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Study of Procollagen-lysine 5-dioxygenase and some biochemical parameters in coronary artery disease patients

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Abstract

Cardiovascular diseases, specifically coronary artery disease, is among the most common causes of death at all ages and in both sexes, with coronary artery disease accounting for more than 40% of deaths attributable to cardiovascular disease. This clinical study included 160 individuals (80 males aged 35-75 years) with coronary artery disease and (80 of healthy males aged 35-67). The activity of procollagen-lysine 5-dioxygenase, renin, angiotensin-converting enzyme, and glutathione peroxidase were determined, in addition to the levels of glutathione, vitamin C, iron, glucose, malondialdehyde and C-reactive protein, in blood serum using ELISA kits and spectrophotometric method. The results showed a significant decrease in the activity of procollagen-lysine 5-dioxygenase, angiotensin-converting enzyme, and glutathione peroxidase, but a nonsignificant decrease in the activity of renin. As well as a significant decrease in the level of glutathione, vitamin-C and iron. On the other hand, the levels of glucose, malondialdehyde, and C-reactive protein were significantly increased in the patient group compared with the control group.

Introduction

Currently, vascular diseases are among the most serious diseases affecting human life and health globally [1]. The most common forms of cardiovascular diseases are atherosclerosis, coronary artery disease (CAD), arrhythmia, and heart failure [2]. Risk factors that contribute to cardiovascular diseases are either non-modifiable (e.g., family history, gender, and age) or modifiable (e.g., high cholesterol, obesity, high blood pressure, and diabetes), so primary prevention of cardiovascular diseases by identifying and treating at-risk individuals remains a major public health problem [3,4].

Hypertension is a common problem worldwide and is a major risk factor for cardiovascular diseases leading to atherosclerosis and heart failure [5]. When blood pressure rises, the balance between vasodilators (the most important of which are nitric oxide and bradykinin), and vasoconstrictors such as angiotensin-II (Ang II) is disturbed [6,7]. Another pathophysiological event of hypertension is the activation of the Renin-Angiotensin-Aldosterone System (RAAS), as the RAAS contributes to causing pathological changes in the endothelium of arterial blood vessels, which leads to endothelial cells become dysfunctional

and thus blood vessels becoming inflamed and oxidative stress, making the coronary arteries more susceptible to plaque deposition, which is crucial in the development of atherosclerosis [8,9]. Also, when blood pressure is high, oxidative stress will enhance blood vessel damage and promote fibrosis and cardiac hypertrophy [10].

Oxidative stress is one of the main mechanistic pathways that contribute to the development of cardiovascular diseases, including myocardial ischemia, as oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and antioxidants, as increased production of (ROS) is closely associated with decreased antioxidant capacity [11]. Antioxidant enzymes including glutathione peroxidase (GPx), glutathione reductase (GRx), glutathione-S-transferase (GST), superoxide dismutase (SOD), and catalase (CAT) are the main cellular defense against injury [12]. Disturbance in glutathione (GSH) homeostasis is also associated with cardiovascular diseases as well as cancer, diabetes, aging, and diseases associated with excessive oxidative stress [13,14]. Excessive production of reactive oxygen species (ROS) combined with decreased antioxidants has been identified as a key mechanism in the pathogenesis of ischemia, making it a potential therapeutic target [15,16].

The importance of blood vessels comes from the fact that they are the sole carrier and distributor of oxygen and nutrients to the tissues in the human body. The walls of these vessels (veins and arteries) are composed mainly of the structural protein known as collagen and elastin [17]. Procollagen-lysine 5-dioxygenase (PLOD) or lysyl hydroxylase (LH) is a protein found in the lumen of the endoplasmic reticulum. Functionally, this enzyme catalyzes hydroxylation (adding hydroxyl group) of lysine amino acid units in the peptide chains that form the collagen protein in the walls of blood vessels in humans [18,19]. Hydroxylysine resulting from the latter process is essential for the stability of the cross-linked structures of collagen [20]. Disease conditions have been found associated with the occurrence of genetic mutations in this gene (*PLOD*) that encodes the construction of collagen protein, such as Thoracic Aortic Aneurysm disease (TAA) [21], as genetic factors “genes”, play a major role in atherosclerosis and coronary artery disease, accordingly, studies have identified the association between genetic variations (Extracellular matrix genes) and coronary artery disease, and have emphasized the importance of cell attachment to the extracellular matrix (ECM) in vascular diseases. Therefore, changes in proteins within the ECM may affect key cells and cause the development of coronary artery disease. Further studies are needed to understand the major role played by the ECM and the mechanisms by which ECM-associated proteins influence the development and progression of atherosclerosis (AS) [21].

In addition, there are some genetic diseases resulting from defects and mutations in the PLOD gene, which cause severe disorders, such as Ehlers-Danlos syndrome (EDS). Six types of (EDS) have been identified, which is a group of connective tissue diseases characterized by hyperextensible skin, fragility of blood vessels, and fragility of connective tissue in general. Rare cases are characterized by lateral curvature of the spine and hypermobility of the joints [22,23]. Evaluate the correlation between low PLOD and antioxidants state in patients with CAD is a main aim of the study.

Materials and methods

The chemicals used in this study were provided by international companies: (Chinese company, Shanghai ideal medical technology) for ELISA measurements of the enzymes (PLOD, Renin, ACE). Standard kits were prepared by the Italian company (Giesse diagnostics) to measure C-reactive protein. For glucose, iron, the several analyses were prepared by the French company (Biolabo). The activity of the enzyme glutathione peroxidase, also the level of glutathione, malondialdehyde and vitamin-C were measured using materials prepared by the Chemistry Department store in the College of Science and the central store of the University of Mosul.

The samples were divided into two groups; a patients group included 80 blood samples of people with coronary artery disease ranging in age from 35-75 years for males. The control group containing 80 samples of blood for healthy people aged 35-67 years for males. The activity of the enzymes (PLOD, Renin, ACE) in the serum estimated in Enzyme-Linked Immunoassay using several Elisa Kits. The activity of glutathione peroxidase (GP_X) was estimated using the method followed by the researchers [24]. The GSH level was estimated based on the method used by Sedlak and Lindsay, 1986 [25]. The concentration of vitamin-C was determined using the method described in [26]. iron concentration was determined by the Colorimetric method, and the analysis kit from the French company Biolabo was used [27]. The level of glucose in the serum was estimated by enzymatic method using (Kit) from the French company Biolabo [28]. malondialdehyde level in the serum were estimated using a modified method developed by the researchers Guidet and Shah (1989) [29]. C-reactive protein concentration was estimated using the analysis kit of the Italian company Giesse diagnostics.

Statistical Analysis

Data obtained were analyzed using T-test via the statistical package of the social sciences program SPSS 27, and a $P \leq 0.05$ was considered statistically significant.

Results and discussion

The results in table 1 showed a significant decrease ($P \leq 0.001$) in the level of Procollagen-lysine 5-dioxygenase in serum of coronary artery disease patients. The reason may be attributed to iron deficiency, which leads to a decrease in the activity of the PLOD enzyme and thus a decrease in the levels of hydroxylysine, which leads to a defect in the structural composition of collagen [30], as Fe^{2+} is essential for the catalytic activity of the procollagen-lysine 5-dioxygenase enzyme, which facilitates the process of adding a hydroxyl group to lysine residues in collagen [31]. Or it may be due to a deficiency of vitamin C, as studies have indicated the importance of the regulatory effects of ascorbic acid, including stimulating the activity of the PLOD enzyme and accelerating collagen production [32]. The importance of vitamin C in the activity of the enzymes lysyl hydroxylase in the synthesis of healthy collagen, as its role is as a cofactor for the enzymes, and the function of vitamin C in this enzyme usually include the chemical reduction of iron. Therefore, vitamin C is necessary to return iron to its reduced state, and if iron is not reduced by vitamin C, the enzyme will remain inactive [33]. Low levels of vitamin C inhibit collagen formation in various tissues, including the skin and blood vessels. Low collagen production in the body leads to fragility of the skin and blood vessels, bleeding gums, and poor wound healing [34].

Table 1: comparison of the level of activity of the PLOD Enzyme with some biochemical variables between male coronary artery disease patients (mean±SD)

Parameters	Control/80	Patients/80	*P*
Procollagen-lysine 5-dioxygenase (U/l)	8.80 ± 1.14	5.76 ± 1.96	0.001
Renin (U/l)	71.87 ± 12.64	66.22 ± 15.82	0.288
Angiotensin converting enzyme (U/l)	13.82 ± 2.46	11.96 ± 2.22	0.018
Glutathione peroxidase (U/l)	1.80 ± 0.11	1.23 ± 0.12	0.001
Glutathione (µmol/l)	3.38 ± 1.45	1.56 ± 0.42	0.001
vitamin-C (mg/100ml)	1.12 ± 0.32	0.28 ± 0.13	0.001
Fe (µg/l)	142.42 ±14.42	60.78 ± 12.46	0.001
Glucose (mmol/l)	5.40 ± 0.62	7.18 ± 2.01	0.001
Malondialdehyde (µmol/l)	0.77 ± 0.61	1.09 ± 0.34	0.001
CRP (mg/l)	1.92 ± 1.24	24.34 ± 35.45	0.001

The results shown in Table (1) indicate a non-significant decrease in the level of renin (at the probability level P≤0.288) in serum of patients compared to control group. But we notes a significant decrease in the level of angiotensin-converting enzyme in serum of patients compared to the control group at a probability level of (P≤ 0.018), which is consistent with the study of Bangalore and his group. The reason for the decrease in the level of renin and angiotensin-converting enzyme in coronary artery disease patients is due to the use of renin-angiotensin system inhibitors (RASI) [35], as these drugs prevent the release of renin from the kidneys, so the decrease in renin release leads to a decrease in the concentrations of angiotensin 1 and 2, thus contributing to reducing the risk of disease progression, while ACE inhibitors work to prevent the conversion of angiotensin-1 to angiotensin-2, so these drugs reduce the level of angiotensin-2 and increase the level of angiotensin-1 and angiotensin-(1-7) [36], so the observed results in patients are attributed to the different mechanisms of action of RASI inhibitors. Angiotensin and angiotensin receptor blockers, including increased bradykinin levels and nitric oxide production stimulated by angiotensin inhibitors [37].

The results in Table (1) showed a significant decrease at the probability level (P ≤0.001) in the level of glutathione peroxidase activity in serum of patient group compared to control group. This was in agreement with Bastani and his group, as the GPx enzyme is a sensitive biomarker for assessing oxidative stress and has antioxidant activity, as the increase in ROS leads to an increase in the level of oxidative stress and thus causes a decrease in the level of the antioxidant GPx enzyme, that increases the possibility of lipid oxidation[40], and lead to damage the lining of the blood vessels and the onset of atherosclerosis, and thus the development of various cardiovascular diseases[38,39].

The results in Table (1) showed a significant decrease at the probability level (P ≤0.001) in the level of glutathione for the patient group compared to the control group. This was in agreement with Musthafa and his group (2017) as well as Varadhan and his group

(2022), as oxidative stress associated with cardiovascular diseases is the main reason for reducing the level of glutathione, which is an antioxidant in the body to defend cells, as it works to destroy free radicals formed as a result of increased oxidative stress [41], so oxidative stress and the inflammation associated with it are considered major risk factors for coronary artery disease, through a decrease in the level of GSH and an increase in the level of MDA [42].

The results of estimating the level of vitamin-C in serum of coronary artery disease patients showed a significant decrease at the probability level ($P \geq 0.001$) compared to the control group as shown in Table (1). This is consistent with Karajibani and his group (2009), and also agreed with Agha and his group (2022). That low levels of vitamin-C with high levels of lipid peroxidation are associated with an increased risk of coronary heart disease, because vitamin-C has an important role in cardiovascular diseases as an antioxidant that protects cell membranes from lipid oxidation by free radicals, as it prevents oxidative modification of LDL primarily by removing free radicals and other reactive species and preventing them from reacting with LDL, thus playing a pivotal role in maintaining the function of the vascular endothelium [43]. The reason for the low level of vitamin C may be attributed to high blood sugar, which leads to an increase in the production of oxidative compounds [44], that increase oxidative stress, and increases the depletion of vitamin-C to inhibit oxidative compounds [45].

The results of the iron level assessment showed that there was a significant decrease at the probability level ($P \geq 0.001$) in its level in the patient group compared to the control group, as shown in Table (1). This is consistent with what Gill et al. (2017) reported, and also consistent with a study by Guo et al. (2022), as iron deficiency is common in patients with cardiovascular disease, and approximately 60% of patients with coronary artery disease suffer from iron deficiency, which may be attributed to insufficient dietary iron intake, poor absorption, or increased blood loss due to anticoagulant therapy, gastrointestinal disease, or renal disease [46,47]. Serum iron values show daily variation depending on dietary iron intake or patient condition, and it has been observed that iron deficiency may have a causal effect on cardiovascular disease. Iron plays a role in many basic processes including red blood cell formation, and iron deficiency may affect the risk of cardiovascular disease by affecting red blood cells. Iron deficiency is also known to affect cellular metabolism, and thus, iron deficiency may lead to impaired function of various tissues including the central nervous system, muscle tissue, myocardium, immune system, and thyroid gland, thus increasing the risk of cardiovascular disease. Therefore, higher iron levels reduce the risk of cardiovascular disease [48,47].

The results shown in Table (1) indicate a significant increase at the probability level ($P \leq 0.001$) in glucose level in serum of patients compared to control group, which is consistent with the study of Riise and his group, where they found that high levels of glucose, fatty acids and insulin resistance together lead to oxidative stress and activation of Protein kinase C, which may lead to vasoconstriction, inflammation and clots [49]. The reason for high blood glucose level may also be due to an increase in the body mass of patient group, which may later cause insulin resistance, diabetes and cardiovascular diseases [50], as high blood sugar leads to reduced vasodilation, including microvascular occlusion, increased coronary artery thrombosis and increased myocardial damage [51].

Table (1) shows a significant increase in the level of malondialdehyde at the probability level ($P \leq 0.001$) in serum of coronary artery disease group compared to the

control group. This is what was indicated by the study of Zavar-Reza and his group that the level of malondialdehyde in serum of coronary artery disease patients was significantly higher than in serum of control group, as malondialdehyde plays a role as an important factor in atherosclerosis, as the increase in MDA in patients with coronary artery disease leads to cell damage [52], and the reason may be attributed to the decrease in antioxidants and the increase in the generation of free radicals in the body, which leads to an increase in the oxidation process of fats and thus an increase in the formation of MDA[53], as MDA is a sign of lipid peroxidation and oxidative stress. It also indicates the severity of coronary artery disease and plaque formation, as its concentration increases in coronary artery patients and is inversely related to antioxidants [54].

The results in Table (1) showed a significant increase at the probability level ($P \leq 0.001$) in the concentration of C-reactive protein in the group of coronary artery disease patients compared to the control group. This is consistent with what Liu and his group indicated, considering C-reactive protein as a risk factor for coronary artery disease [55], as the high level of C-reactive protein is an indicator of inflammation, and is a major risk factor for cardiovascular disease (CVD) [56], and its increase indicates the process of local inflammation in the coronary artery [57]. Inflammation plays a major role in initiating and promoting atherosclerosis and may lead to acute coronary syndrome (ACS) by inducing plaque instability [58].

Conclusions

Individuals diagnosed with CAD, had low levels of PLOD, glutathione peroxidase, glutathione, vitamin C, and iron compared to the control group. And the study results shows that glucose and malondialdehyde were associated with an increased risk of CAD.

Also, renin, angiotensin-converting enzyme plays an essential role in developing of coronary artery disease in patients group compared with control group. And elevated CRP levels indicate local inflammatory processes in the coronary artery.

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دراسة إنزيم البروكولاجين-لايسين5-داي اوكسجنيز وبعض المتغيرات الكيموحيوية لدى مرضى الشريان التاجي

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الخلاصة:
تعد أمراض القلب والأوعية الدموية، وتحديداً مرض الشريان التاجي، من أكثر أسباب الوفاة شيوعاً في جميع الأعمار وفي كلا الجنسين، حيث يشكل مرض الشريان التاجي أكثر من 40% من الوفيات المنسوبة إلى أمراض القلب والأوعية الدموية. وقد شملت هذه الدراسة السريرية 160 فرداً (80 من الذكور الذين تتراوح أعمارهم بين 35-75 عاماً) مصابين بمرض الشريان التاجي و(80 من الذكور الأصحاء الذين تتراوح أعمارهم بين 35-67 عاماً). وتم تحديد نشاط البروكولاجين-لايسين5-داي اوكسجنيز ، والرينين، والإنزيم المحول للأنجيوتنسين، وكلوتاثايون بيروكسيديز، بالإضافة إلى مستويات الكلوتاثايون، وفيتامين-سي، والحديد، والكلوكوز، والمالونداياألديهايد ، والبروتين التفاعلي-سي، في مصل الدم باستخدام قياسات الإليزا وطريقة القياس الطيفي. وأظهرت النتائج انخفاضاً معنوياً في نشاط البروكولاجين-ليسين 5-داي أوكسجنيز والإنزيم المحول للأنجيوتنسين والكلوتاثايون بيروكسيديز، ولكن انخفاضاً غير معنوي في نشاط الرينين. وكذلك انخفاضاً معنوياً في مستوى الكلوتاثايون وفيتامين-سي والحديد، ومن ناحية أخرى ارتفعت مستويات الكلوكوز والمالونداياألديهايد والبروتين التفاعلي-سي بشكل معنوي في مجموعة المرضى مقارنة بمجموعة السيطرة.