CVD and atherosclerosis.

دراسة العلاقة بين سيرتوين-1 وox-LDL لدى الرجال العراقيين المصابين بتصلب الشرايين.

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الخلاصة:

المقدمة: يُعدّ تصلب الشرايين مرضًا التهابيًا مزمنا، وأحد الأسباب الرئيسية للوفاة في العراق. وهو حالة تتراكم فيها الدهون والكوليسترول على جدران الأوعية الدموية. يهدف هذا البحث إلى تحديد العلاقة بين سيرتوين-1(SIRT-1) الدهني منخفض الكثافة المؤكسد(ox-LDL) لدى مرضى تصلب الشرايين، وتحديد الأدوار البيولوجية لكل من سيرتوين-1 و OX-LDLلدى المرضى العراقيين المصابين بهذا المرض.

المرضى وطرق العمل: أجريت الدراسة في مستشفى الفلوجة التعليمي على 42 مريضًا و42 شخصًا سليمًا، وتم تقدير مستويات السيرتوين-1 وOx-LDL في مصل الدم باستخدام مقايسة الامتصاص المناعي المرتبط بالإنزيم (ELISA)، بينما تم تحديد المعايير الأخرى باستخدام الطرق الإنزيمية اللونية، تم إجراء مجموعة من التحاليل الكيميائية، تروبونين، سيرتوين-1 ، البروتين الدهني منخفض الكثافة المؤكسد وحسابات BMI للتصنيف في مجموعات الوزن.

النتائج: ظهرت بيانات هذه الدراسة انخفاضًا. ملحوظًا في مستويات SIRT-1 في مصل الدم لدى مرضى تصلب الشرايين مقارنةً بالأفراد الأصحاء، بينما أظهرت مستويات OX-LDL في مصل الدم ارتفاعًا ملحوظًا لدى مرضى تصلب الشرايين مقارنةً بالمجموعة الصحية لخصت هذا الدراسة الى ان ارتفاع مستويات OX-LDL وانخفاض مستويات SIRT-1 في مصل الدم قد يؤديان الى الإصابة بمرض تصلب الشرايين لدى الرجال العراقيين وان مستويات OX-LDL في مصل الدم قد تستخدم كمؤشر حيوي ممتاز للتنبؤ بمرض تصلب الشرايين.

الاستنتاج: يظهر مرضى تصلب الشرايين مستويات أعلى من OX-LDLفي المصل ومستويات أقل من SIRT1 مقارنة بالأشخاص الأصحاء. تشير العلاقة السلبية بين OX-LDLوSIRT1 إلى دور بيولوجي جديد لـ SIRT1 كعامل scavenger لمجموعة الأسيتيل من LDL، مما يقلل من تطور تصلب الشرايين وتوقعاته لدى الرجال العراقيين. قد تكون مستويات SIRT1 في المصل مؤشرات ممتازة في التنبؤ وتشخيص أمراض القلب والأوعية الدموية وتصلب الشرايين

1. Introduction

Atherosclerosis is the thickening of the artery wall due to the accumulation of non-fatty components and cholesterol and is the primary cause of most cardiovascular diseases (Itabe and Obama, 2023). It occurs as a result of complex interactions between endothelial cells, fats, and inflammatory markers. AS Plaques can be classified as unstable or stable based on their composition and structure. Often, the basic criterion for simplifying the concept of plaque stability and unstableness involves the presence of a thin fibrous coating of extracellular matrix (ECM) encapsulated within smooth muscle cells (SMCs) with an inflamed, lipid-rich nucleus (Papatriantafyllou,2013). Risk factors for AS are more likely to develop middle cerebral artery aneurysms (Ekholm et.al., 2024). Some studies have shown that AT1 receptor blockers, peroxisome proliferator-activated receptor gamma (PPAR-γ) receptor blockers, angiotensin-converting enzyme inhibitors, erythropoietin, and statins significantly increase the bodily functions of Endothelial Progenitor Cells (EPCs) (Besler et.al.,2008). Many Iraqi studies deal with Iraqi men with inflammatory diseases (AL-Rawi et.al., 2022; Alaaraji,2019), but this data was studied new inflammatory parameters in atherosclerosis. Sirtuin-1 plays a crucial role in the function of endothelial cells by controlling various aforementioned factors at the biochemical and genetic levels, and by reducing cellular aging and inflammation, SIRT1 can inhibit cellular degeneration by removing the acetylated p53 protein, thereby reducing its activity during DNA damage or oxidative stress, which leads to a reduction in programmed cell death. (Hashimova et.al., 2025). SIRT1 controls cholesterol production in the liver, which plays a key role in reducing serum lipid levels (Elmorsy et.al., 2025). These effects are related to the fact that SIRT1 positively regulates hepatic receptor X proteins, which are important regulatory factors for cholesterol, glucose, and fatty acid metabolism (Fischer et.al.,2025). SIRT-1 expression and regulation are influenced by several inhibitors and inducers acting at post-transcriptional and transcriptional levels, and it includes the control of inflammatory pathways that produce the cascade leading to plaque, regulated in expression by multiple upstream activators and suppressors at transcriptional/post-transcriptional levels. This is mediated by the modulation of inflammation, and more specifically, the inflammatory pathways resulting in a cascade leading to plaque destabilization. It also does not include the sirtuins role in the reduction of pro-inflammatory mediators (Wang et.al.,2025). Injury transmitted through AS or vascular intervention during arterial occlusion leads to the release of risky genetic constructs that activate inflammatory pathways by stimulating toll-like receptors (TLRs) and receptor-advanced glycosylated end products (RAGEs), resulting in an immune response that includes increased recruitment of adaptive and innate immune cells, ganglion-like receptor family, and the release of pro-inflammatory cytokines (Zhang et.al.,2024). A family of NOD-like receptors containing the pirin domain 3 (NLRP3) is pro-inflammatory; these factors lead to persistent inflammation in plague and cause weakness. Damage to the inner layer leads to vascular dysfunction, resulting in oxygen deficiency and

oxidative stress, which, in turn, stimulates sirtuins. Increased sirtuins work to repair oxidative damage, leading to a reduction in oxygen radicals and oxidative stress. This, in turn, weakens plaque formation through their biological effects, including deacetylation of various proteins, modifications, and post-translational processes (Yang et.al.,2022). A recent study found that SIRT-1 decreased in patients AS (Xu et.al.,2024). New studies have shown high levels of bad cholesterol in the blood of patients with ankylosing spondylitis. The loss of electrons in LDL is one consequence of changes in the production of antioxidant and oxidant systems; ox-LDL cholesterol is obtained from common LDL. It may include byproducts generated from the breakdown of the LDL molecule, such as peroxides, or from other locations in the body associated with the particle (Li et.al., 2020; Klisic et.al., 2024). This is formed by the oxidation of LDL cholesterol, which contributes to endothelial dysfunction and promotes inflammatory pathways. Oxidation of LDL particles is one of the consequences of alterations in its function, both prooxidant and antioxidant systems. Moreover, oxidation of LDL particles in the vascular endothelium was reported to be an initial event in atherosclerotic plaque formation. LDL promotes the expression of adhesion proteins that mediate the inflammatory response, leading to dysfunction and apoptosis. Furthermore, LDL molecules regulate the formation of reactive oxygen species (ROS) and contribute to vesicular stromal cell (VSMC) proliferation and cell suicide (Sánchez et.al., 2024). The loss of electrons in LDL is a consequence of the atherosclerotic modification necessary for true "bad" cholesterol, and it mostly occurs in the vascular membrane (Li et.al., 2022). Oxidation is expected to be the sole repair mechanism involved in the LDL cholesterol molecules. However, despite these earlier findings, there is growing evidence of the importance and presence of numerous modified LDL cholesterol molecules, which influence their chemical and physical properties. All these modifications constitute a series of steps involved in the progression of AS (Poznyak et.al., 2021). ox-LDL increases LOX-1 mRNA and protein expression in a dose-dependent manner (Sánchez et.al., 2024). Several studies have demonstrated increased ox-LDL in patients with AS (Cha et.al., 2020). The primary objective of this study is to estimate the serum level of SIRT-1 and the serum level of ox-LDL in patients with AS and to explore the relationship between SIRT-1 and ox-LDL in the context of atherosclerosis, particularly in Iraqi men, also to explore how the levels of SIRT-1 correlate with ox-LDL, age, BMI, and cTnI in Iraqi men diagnosed with AS

2. Materials, Patients and Methods

2.1 Patients' Constant and Enrollment

A total of 84 AS patients from Al-Fallujah Teaching Hospital. (Fallujah, Anbar, Iraq) were enrolled in this study. A control group involved 42 healthy people matched with patients in age and ethnic backgrounds, the age range was from 40→70 years, with no clinical symptoms of any disease. All blood samples were

collected from the ulnar vein. All subjects underwent full history taking and clinical examination. Height and weight were measured for all subjects.

2.2 Inclusion Criteria

Participants were included in the study according to the following criteria:

1. Male patients aged 40 years or older.
2. Patients diagnosed with atherosclerosis.
3. Patients attending Al-Fallujah Teaching Hospital during the study period.

2.3 Exclusion Criteria

Participants were excluded from the study if they had:

1. Age less than 40 years.
2. A history of smoking.
3. Diabetes mellitus or other metabolic disorders.
4. Chronic systemic diseases such as liver or kidney diseases.
5. Patients receiving medications that may affect lipid metabolism or oxidative stress markers.

2.4 Blood Sample Collection

Blood samples were collected into gel tubes. Serum samples were separated by centrifugation at 1500 × g for 10 min and stored at -20°C until analysis. Individuals were analyzed for SIRT1 and ox-LDL using an ELISA kit purchased from a Shanghai company (China). The evaluation was performed using an ELISA microplate reader. Cardiac troponin-I (cTnI) was determined by (Boditech, Korea)

2.5 Biochemical and Hormonal Assay Methods

1. Serum levels of Sirtuin-1 (SIRT-1) and oxidized low-density lipoprotein (ox-LDL) were measured using enzyme-linked immunosorbent assay (ELISA) kits purchased from a Shanghai company (China). Measurements were performed using an ELISA microplate reader.
2. Serum cardiac troponin-I (cTnI) levels were determined using a commercial kit supplied by Boditech (Korea) according to the manufacturer's instructions.
3. Body mass index (BMI) was calculated using the formula:
4.BMI = Weight (kg) / Height² (m^2)

2.6 Statistical Analysis

Statistical analysis was performed using GraphPad Prism version 10.4. Data were expressed as mean ± standard deviation (SD). Differences between groups were analyzed using the independent t-test, while the relationships between variables were evaluated using Pearson correlation analysis. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Demographic Characteristics of Control and Patient Groups:

As shown in Table 1, results for subjects were expressed as mean ± SD. The data showed non-significant differences between AS patients and healthy controls (HCs) in age (years) and BMI (kg/m2) (55.10 ± 8.482 for AS patients and 52.43±9.686 for HCs) and (28.50±3.028 for AS patients and 27.44 ± 2.245 for HCs), respectively, according to the scoring criteria given in Table 1. Results showed that patients with AS had significantly lower serum SIRT-1 levels (IU/mL) than HCs, with P>0.0001 (72.14±17.15 for AS patients and 103.1±20.69) as shown in Fig.1, while serum levels of ox-LDL (mmol/L) showed a rise in patients with AS compared to HCs, P>0.0001 (183.1±26.52 for AS patients and 121.6±27.42), as shown in Fig.2, serum levels of cTnI (ng/mL) were significantly higher in patients with AS than HCs, P>0. 0001 (21.02±13.04 for AS patients and 0.0214±0.0098).

Table1: Comparisons of Parameters between Studied Groups.

Parameter	**AS Patients**	**Healthy Controls**	***P-Value***
	Mean ± S. D	**Mean ± S. D**	
Age years	55.10± 8.482	52.43±9.686	0.1832
BMI kg/m^2	28.50±3.028	27.44±2.245	0.0738
CTnI ng/mL	21.02±13.04	0.0214±0.0098	<0.0001
SIRT-1 IU/mL	72.14±17.15	103.1±20.69	<0.0001
Ox-LDL mmol/L	183.1±26.52	121.6±27.42	<0.0001

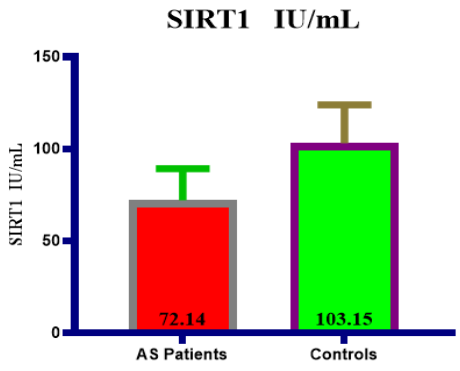

Figure1: Mean ± SD of SIRT1 in AS Patients and Controls.

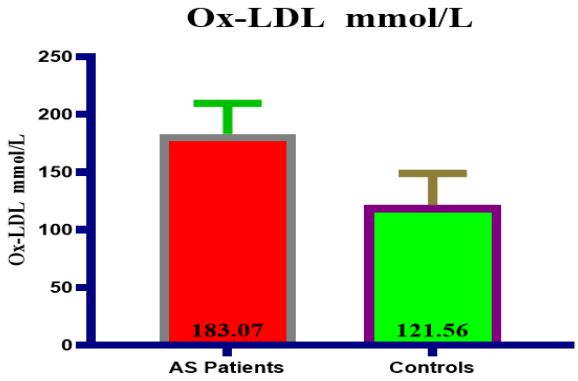

Figure2: Mean ± SD of Ox-LDL in AS Patients and Controls.

A significant negative correlation of SIRT-1 with ox-LDL, cTnI, and BMI was detected between (r =-0.497, p <0.0001), (r =-0.451, p = <0.0001), and (r =-0.253, p = 0.020), respectively as shown in Table2 and Fig.3. while ox-LDL showed an important positive relationship with cTnI (r =0.507, p <0.0001), as shown in Table3 and Fig.4.

Table2: Association of SIRT-1 with Studied Parameters

Parameter	r (SIRT-1 IU/mL)	*P*-value
SIRT1 IU/mL	1.000	0.000
Age years	-0.094	0.395
BMI kg/m2	-0.253	0.020
cTnl ng/mL	-0.451	<0.0001
Ox-LDL mmol/L	-0.497	<0.0001

Table3: Association of Ox-LDL with Studied Parameters

Parameter	r (Ox-LDL mmol/L)	*P*-value
Ox-LDL mmol/L	1.000	0.000
SIRT1 IU/mL	-0.497	<0.0001
Age years	**0.160**	**0.146**
BMI kg/m2	**0.153**	**0.165**
cTnl ng/mL	**0.507**	**<0.0001**

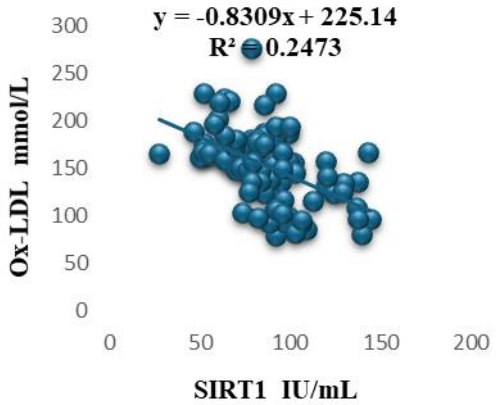

Figure3: Association of ox-LDL with SITR-1

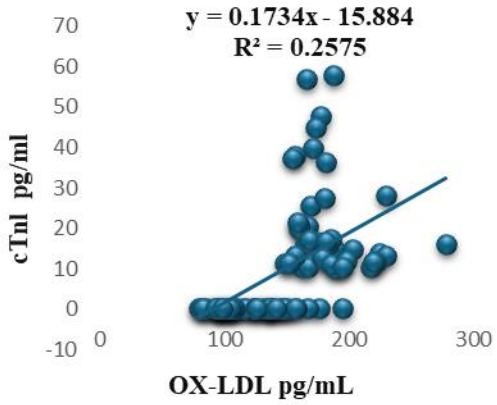

Figure4: Association of ox-LDL with cTnI

Table4 showed the result of receiver operating characteristic (ROC) curve of this study, our data was explored that the best effective biomarkers were suitable for the identification of patients with AS was ox-LDL [AUC:0.9569, Cut-off value: < 156.9, Sen %: 90.48, Spec%: 88.10, Likelihood Ratio (LHR): 7.600] as shown in Fig.5. in the second rank to diagnosis AS disease was SIRT-1parameter [AUC: 0.8787, cut-off value: > 85.10, Sensitivity% (sen %): 80.95, Specificity% (spec %): 78.57] as shown in as shown in Fig.6.

Table4: Area under the ROC curve for all analyzed Parameters in Atherosclerosis

Parameter	AUC	Positive if COV	Sensitivity٪	Specificity٪	Likelihood Ratio
SIRT1 IU/mL	0.8787	> 85.10	80.95	78.57	3.778
Ox-LDL mmol/L	0.9569	< 156.9	90.48	88.10	7.600

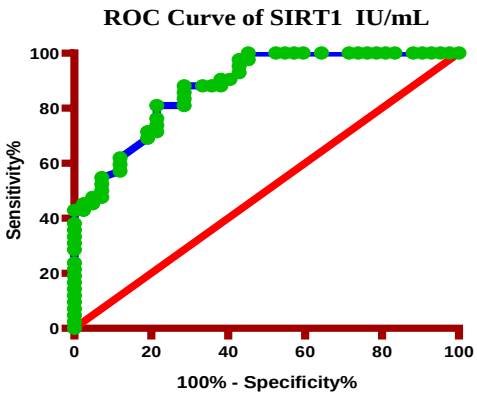

Figure5: ROC curve of SIRT-1 in AS patients

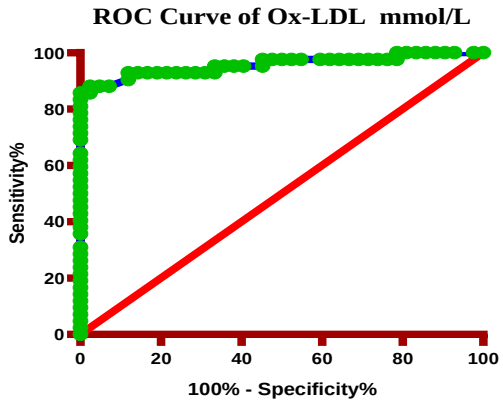

Figure6: ROC curve of ox-LDL in AS patients.

4. Discussion

Atherosclerosis is a recurring inflammatory process that occurs in the arterial wall, causing damage to the inner arterial membrane, where inflammatory cells and fatty deposits accumulate, leading to narrowing of the artery, small arteries make it difficult for oxygen and blood to reach the heart, which can lead to chest pain (angina) or a heart attack (Sánchez et.al.,2024). This demonstrates that AS is very common and plays an important role in CVD. It is an important factor in the pathogenesis of all cardiovascular diseases - coronary artery disease, stroke and peripheral arterial disease. (Centers for Disease Control and Prevention ,2019). Sirtuin-1, the most widely studied link of the serotonin family among mammalian sirtuins, is a member of this gene family. This enzyme is involved in the regulation of several cellular processes such as response to stress, vascular health, ageing and metabolism. It acts through cytoprotection of cells from oxidative damage, employment of metabolic pathways, and down-regulation of inflammation (Imai and Guarente,2016). Although SIRT-1 is thought to predominantly reside in the nucleus, previous works have demonstrated its

localization also in the cytoplasm (Vázquez et.al., 2025). The body is constantly bombarded by pathogens, including bacteria, fungi, and viruses, which trigger a defensive response through a highly controlled system of adaptive and innate immunity (Wilking et.al., 2014). The targets of SIRT-1 could modulate immune response and immune cells' behavior, which are possibly implicated in the development of chronic inflammatory or autoimmune diseases (Khuzin et.al., 2025). The study also showed that the serum SIRT-1 levels among ankylosing spondylitis AS patients were substantially lower compared to the controls ($P<0.05$), consistent with many previously reported studies (Alaaraji et.al.,2019). Previous studies have shown that the upregulation of SIRT-1 not only improves endothelial cell function and reduces inflammatory signaling but also enhances nitric oxide production. For example, SIRT-1 inhibition has been associated with the development of AS and vascular damage. Resveratrol, also known as a deacetylase enzyme activator, is considered an important anti-aging molecule involved in the regulation of longevity (Carollo et.al., 2025). Deacetylated protein SIRT-1 appears to play an important role in regulating phosphorylation by directly deacetylating kinases and mediating the cardiovascular protection induced by resveratrol. Studies have shown the beneficial effects of sirtuins in rheumatoid arthritis. Not only they help in the repair of damaged vascular tissue but their interactions with ox-LDL are also significant, as it is a critical factor for rheumatoid process progresses. The current evidence indicates that sirtuins may exert anti-RA effect by inhibiting inflammation, ameliorating oxidative stress, enhancing vascular function, and modifying lipid profile. (Ding et.al., 2025). The function of SIRT1 in CVD has been confirmed, and its mechanisms have been gradually revealed. The mechanisms include antioxidation, anti-inflammation, anti-senescence, improvement of endothelial function, inhibition of foam cell formation, and enhancement of autophagy. More insight has been gained into the role of SIRT-1 in AS, particularly in vascular smooth muscles cells (VSMCs). In AS, VSMCs are recruited to the arterial wall, where they acquire pro-inflammatory characteristics and represent the most common cellular component of the arterial intima in the early phase of intimal thickening. The most recent data have revealed that SIRT-1 has a significant regulatory role in coagulation, including cardiovascular function and vascular biology, cholesterol transport, inflammation, endothelial activation, foam cell formation, and platelet aggregation. This further highlights the importance of SIRT-1 in inflammatory coagulation pathways (Soni et.al., 2021). Sirtuin-1activation is considered as an attractive therapeutic option for diseases such as rheumatoid arthritis and AS (Becatti et.al., 2016). The regulation of eNOS and oxidative stress by SIRT1 is important in explaining its role in AS and thrombosis (American Heart Association, 2022). SIRT1 has been characterized as an antioxidant and its capability to ameliorate reactive oxygen species in endothelial cells was also discussed (Ding et.al., 2025). SIRT-1 has been shown to mediate improvement in endothelium-dependent vascular function through stimulation of endothelial nitric oxide synthase (eNOS) and reduction of oxidative stress. In addition, laminar shear stress induces an increase in the activity of SIRT-1, resulting in

increased eNOS activation (American Heart Association, 2022). There were significantly higher levels of ox-LDL in AS patients than in the controls. ox-LDL is the modified LDL resulting from oxidative modification, which affects its structural features (He and Liu, 2023). The increase of ox-LDL is supposed to play a crucial role in the process of AS and other related diseases (Hartley et.al., 2019). These oxidatively modified lipoproteins are generated by modification of LDL (Babakr, 2025). These oxidative alterations usually take place in situations where there is excessive oxidative stress as consequence of inflammation and ROS overproduction and antioxidant protect capacity reduced (Forman and Zhang, 2021) .ox-LDL has already been recognized as a key player in the atherosclerotic process (Sies and Jones, 2020)Acute phase markers elevation we found in the present study suggests that ox-LDL is involved in atherogenesis, especially as an inducer from inflammation and inflammation induced foam cell formation and endothelial dysfunction for arterial wall (Li et.al., 2022). The relationship between ox-LDL and its receptors is complicated; nevertheless, when the evidence is examined closely, it becomes clear that understanding this relationship increases our knowledge about molecular mediators in the development and progression of atherosclerotic CVD (Klisic et.al., 2024). The metabolism of intracellular cholesterol in endothelial cells is significantly reprogrammed in atherosclerotic lesions after lipids have been digested and absorbed. This disturbance in cellular homeostasis increases the inflammatory stimulus which, if unchecked, becomes a self-sustaining cycle promoting further damage of the endothelium and formation of plaque. This paper examines oxidative injury in terms of its potential to convert LDL into atherogenic promoters. It also comments on the effect of ox- LDL on foam cells (derived from smooth muscle) and this regulation, their effects in two pathogenic situations: conversion of injured vascular smooth muscle cells into foam cells as well as cholesterol catabolism in foam cells and the importation system into those with ox-LDL (Wang et.al., 2024). Management of these components with specific interventions can ease the weight of cardiovascular disease (CVD), which remains the number one cause of death. The challenges in applying ox-LDL as a biomarker to clinical practice are indicative of an important avenue for future research. This research is critical to improve the prevention and treatment of AS and associated CVD.

Conclusion

Atherosclerosis patients show higher serum ox-LDL levels and lower SIRT1 levels than HCs. The negative relationship between ox-LDL and SIRT1 suggests a new bio-role for SIRT1 as an acetyl group scavenger from LDL, which reduces AS development and prognosis in Iraqi men. SIRT1 Serum levels may serve as excellent parameters in predicting and diagnosing CVD and atherosclerosis.

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