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Study of the Arginase Activity and Other Biochemical Parameters in Patients with Coronary Artery Disease in Baghdad Governorate-Iraq

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ABSTRACT

The most prevalent form of heart disease and the main cause of death in both developed and developing nations is CAD. It happens when "plaque," or cholesterol or other fatty deposits that accumulate on the inner wall of the artery, narrows or blocks the arteries that deliver blood to the heart. Over time, chest pain might develop as a result of the reduction in blood flow to the heart caused by this plaque accumulation. The study was designed to find if Arginase acts as a biomarker for diagnosing Coronary Artery Disease (CAD). A total of 90 individual samples were included in the present study, the control group consist of 40 healthy individual samples, while the CAD patients were 50 individual samples. Some biochemical parameters such as fasting blood glucose (FBG), troponin I(TnI), high sensitivity C-reactive protein (hs-CRP), lipid profile, lactate dehydrogenase (LDH), and Arginase activity were analyzed. The results of the current study showed no significant differences in the average age of patients (67.00±6.78) when compared with the control group (61.10±6.46), P>0.05. A significant increase Was found in the FBI level, cholesterol, triglycerides, very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), TnI, hs-CRP, LDH, and Arginase activity in the patient's group when compared with the control group. While significant decrease (P<0.05) was revealed in the high-density lipoprotein (HDL) level in CAD patients in comparison to the control group. Also, there was a positive significant correlation between Arginase activity with each age and FBG. As for the ROC operator curve for Arginase, it was found that the area under the curve (AUC) was 0.953 with a sensitivity of 90%, and specificity of 95%. The results in the present study indicate a possible use of Arginase as a diagnostic marker for CAD.

KEYWORDS: Coronary artery disease; arginase; troponin I; lipid profile; hs-CRP.

الخلاصة

يعتبر مرض الشراين التاجي الشكل الأكثر انتشارًا لأمراض القلب والسبب الرئيسي للوفاة في كل من الدول المتقدمة والنامية. يحدث ذلك عندما تضيق "اللويحات" أو الكوليسترول أو الرواسب الدهنية الأخرى التي تتراكم على الجدار الداخلي للشريان أو تسد الشرايين التي توصل الدم إلى القلب. بمرور الوقت، قد يتطور ألم الصدر نتيجة لانخفاض تدفق الدم إلى القلب الناجم عن تراكم هذه اللويحات. تم تصميم هذه الدراسة لمعرفة ما إذا كان Arginase بمثابة علامة حيوية لتشخيص مرض الشريان التاجي.تضمنت هذه الدراسة دراسة بعض المتغيرات البيوكيميائية مثل (جلوكوز الدم الصائم (FBG)، التروبونين (TnI) I، البروتين التفاعلي C عالي الحساسية (hs-CRP)، ملف الدهون، نازعة هيدروجيناز اللاكتات (Arginase (LDH,، في مصل 50 مريضا يعانون من مرض الشريان التاجي تم جمعها من مستشفى الكاظمية التعليمي ومقارنتها مع 40 شخصا صحياً. أظهرت نتائج الدراسة الحالية عدم وجود فروق ذات دلالة إحصائية في متوسط عمر المرضى (6.78±67.00) بالمقارنة مع المجموعة الضابطة (6.46±61.10)، P > 0.05.A تم العثور على زيادة معنوية في مستوى FBG ، الكوليسترول ، الدهون الثلاثية ، البروتين الدهني منخفض الكثافة (VLDL)، البروتين الدهني منخفض الكثافة (LDL) ، TnI، hs-CRP، LDH ، ونشاط Arginase في مجموعة المرضى عند مقارنتها بالمجموعة الضابطة . في حين تم الكشف عن انخفاض كبير (P<0.05) في مستوى البروتين الدهني عالي الكثافة (HDL) في مرضى CAD مقارنة بالمجموعة الضابطة. أيضاً، كان هناك ارتباط معنوي إيجابي بين نشاط Arginase مع كل من العمر و FBG. أما بالنسبة لمنحنى مشغل ROC لـ Arginase، فقد وجد أن المساحة تحت المنحنى (AUC) كانت 0.953 مع حساسية 90٪، وخصوصية 95٪.

INTRODUCTION

The most prevalent form of heart disease and the main cause of death in both developed and developing nations is coronary artery disease (CAD) [1], [2]. It happens when "plaque," or cholesterol or other fatty deposits that accumulate on the inner wall of the artery, narrows or blocks the arteries that deliver blood to the heart. Over time, chest pain might develop as a result of the reduction in blood flow to the heart caused by this plaque accumulation. If the artery is blocked, which is typically the consequence of a blood clot, oxygen cannot reach the heart, which may lead to a heart attack and/or injury to the heart tissue [3]. Maintaining the integrity of blood vessels protects the human body from these changes by preventing vascular tone, inflammation, and platelet aggregation. These actions are carried out through the synthesis of a molecule of nitric oxide (NO). NO's vasodilatory activity contributes to preserving vascular homeostasis [4].

The NO was first identified as a key signaling molecule for numerous physiological processes in the 1980s. This was followed by the identification of NO synthase (NOS), which uses L-arginine as its substrate to produce NO and citrulline, this led to competition between Arginase and NOS on L-Arginine. This finding has caused an increase in interest in the interactions between the NOS and Arginase pathways [5]. Arginase can affect the physiological concentrations of polyamines, proline, and NO Arginase/NOS equilibrium may be deregulated by several pathophysiological processes, disrupting the organism's homeostasis and functionality. [6]. Increases in Arginase activity have been associated with cancer, immune system dysfunction, cardiovascular disease (CVD), kidney disease, and central nervous system disorders in mammals [7].

Arginase is the last enzyme in the urea cycle that's responsible for detoxifying ammonia in mammals, by hydrolyzing arginine to ornithine and urea. Arginase is present in two isoforms (Arginase I and II), each with its tissue distribution and physiological function [8]. Arginase I is present in the cytoplasm of the liver cells and has a major role in the urea cycle, while Arginase II is founded in almost all tissues, it is more prevalent in the kidney, prostate, digestive and gastrointestinal system, muscle, and endocrine tissues [8,9]. Arginase's role in vascular dysfunction linked to CVD was primarily researched since studies found that it was expressed in both endothelium and smooth muscle vascular cells [10].

Endothelial dysfunction is associated with decreased NO bioavailability in disease conditions such as acute myocardial infarction (MI). Which contributes to increased vasoconstrictor response, platelet adhesion, and vascular smooth muscle cell proliferation. Future cardiovascular events following acute coronary syndrome are substantially correlated with impaired endothelial vasodilatation. Following Arginase catabolization, Arginine is no longer accessible to NOS, which reduces subsequent NO production. As a result, NO's effects on the heart and vasculature are disrupted, which can be dangerous for cardiac function. Numerous investigations have shown that both stimulation and activation of both forms of Arginase can result in reduced NO generation and endothelial dysfunction. However, polyamines and proline produced in the pathway after the Arginase reaction have been involved in cell proliferation and collagen synthesis, respectively, showing the role of Arginase in reverse remodeling in response to damage [11,12]. In some pathophysiological circumstances, the buildup of asymmetric dimethylarginine (ADMA), an endogenous NOS inhibitor, also limits NO production. There has been extensive research into the link between increased ADMA levels and CVD. MI causes damage to the myocardium, which makes the heart less able to eject blood and decreases ejection fraction [13].

Arginase inhibition may potentially be helpful in several pathological CVD, as was previously mentioned. Patients with coronary artery disease, type 2 diabetes, heart failure, and hypertension showed positive results when the therapeutic effect of Arginase inhibition was examined in a variety of experimental models of cardiovascular illness. The therapy of cardiovascular conditions, cancer, autoimmunity, and inappropriate immunosuppression holds considerable promise when Arginase is interfered with pharmacologically.

MATERIALS AND METHODS

This study included A 50 patients with CAD were collected from Al-Kadhimiya Educational Hospital as a patient group, whereas the control group consists of 40 healthy subjects. Approximately 5 ml of venous blood samples from patients and controls were taken with plastic disposable

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syringes and left at room temperature for 15 minutes. Following coagulation, the serum was separated by centrifugation at 1500 x g for 10 minutes. The hemolysed samples were removed. To prepare for analysis, the serum was separated and kept at -20 ^{0}C. After separating the serum from the blood, FBS, cholesterol, triglyceride, high density lipoprotein (HDL), LDH, were measured by kits from Linear /Spain. The concentrations of TnI and (hs-CRP) was determined automatically by using automated system SIEMEENS ATELLICA. Arginase activity was measured by using the Porembska's procedure as described below [14]. Chemical substances needed in this procedure include Acetic Acid, Hydrochloric Acid, Manganese Chloride, Ninhydrin, Phosphoric Acid, Sodium Hydroxide, Trichloroacetic Acid (TCA)from BDH/ England. Sodium Barbitone and L-Arginine from Rediel Dehien, Germany.

Enzyme assay

To plane tube, 0.5 ml of 0.1 M barbitone buffer (prepared by dissolving two grams of sodium barbitone in 100 ml of water, then pH-adjusted to 9.5 using 0.1 M HCl), 0.1 ml of 200 mM L-arginine solution (This solution was made by dissolving 2.1 g of L-arginine monochloride in 50 mL of water and adjusting the pH with 0.1 M NaOH to 7. 5), 0.1 ml of 50 mM $MnCl_2$ (This solution is made by dissolving 0.9 g of $MnCl_2.4H_2O$ in 100 mL of water), and 0.5 ml of serum are added and incubated for 30 minutes at 37 ℃. The reaction is stopped by the addition of 1.3 ml of 20% TCA (It was prepared at a weight of 20g of TCA in 100 ml of water), and the tube placed for 1 minute in a boiling water bath. After cooling, the precipitated protein is centrifuged off at 4000 rpm for 3 minutes. In the control sample, arginine is added after the addition of TCA. Two ml of Ninhydrin Reagent (The solution was prepared freshly with a weight of 0.25 g of ninhydrin dissolved in 10 ml of a mixture consisting of 4 mL of 6 M H_3PO_4, and 6 mL of concentrated acetic acid) were add to Two ml of supernatant, all tubes were left in the boiling water bath for 1 hour. The absorbance of ornithine - ninhydrin complex in these tubes was read at 515 nm. Then the concentration of ornithine was determined according to standard curve [15].

Calculation

The following equation would be used to determine the Arginase activity:

Arginase units = µg of ornithine (test-control) * 0.505

Statistical analysis

Statistical Package for Social Sciences (SPSS) 25 was used to compute and analyze the data that were presented as (mean ±SD). To assess the association between the data, independent samples t-test and correlation were used. It was considered statistically significant when the probability (p-value) was less than 0.05. To evaluate the sensitivity and specificity of Arginase, a different statistical methodology called the ROC test was utilized.

EXPERIMENT RESULTS

Table 1 summarizes the study participants' characteristics, including fasting blood glucose (FBS), troponin I, cholesterol, Triglyceride, HDL, LDL, VLDL, LDH, hs-CRP and Arginase Activity. The current study revealed that there was non-significant change in mean±SD of age for normal subjects (61.10±6.46) compared to CAD patients (67.00±6.78). Serum glucose levels had highly significant rise (p= 0.001) in the patients group (210.30±62.279 mg/dl) when compared to the control group (96.05±5.384 mg/dl). In addition, CAD patients had highly significant increase (p=0.010) in the TnI level comparing to control group. Also, significant increase (P<0.05) in the levels of cholesterol, triglycerides, LDL, and VLDL as well as a significantly decreased (P<0.05) was found in the level of HDL in the patient group when compared to the control group as shown in Table 1. Moreover, LDH activity revealed highly significant increase (p=0.001) in patient group (317.055±93.132) compared to the control group (166.550±23.360). The results of this study also show a significance increase (P = 0.004) in the activity of Arginase in patients (27.141±8.879 mg/dl) compared to control group (10.064± 4.417), Table 1.

Table 1. Results of age and clinical parameters in CAD patients and control.

Parameter	Control, N=40 Mean ±SD	Patients, N=50 Mean ±SD	P- value
Age (years)	61.10±6.46	67.00±6.78	0.740NS
Glucose (70_106mg/dl)	96.05±5.38	210.30±62.279	0.001
Cardiac Troponin I (<45.2pg/ml)	7.77±2.92	67.252±32.932	0.010
Cholesterol (<200mg/dl)	149.05±11.19	208.620 ± 23.870	0.016
Triglyceride (<150mg/dl)	128.20±8.26	185.450 ±22.938	0.011
HDL (40_60 mg/dl)	46.65±3.45	25.450±6.021	0.037
VLDL (0_30mg/dl)	25.64 ±1.65	37.090 ±4.587	0.011
LDL (<100mg/dl)	76.76 ± 10.69	146.080 ±27.233	0.008
LDH (120_246 u/l)	166.55±23.36	317.055±93.132	0.001
hs-CRP (<10mg/l)	6.33±1.77	42.816±20.916	0.001
Arginase activity	10.06± 4.41	27.141±8.879	0.004

Table 2 displays the Pearson's correlation coefficient values for the study's parameters In CAD patients group. The current study observed a highly significant positive association between Arginase levels and FBS (P<0.001) and a significant negative correlation between Arginase levels and age (P<0.05). Furthermore, this study shown that there is a highly significant positive association (P<0.001) between triglycerides and VLDL as well as between cholesterol and LDL. The ROC curve for Arginase activity to control and CAD patients is presented in Figure 1 and Table 3. The results revealed that Arginase's area under curve (AUC) was 0.953, with cut-off value (16.2050), sensitivity was (90%), and specificity was (95%), indicating that Arginase has diagnostic value for CAD.

Table 2. The Pearson correlation between studied variable of CAD Patients group.

	age	Arginase	glucose	Troponin I	Cholesterol	triglyceride	HDL	VLDL	LDL	LDH	hsCRP
age	1	-.497*	-.444	-.262	.223	.097	-.345	.097	.255	-.058	-.206
Arginase	-.497*	1	.933**	.178	-.121	.068	.326	.068	-.189	-.022	.124
glucose	-.444	.933**	1	.105	-.100	.053	.285	.053	-.159	-.083	.025
Troponin I	-.262	.178	.105	1	-.169	-.117	-.067	-.117	-.114	-.149	.483*
Cholesterol	.223	-.121	-.100	-.169	1	.181	-.555*	.181	.969**	-.082	-.244
triglyceride	.097	.068	.053	-.117	.181	1	-.093	1.000**	.011	-.287	.067
HDL	-.345	.326	.285	-.067	-.555*	-.093	1	-.093	-.691**	-.133	.112
VLDL	.097	.068	.053	-.117	.181	1.000**	-.093	1	.011	-.287	.067
LDL	.255	-.189	-.159	-.114	.969**	.011	-.691**	.011	1	.006	-.250
LDH	-.058	-.022	-.083	-.149	-.082	-.287	-.133	-.287	.006	1	-.371
hsCRP	-.206	.124	.025	.483*	-.244	.067	.112	.067	-.250	-.371	1

Table 3. The receiver operator characteristic (ROC) Analysis for studied groups.

Biomarker	cut-off	AUC	Std. Error[a]	Asymptotic Sig.[b]	Sensitivity%	Specificity%	Asymptotic 95% Confidence Interval	
							Lower Bound	Upper Bound
Arginase	16.2050	0.953	0.035	0.000	90%	95%	0.885	1.000

a. Under the nonparametric assumption, b. Null hypothesis: true area = 0.5

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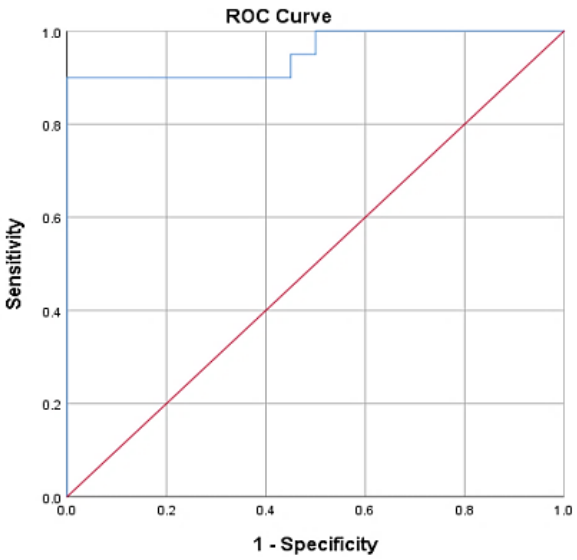

Figure 1. The ROC curve between control and CAD patients.

DISCUSSION

The current study estimates the activity of Arginase for the first time in In Iraqi CAD patients. The results of the current study indicated a significant increase of Arginase activity in CAD patients compared to control.

The vascular endothelium's functional integrity is crucial for appropriate vascular function. Nitric oxide (NO) bioavailability plays a significant role in controlling endothelial function. It was discovered that the enzyme Arginase, which competes with NO synthase for the substrate L-Arginine, has become a key regulator of NO synthesis. The progression of CVD and endothelial dysfunction could be accelerated by elevated Arginase activity, which could decrease the availability of L-Arginine for NO synthase, lower NO production, and increase the synthesis of reactive oxygen species (ROS) [16]. This research supports findings from other studies, such as those by Kövamees and co-workers [16], who observed that diabetes patients with macrovascular complications have higher ratios of certain amino acids, such as ornithine/citrulline, proline/citrulline, and ornithine/arginine, which indicate a change in arginine metabolism as a result of the high activity of Arginase. These alterations show a negative correlation with endothelial function, indicating that Arginase activity is a factor in the dysfunction of the endothelium. Ryoo S. and co-workers [17] found that, allele T of both ARG1 rs2781666G/T and ARG1 rs2781667C/T enhance susceptibility to developing CAD. They also reported a highly substantial increase in Arginase-1 activity in CAD Pakistani patients compared to normal participants (p 0.0001).

Additionally, Zhang and co-worker [18] demonstrated that serum Arginase 1 functioned as a distinct risk factor towards AMI, being significantly higher among patients with AMI compared to normal participants. Furthermore, Arginase 1 had a more accurate AMI diagnosis value and exhibited a positive correlation with Gensini score.

Arginase expression is stimulated by a number of pro-inflammatory elements as well as interleukins. OxLDL (oxidized low-density lipoprotein), glucose, angiotensin II, hypoxia, thrombin, reactive oxygen and nitrogen species, including H_2O_2 as well as peroxynitrite generated from eNOS, and NADPH oxidase are additional stimuli for Arginase production. These substances can trigger a variety of intracellular signaling cascades, such as the protein kinase C/RhoA/Rho kinase (ROCK) pathway, tyrosine kinases, cyclic adenosine monophosphate/protein kinase A, and mitogen-activated protein kinase. Additionally, a number of transcription factors control the expression of Arginase [13] . The consumption of L-Arginine, which eNOS needs to produce NO, was found to be a consequence of increased Arginase activity. This reduced NO generation eventually led to endothelial dysfunction. A connection was demonstrated between Arginase activity and endothelial dysfunction in experimental models of some cases including diabetes [19], [20], aging [21], hypertension [13], pulmonary hypertension [22], and atherosclerosis [23]. Additionally, rabbits with hyperlipidemia who developed atheromatous lesions showed elevated Arginase activity [24]. In apoE-/- atherosclerotic mice, Arginase II is thought to be the dominant isoform of Arginase [25], [20], [26]. Furthermore, Arginase 1 has shown that the impact of cardiac damage in wild mice following AMI by suppressing NO production and enhancing the concentration of inflammatory cells in infarcted regions [27].

In order to determine Arginase's potential function as a CAD biomarker, this study examined the ROC analysis of Arginase for patients with CAD, Figure

1and Table 3. results revealed that Arginase's area under curve (AUC) was 0.953, cut-off was 16.2050, sensitivity was 90%, and specificity was 95%, indicating that Arginase has diagnostic value for CAD. Ren B. and co-workers [28] noted that Troponin I's AUC was 0.998 whereas Arginase 1's AUC was 0.776. Arginase 1 has a considerable diagnostic value for AMI, as evidenced by the best cut-off value for its relative level being 10.191 with a sensitivity of 0.67 and a specificity of 0.761.This study supports a number of other investigations, such as those by, Shatanawi and co-worker [29]and Khaleel and co-worker [30] who found a strong and positive association between glucose and Arginase activity in T2DM Iraqi patients, as well as Kashyap and co-worker [31] who discovered that an increase in FBS in T2DM is correlated with an increase in Arginase activity. It was shown that diabetes is associated with increased food consumption, amino acid metabolism, and blood glucagon to insulin ratio, all of which would contribute to enhancing the urea cycle's activity as well as the activity of Arginase [30]. It was found that upregulation of Arginase-1 induced by hyperglycemia, which inhibited NO-mediated relaxation in human coronary arteries. Arginase up-regulation, which lowers the level of L-Arginine and hence restricts NO production, may be caused by changes in insulin signaling [32]. Also, lipid profile results showed a significant increase in their levels in CAD group, The importance of the lipid profile in the development of CVD has been shown in numerous research. The narrowing and abstraction of cardiac vessels, which are strongly connected with the risk of CVD, may be impacted by increases in total cholesterol and triglyceride levels. The accumulation of LDL-cholesterol in the artery's intima-media due to rises in LDL levels may also cause arteriosclerosis, which may subsequently induce thrombocytopoiesis. A strong correlation between high triglycerides and LDL and the development of CAD has been demonstrated by a large body of research. Damage to endothelium and plaque rupture are caused by oxidized LDL particles. the primary ways by which LDL particles act as a risk factor. They demonstrated that LDL-cholesterol was taken up by cells through receptors after cholesterol was incorporated into the cells [33], [35].

CRP is a pentraxin that is generated from the liver and has five subunits with the MW 23KD. It is essential for the innate immune response. Hs-CRP is recognized as a measure low grade systemic chronic inflammation and has a direct role in atherosclerosis, endothelial dysfunction, and platelet aggregation. It has been demonstrated that this protein plays a variety of roles in the pathophysiology of atherosclerosis and has prognostic significance in individuals with ACS [36]. High hs-CRP levels have been suggested to be linked to metabolic diseases like dyslipidemia. Therefore, in CAD patients, elevated CRP levels with dyslipidemia have a significant risk prediction value compared to those based solely on lipids. As well as according to numerous studies, it was found that both males and females with CAD who were older than 50 years had higher serum levels of hs-CRP [37].

CONCLUSIONS

From this study, it can be concluded the presence of a positive significant correlation between Arginase activity and glucose. This association may be attributed to hyperglycemia promoting the activity of the Arginase and decreasing NO levels. Thus, it increases the risk of heart disease. Also, ROC analysis of Arginase for patients with CAD showed high sensitivity and specify of Arginase, indicating that Arginase has diagnostic value for CAD.

Disclosure and conflict of interest: The authors declare that they have no conflicts of interest.

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