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Analysis of Adiponectin, TNF-α, and Biochemical Markers in Fallujah Atherosclerosis Patients

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Abstract.*Background: Atherosclerosis is a chronic inflammatory cardiovascular disorder strongly associated with elevated low-density lipoprotein cholesterol (LDL-C) levels and serves as a major predictor of adverse cardiovascular events. This study aimed to investigate the relationship between inflammatory markers (adiponectin and TNF-α) and key biochemical parameters in atherosclerosis patients. Methods: A case-control study was conducted on 60 participants (aged 40–65 years) recruited from private cardiac clinics in Fallujah, Iraq, between October and December 2024. Subjects were stratified into two groups: 30 atherosclerosis patients (diagnosed by specialists) and 30 age-matched healthy controls. Blood samples were collected, centrifuged, and analyzed for CRP, TNF-α, adiponectin, PAI-1, MDA, GSH, sodium (Na), and magnesium (Mg) levels using standardized biochemical assays. Statistical analysis was performed using SPSS, with significance set at *p* ≤ 0.001. Results: Atherosclerosis patients exhibited significantly elevated serum levels of CRP (2.21 ± 14.46 vs. 1.07 ± 7.76 mg/dL), TNF-α (15.14 ± 120.86 vs. 4.27 ± 65.16 pg/mL), PAI-1 (6.52 ± 0.82 vs. 2.02 ± 0.42 ng/dL), MDA (590.26 ± 29.64 vs. 155.52 ± 25.19 ng/mL), and Na (140.16 ± 1.18 vs. 125.46 ± 6.17 nmol/L) compared to controls (*p* ≤ 0.001). Conversely, adiponectin (0.18 ± 1.81 vs. 0.67 ± 4.18 mg/dL), GSH (22.79 ± 1.37 vs. 40.81 ± 3.05 μg/mL), and Mg (1.46 ± 0.175 vs. 1.84 ± 0.67 nmol/L) were markedly reduced in patients. ROC curve analysis demonstrated perfect diagnostic accuracy (AUC = 1.0) for CRP, TNF-α, and adiponectin in distinguishing patients from controls. Conclusion: The study highlights pronounced dysregulation of inflammatory, oxidative, and metabolic pathways in atherosclerosis, with CRP, TNF-α, and adiponectin serving as robust discriminative biomarkers. These findings underscore the potential of targeting these pathways for therapeutic intervention and early diagnosis.*

Keywords: *Atherosclerosis; Inflammatory cytokines; Metals; PAI-1*

Abstrak.Aterosklerosis merupakan gangguan kardiovaskular kronis yang melibatkan proses inflamasi dan berkaitan erat dengan peningkatan kadar kolesterol LDL. Penelitian ini bertujuan untuk mengevaluasi hubungan antara penanda inflamasi (adiponektin dan TNF-α) dengan parameter biokimia utama pada pasien aterosklerosis. Studi kasus-kontrol ini melibatkan 60 partisipan berusia 40–65 tahun, yang terdiri dari 30 pasien aterosklerosis dan 30 individu sehat yang sesuai usia, yang direkrut dari klinik jantung di Fallujah, Irak, antara Oktober hingga Desember 2024. Sampel darah dikumpulkan dan dianalisis untuk kadar CRP, TNF-α, adiponektin, PAI-1, MDA, GSH, natrium (Na), dan magnesium (Mg). Hasil menunjukkan bahwa pasien aterosklerosis memiliki kadar CRP, TNF-α, PAI-1, MDA, dan Na yang secara signifikan lebih tinggi dibandingkan kelompok kontrol (p ≤ 0,001). Sebaliknya, kadar adiponektin, GSH, dan Mg lebih rendah pada pasien dibandingkan kontrol. Analisis kurva ROC menunjukkan bahwa CRP, TNF-α, dan adiponektin memiliki akurasi diagnostik sempurna (AUC = 1,0) dalam membedakan pasien dan kontrol. Temuan ini menunjukkan adanya disregulasi yang signifikan pada jalur inflamasi, oksidatif, dan metabolik pada penderita aterosklerosis. Dengan demikian, CRP, TNF-α, dan adiponektin berpotensi digunakan sebagai biomarker diagnostik yang kuat serta target intervensi terapeutik untuk deteksi dan pengobatan dini aterosklerosis.

Kata kunci: Aterosklerosis; Logam; PAI-1 Sitokin inflamasi

1. INTRODUCTION

Atherosclerosis is one of the leading causes of vascular diseases that seriously threaten human health worldwide. This condition is characterized by the narrowing and hardening of arteries due to the accumulation of fatty plaques on the arterial walls. Despite numerous

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therapeutic efforts, there is currently no truly effective method to halt the progression of atherosclerosis, especially in its advanced stages. This makes atherosclerosis a significant public health concern requiring serious attention.

Pathologically, atherosclerosis is classified as a chronic inflammatory condition that begins with damage to the endothelial layer of blood vessels. This damage can occur due to the accumulation of cholesterol and triglycerides within the vessel wall, triggering inflammatory responses and structural changes in the endothelium. The ongoing inflammatory response accelerates the process of atherogenesis and the formation of both stable and unstable atherosclerotic plaques.

One of the main factors in the development of atherosclerosis is low-density lipoprotein cholesterol (LDL-C), particularly its oxidized form (ox-LDL). Ox-LDL contributes to endothelial dysfunction, promotes the migration of smooth muscle cells, and intensifies inflammatory responses that worsen vascular damage. Moreover, the presence of senescent cells in vascular tissue has also been found to contribute to disease progression through the secretion of inflammatory and pro-atherogenic mediators.

Recent studies have indicated that various biomolecules, such as adiponectin and TNF-α, play crucial roles in the inflammatory and metabolic mechanisms underlying atherosclerosis. Adiponectin, an anti-inflammatory molecule, is generally reduced in individuals with atherosclerosis, whereas TNF-α, a pro-inflammatory cytokine, tends to increase. The imbalance between these two molecules reflects significant dysregulation in immune and metabolic regulation in affected individuals.

Therefore, it is important to further investigate the relationship between inflammatory biomarkers such as adiponectin and TNF-α and other biochemical parameters to better understand the pathophysiology of atherosclerosis. This information is expected to provide a scientific basis for the development of more effective diagnostic and therapeutic strategies to manage this disease.

2. LITERATURE REVIEW :

Atherosclerosis is a specific type of arteriosclerosis, a chronic inflammatory disease of the arterial wall. The underlying cause of the disease and its subsequent development into cardiovascular disease [3], atherosclerosis is the result of a pathological process that begins with a local lesion in the inner layer of medium and large arteries, where fats are deposited in the inner layer, causing inflammation [4,5].

Atherosclerosis leads to the rupture of unstable atherosclerosis plaques, narrowing of blood vessels, or blockage caused by platelet aggregation and clotting, which increases the incidence of acute cardiovascular diseases [6,7]. Atherosclerosis is characterized by the accumulation of cholesterol and triglycerides, the occurrence of an inflammatory response, programmed cell death, and the occurrence of fibrosis in the arterial wall, and it is one of the main causes of coronary heart disease [8].

Atherosclerosis is characterized by weakening and inflammation of the blood vessel lining, and the formation of plaques. The accumulation of atherosclerotic plaques in the arteries may lead to an insufficient supply of oxygen to the myocardial tissue, leading to hypoxia in the muscle. Plaque rupture and arterial thrombosis cause further narrowing of the coronary artery and blockage of blood flow, leading to acute coronary syndrome and consequently acute myocardial infarction [9,10].

Atherosclerosis is characterized by the formation of plaques under the lining of blood vessels, which consist of lipids, inflammatory cells, and fibrous deposits. Molecular, cellular, genetic, and environmental factors play a major role in the development of the disease. Atherosclerosis is a pathological process that occurs within the artery where many types of cells interact, including T-cells, macrophages, endothelial cells, and smooth muscle cells, It causes chronic inflammation in response to various internal or external cellular stimuli. Atherosclerosis is characterized by a complex interaction between inflammation, lipid deposition and proliferation of vascular smooth muscle cells with endothelial dysfunction and remodeling of the extracellular matrix, leading to the formation of an intimal plaque [11,12].Inflammatory signaling is stimulated by proinflammatory cytokines, inflammatory signaling pathways, bioactive lipids, adhesion molecules, and the formation of atherosclerotic plaques [13].

Adiponectin is secreted from adipose tissue, a tissue found throughout the body and an important endocrine system (organ), and adipokines are essential for controlling immune responses and energy [14]. It is involved in a number of physiological processes, such as lipid metabolism, energy control, immune response, and inflammation [15]. Low levels of adiponectin are associated with metabolic syndrome, cardiovascular disease, and hypertension, and it has a wide range of biological effects, including antidiabetic, antiatherosclerotic, and anti-inflammatory properties [16].

Atherosclerosis develops due to the accumulation of fats in the arterial wall as a result of increased hyperlipidemia, oxidative stress, lipid peroxidation, and protein oxidation. Therefore, improving the level of antioxidants through the diet may prevent the development

of the disease, as antioxidants work to combat free radicals and regulate inflammatory signals in the cells of atherosclerotic plaques. Including macrophages and endothelial cells, thus reducing the effects of disease progression [17]. Through the high levels of diagnostic indicators for benign prostatic hyperplasia, the current research aimed to study the effect of the level of (adiponectin and TNF-α) and its relationship with some biochemical variables in patients with atherosclerosis in the city of Fallujah.

3. METHODS

Collection of specimens

This study was conducted on 60 samples whose ages ranged between (40-65) years. The samples were collected from private clinics for heart diseases after diagnosis by a specialist doctor and separated in private laboratories in the city of Fallujah, affiliated with Anbar Governorate, for the period starting from (October September) until (December) of the year (2024). The samples were divided into two groups:

- **Control group:** It included (30) blood samples from healthy men (as a healthy group) after ensuring that they were free of chronic diseases and within the same age group.
- **Patient group:** It included (30) blood samples from patients suffering from atherosclerosis after they were diagnosed by specialist doctors.

Then, blood was collected from the group of patients and healthy people and separated by centrifugation. Then, biochemical variables were measured, which included (CRP, TNF-α, Adiponectin, PAI-1, MDA, GSH, Na, Mg).

Estimating diagnostic markers and hormone levels in both patient and healthy groups

The sandwich method was used to estimate the concentration of CRP, TNF-α, adiponectin, PAI-1, MDA, and GSH. This method is one of the Enzyme Linked Immunosorbent Assay (ELISA) techniques, which is an enzyme-linked immunosorbent technique in which antigens in blood serum are detected using antibodies that coat the holes of the plate intended for measurement.

Serum magnesium level assessment:

Magnesium reacts enzymatically with the reagent to form a colored solution. The color intensity is proportional to the magnesium concentration in the sample. The absorbance is read at 450 nm on a microplate reader.

Serum sodium level determination:

This is a colorimetric method. The sodium ions in the serum react enzymatically with the enzyme beta-galactosidase to produce an intermediate compound. This intermediate reacts with a colored indicator to produce a colored compound whose color intensity is proportional to its concentration and absorbs at 405 nanometers.

Statistical analysis

The results were analyzed using the Statistical Package for the Social Sciences-SPSS using the Completely Randomized Design (CRD) method, using the t-test to analyze the variance between two groups at a probability level of ($P \leq 0.001$). The Receiver Operating Characteristic (ROC) was also calculated to determine (Sensitivity, Specificity) and its value (Curve) was also calculated. The simple linear correlation coefficient was also found to find the relationship between the variables under study.

4. RESULTS

Measuring the levels of biochemical variables for the samples studied in both groups:

Table (1) shows the mean ± standard deviation of the biochemical variables for the samples studied in both groups.

Groups / Parameter	Mean ± SD		P-Value
	Control n=30	Patients n=30	
CRP (mg/dl)	1.07 ±7.76	2.21±14.46	P ≤ 0.001
TNF-α (Pg/ml)	4.27 ±65.16	15.14±120.86	P ≤ 0.001
Adiponectin (mg/dl)	0.67 ±4.18	0.18±1.81	P ≤ 0.001
PAI-1 (ng/dl)	2.02±0.42	6.52±0.82	P ≤ 0.001
MDA (ng/ml)	155.52±25.19	590.26±29.64	P ≤ 0.001
GSH (µg/ml)	40.81±3.05	22.79±1.37	P ≤ 0.001
Mg (nmol)	1.84±0.67	1.46±0.175	P ≤ 0.001
Na (nmol)	125.46±6.17	140.16±1.18	P ≤ 0.001

The results of the current study showed a significant increase in the levels of (CRP, TNF-α, PAI-1, MDA) in the blood serum of patients with atherosclerosis compared to the control group, with a significant decrease in the level of (Adiponectin, GSH, Mg) in both groups at a probability level of $P \leq 0.001$. As shown in the figures below:

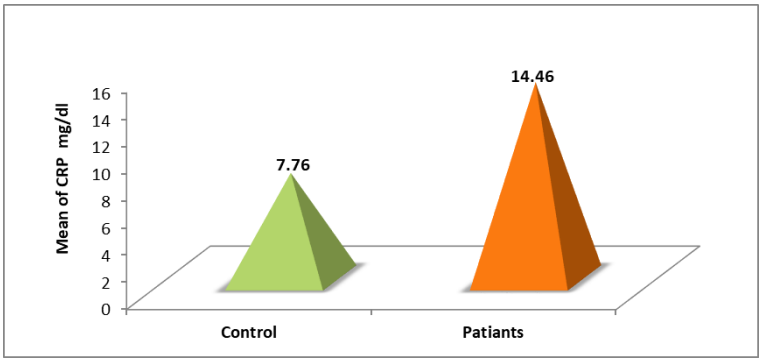

Figure (1): CRP in the group of patients and healthy people

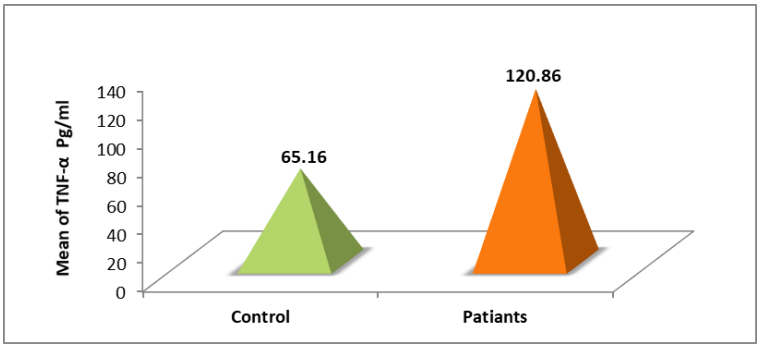

Figure (2): TNF-α in the group of patients and healthy people

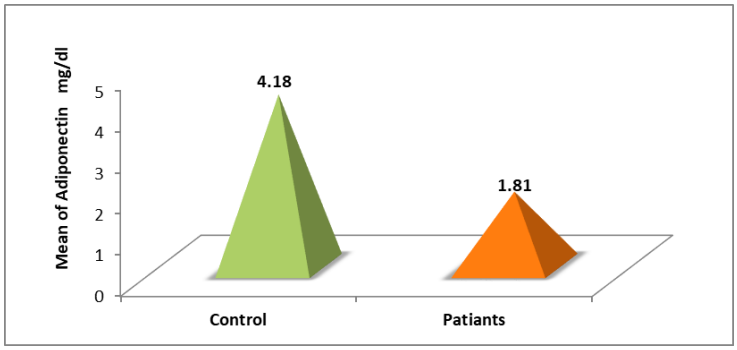

Figure (3): Adiponectin in the group of patients and healthy people

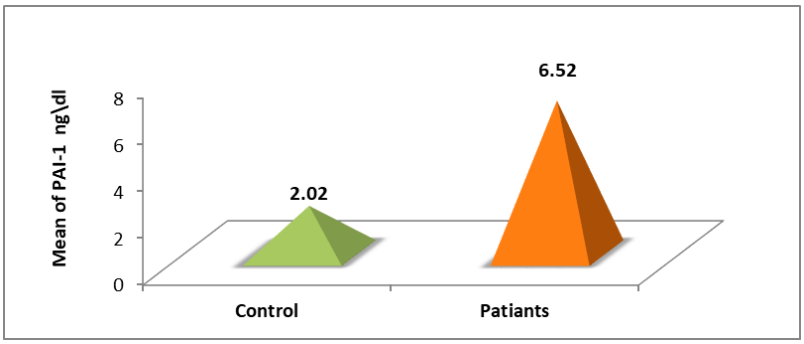

Figure (4): PAI-1 in the group of patients and healthy people

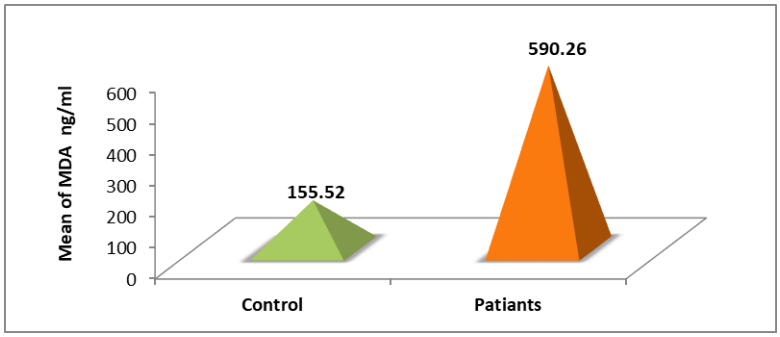

Figure (5): MDA in the group of patients and healthy people

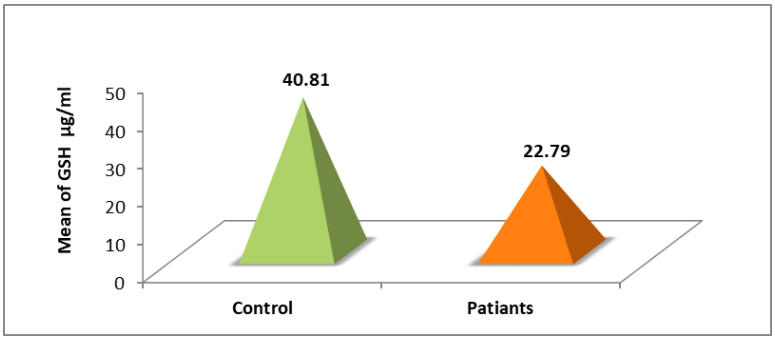

Figure (6): GSH in the group of patients and healthy people

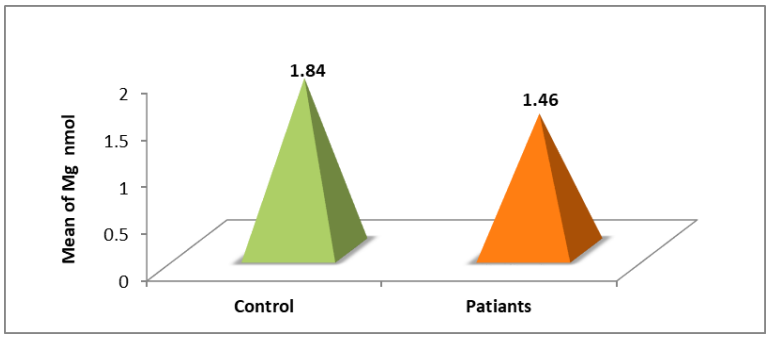

Figure (7): Mg in the group of patients and healthy people

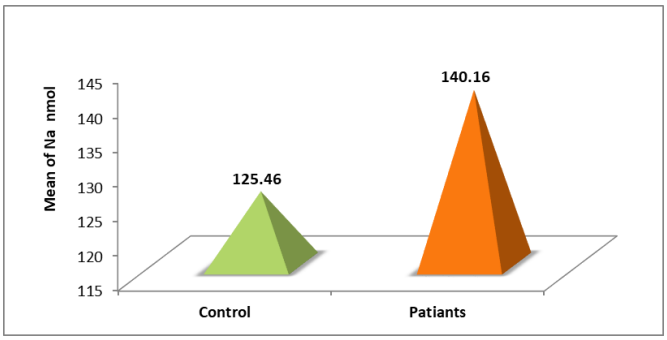

Figure (8): Na in the group of patients and healthy people

ROC curve calculation

The ROC curve was calculated for diagnostic and biochemical variables for patients with benign prostatic hyperplasia (BPH), including CRP, TNF-α and Adiponectin in addition to the healthy control group, as shown in Table (2).

Table (2) shows the area under the curve, specificity, and sensitivity values for diagnostic and biochemical variables for the patient and healthy control groups.

Parameters	AUC	Cut off	Sensitivity %	Specificity %	Accuracy	P-value
CRP	1.000	>8	100.00	100.00	1.000	<0.001
TNF-α	1.000	>73.66	100.00	100.00	1.000	<0.001
Adiponectin	1.000	≤2	100.00	100.00	1.000	<0.001

The results of CRP showed that the area under the curve (AUC) value was (1) and (Cut off) was (>8) and the sensitivity ratio was (100) while the specificity ratio was (100) and the accuracy was (1), while for TNF-α the area under the curve (AUC) value was (1) and (Cut off) was (>73.66) and the sensitivity ratio was (100) while the specificity ratio was (100) and the accuracy was (1), As for Adiponectin, the area under the curve (AUC) value was (1) and (Cut off) was (≤ 2) and the sensitivity ratio was (100) while the specificity ratio was (100) and the accuracy was (1)., at a probability level (<0.001) for the patient and healthy groups, as in the following figures:

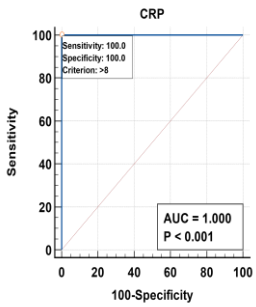

Figure (1): Diagnostic validity criteria for CRP for TNF-α

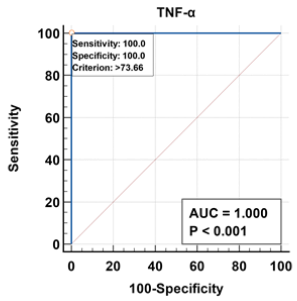

Figure (2): Diagnostic validity criteria

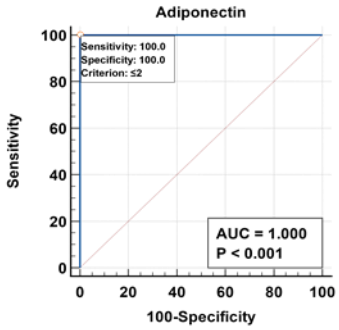

Figure (3): Diagnostic validity criteria for Adiponectin

Correlation between CRP and levels of parameter under investigation:

The relationship between the CRP level and the level of the data under study was studied, as shown in the table:

Table (3): shows the correlation relationships between the CRP level and the level of the patient and healthy groups

Parameters	CRP			
	Control		Patients	
	r	p-value	r	p-value
TNF-α	0.144	0.416	-0.144	0.417
Adiponectin	0.019	0.917	-0.052	0.770

The relationship between CRP and PSA TNF-α levels in the blood serum of the patient and healthy groups:

The results showed that the correlation between CRP and TNF-α in the patient group was negative and insignificant, with a correlation coefficient of (r = -0.144), while the correlation in the control group was positive and insignificant, with a correlation coefficient of (r = 0.144).

The relationship between CRP and Adiponectin levels in the serum of patients and healthy controls:

The results showed that the correlation between CRP and Adiponectin in the patient group was negative and insignificant, with a correlation coefficient of (r = -0.052), while the correlation in the control group was positive and insignificant, with a correlation coefficient of (r = 0.019).

5. DISCUSSION

Atherosclerosis is the leading cause of death worldwide. Atherosclerosis begins with activation of the endothelium, followed by a series of processes (such as increased lipid and fibrous elements and calcification), leading to narrowing or occlusion of blood vessels and activation of inflammatory pathways. The resulting atherosclerotic plaque, along with these processes, leads to cardiovascular complications [(18).]

C-reactive protein (CRP) is an inflammatory protein that plays an important role as an acute phase protein. Cardiovascular disease is an inflammatory condition, but the relationship between CRP and cardiovascular disease remains controversial. In some recent clinical studies, it has been considered an important diagnostic indicator for cardiovascular disease, However, its role in the development and progression of the disease is still not completely clear, but it has been found that low levels of CRP in the blood may reduce the risk of cardiovascular disease in addition to preventing the disease from developing [(19,20).] The results of the current study are consistent with the results of the study by Denegri [(21)] and Yang [(22)], who indicated that C-reactive protein (CRP) is an important and established marker of cardiovascular disease (CV), as high levels of CRP were associated with the outcomes of acute coronary syndrome (ACS).

Since CRP has an active role in the initiation and development of atherosclerotic plaque, it has been considered an indicator rather than a therapeutic target [(23).] The risk of cardiovascular disease increases with the increase in the level of CRP in the serum, as CRP has a role in activating platelets, adhesion and aggregation molecules, activating the vascular endothelium, recruiting and polarizing leukocytes, and forming foam cells in the blood vessels , It was found that CRP is present in the form of deposits in atherosclerotic plaques and damaged tissues, so CRP is considered an important test and an important indicator in diagnosing atherosclerosis [(24,25).]

The result of the increase in the level of TNF-α in patients with atherosclerosis was consistent with the result of (Li) [(26).] The reason for the increase is that tumor necrosis factor-α

is one of the inflammatory cytokines that has a role in initiating vascular inflammation TNF-α stimulates the production of reactive oxygen species that lead to oxidation and reduction reactions, Reactive oxygen species may also cause oxidative stress that contributes to endothelial dysfunction. People with TNF-α-stimulated inflammatory conditions are therefore at greater risk of cardiovascular disease. TNF-α also has significant effects on vascular smooth muscle cells (VSMC) including promoting lipid storage and enhancing their motility. which supports the contribution of VSMCS to neogenesis and atherosclerotic plaque formation, and thus TNF-α plays an important role in driving inflammatory changes in VSMCS biology that contribute to cardiovascular disease [(27).]

Normal vascular endothelial cells play an important role in maintaining vascular balance and preventing atherosclerosis by regulating vascular tone, preventing blood clots, and regulating inflammation. Multiple indicators have shown that programmed cell death of endothelial cells is the first step in the development of atherosclerosis , excess apoptosis of endothelial cells caused by atherosclerosis risk factors is an initial event in the development of the disease, and after tumor necrosis factor-α, risk factors that may induce endothelial cell apoptosis that causes atherosclerosis [(28).]

The result of the decrease in the level of Adiponectin in the group of patients with atherosclerosis was consistent with the result of (Mihalopoulos) et al [(29).] The reason for this decrease is due to the way in which the fatty tissue expands, such as increasing its size and swelling in most cases, and that this swelling will regulate the synthesis and secretion of adiponectin. In addition, some studies have shown an inverse relationship between the average diameter of the body's adipocytes and the secretion of adiponectin [(30).] Low levels of adiponectin in the serum are associated with metabolic conditions accompanied by chronic inflammation in the body, such as obesity and atherosclerosis [(31).] Furthermore, low levels of adiponectin can lead to endothelial dysfunction and a atherogenic effect in obese individuals [(32).]

The increased level of PAI-1 in the group of patients with atherosclerosis was consistent with the result of (Córdova-Pérez) et al. [(33).] The reason for this increase is related to several causes such as endothelial dysfunction and inflammation, which are the main cause of the development of atherosclerotic plaques, which is a chronic systemic disease, and endothelial dysfunction has the ability to change the fibrinolysis system. It is critical for the formation of atherosclerotic plaques [(34).] Atherosclerosis tends to show increased levels of PAI-1 expression. PAI-1, the main inhibitor of tissue plasminogen activator (tPA) and urokinase (uPA), is an inhibitor of fibrinolysis and plays a critical role in AS [(35).] Overexpression of PAI-

1 is associated with atherosclerosis, which is characteristic of overweight or obese individuals, and hepatic lipid metabolism is also significantly regulated by PAI-1 [36,37].

The result of the increase in the level of oxidative stress (MDA) in patients with atherosclerosis was consistent with the result of both (Iswar) et al [38] and (Alada) et al [39]. It is believed that the reason for the increase is that oxidative stress causes damage to the inner lining of blood vessels and arteries due to oxidizing substances, especially active oxygen species, and the resulting peroxidation of biological molecules, especially unsaturated fats (lipid peroxidation) [40]. MDA has an important and key role in the molecular mechanisms of vascular wall lesions formation causing primary atherosclerosis [41]. Malondialdehyde-modified low-density lipoprotein (MDA-LDL-C) acts as a marker of oxidative stress and is associated with cardiovascular disease and atherosclerosis [42].

The result of the decrease in antioxidants (GSH) in patients with atherosclerosis was consistent with the result of both (Subramani) et al. [43] and (Labarrere) et al [44]. It is believed that the reason for the increase is that the low level of glutathione (GSH) increases the risk of cardiovascular diseases, and glutathione plays a fundamental role in many cellular processes, Such as antioxidant defenses, regulation of protein function and stability, DNA synthesis, gene expression, cell proliferation, cellular signaling, metabolism, and glutathione-dependent signaling for a wide range of biological processes, spanning the human lifespan from early development to aging [45,46]. Glutathione is involved in the detoxification of free radicals, peroxides, and xenobiotics, protects biological membranes from lipid peroxidation, and is an important regulator of cell homeostasis [47]. GSH is produced in the heart, which is of great importance in preventing or reducing the harmful effects of reactive oxygen species and reactive nitrogen species in cardiovascular diseases [48].

The result of low magnesium (Mg) levels in patients with atherosclerosis was consistent with the results of both (Sun XiuTing) et al [49] and (Rodríguez-Ortiz) et al [50]. It is believed that the reason for the decrease is due to magnesium being an essential nutrient for maintaining vital physiological functions and participating in many basic processes. Magnesium deficiency is often associated with negative health outcomes, One study suggested that chronic hypomagnesemia may be a contributor to the pathogenesis of several metabolic disorders such as weight gain, obesity, insulin resistance, hypertension, changes in lipid metabolism, and low-grade inflammation [51]. Mg deficiency appears to be a trigger for endothelial dysfunction and low extracellular magnesium affects endothelial cells, and magnesium balance may be a useful and inexpensive intervention to prevent and treat endothelial dysfunction, and thus atherosclerosis [52].

The result of the increase in mineral levels (Na) in patients with atherosclerosis was consistent with the result of both (Peng et al) [53] and (Jia et al) [54]. It is believed that the reason for the increase is due to the effect of sodium intake and polyunsaturated fatty acids on carotid atherosclerosis, Functional changes mediated by sodium and polyunsaturated fatty acids in the carotid endothelium may contribute to the development of atherosclerosis [55]. It was found that an increase in extracellular sodium within the physiological range is accompanied by changes in the blood vessels that facilitate the development of cardiovascular diseases. The results indicate that serum sodium is a risk factor for cardiovascular diseases and give additional support to recommendations regarding restriction of dietary salt containing sodium and adequate water intake as a means of preventing cardiovascular diseases [56].

CONCLUSION

The study investigated the relationship between adiponectin, TNF-α, and other biochemical variables in patients with atherosclerosis in Fallujah city. The results demonstrated significant alterations in inflammatory markers, oxidative stress indicators, and mineral levels in atherosclerotic patients compared to healthy controls. Specifically, patients exhibited elevated levels of CRP, TNF-α, PAI-1, MDA, and Na, alongside reduced levels of adiponectin, GSH, and Mg. These findings underscore the critical roles of inflammation, oxidative stress, and endothelial dysfunction in the pathogenesis of atherosclerosis.

The ROC curve analysis further highlighted the diagnostic potential of CRP, TNF-α, and adiponectin, with all three markers showing high sensitivity and specificity (100%) in distinguishing atherosclerotic patients from healthy individuals. The negative correlation between CRP and adiponectin in patients suggests a potential interplay between inflammation and metabolic dysregulation in disease progression.

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