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Investigating the role of heat shock protein HSP60 in coronary artery disease patients infected with *Helicobacter pylori*

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Abstract

Background: Coronary artery disease is a disorder of the heart and blood vessels caused by the hardening or blockage of the coronary arteries. Elevated blood cholesterol, high blood sugar, and high blood pressure are prominent risk factors that contribute to the development of arterial hardening. Evaluation of heat shock protein 60 levels in patients with coronary artery disease infected with *Helicobacter pylori* bacteria and comparison of the results with non-infected patients and the control group.

Methods: This study was conducted in Nasiriyah Heart Center and Nasiriyah Teaching Hospital in Nasiriyah**.** A total of 150 samples were collected and divided into three groups: the first group consisted of patients with coronary artery disease infected with *Helicobacter pylori* bacteria, the second group consisted of patients with coronary artery disease but not infected with *Helicobacter pylori*, and the third group served as the control group. *H. Pylori* infection was determined in serum. Heat shock protein-60 levels were determined using enzyme-linked immunosorbent assay.

Results: The level of heat shock protein-60 in the first group was higher than that of the second and third groups, where (P ≤0.001) and (LSD= 1.86).

Conclusion: Infection with certain pathogenic factors, such as bacteria, can lead to inflammation of the blood vessel lining, which in turn affects the development of coronary artery disease. Consequently, inflammatory factors can increase the cellular expression of heat shock proteins as a result of oxidative stress or inflammation. These heat shock proteins are then displayed on the cell surface and contribute to the presence of heat shock proteins in the blood. Efforts should be made to study heat shock proteins resulting from infection with pathogens, and their role in coronary artery disease and other heart diseases.

Introduction

Atherosclerosis, which causes the coronary arteries to narrow or get blocked, is what causes coronary artery disease. Significant cardiovascular risk factors that accelerate the development of atherosclerosis include elevated blood cholesterol, high blood sugar, and hypertension [1]. The prevention and treatment of risk factors linked to CAD have made tremendous strides in recent decades, which has led to a decrease in death rates. However, CAD remains the biggest cause of mortality globally, accounting for over 17.9 million fatalities annually [2]. Considering the crucial role of inflammation in the pathophysiology of atherosclerosis and the progression of CAD, there has been a renewed emphasis on this area of research. Exploring the residual risk associated with inflammation could potentially lead to clinical benefits and advancements in identifying effective interventions [3]. Risk factors for CAD can be categorized into two groups: non-modifiable and modifiable. Non-modifiable risk factors encompass factors such as age, gender, ethnicity, and family history of CAD, which cannot be altered. On the other hand, modifiable risk factors include hypertension, hyperlipidemia, diabetes, obesity, smoking, a poor diet, a sedentary lifestyle, and stress. These modifiable risk factors can be addressed and managed through lifestyle changes and medical interventions [4].

A significant number of individuals with coronary artery disease (CAD) do not have any of the conventional risk factors, including hypertension, smoking, obesity, high cholesterol, or genetic susceptibility [5]. In humans, no one factor can fully explain all the causes of CAD. Highly sensitive C-reactive protein, fibrinogen, serum amyloid and interleukins, tumor necrosis factor (TNF), interleukin-6, and cellular and vascular fibrinogen adhesion molecules are examples of inflammatory markers in the blood that have been linked or correlated with the risk of cardiovascular disease [6-7]. The relationship between coronary artery disease, atherosclerosis, and infectious diseases is supported by three main lines of evidence: epidemiological, pathological, and microbiological. Epidemiological studies, pathological findings, and microbiological research all contribute to establishing this link; animal models, clinical studies, and in vitro data provide biological plausibility and support the idea of a causal relationship. Among the most extensively studied infectious agents or diseases in this context are *Helicobacter pylori*, *Chlamydia pneumonia*, cytomegalovirus (CMV), herpes simplex virus (HSV), and periodontitis [8].

Microbes can directly infect the arterial intima, leading to subsequent damage and an inflammatory response that can induce or accelerate atherosclerosis. Another approach to establishing the connection between infectious agents and atherosclerosis is by identifying organisms within atherosclerotic plaques. However, it is important to note that the presence of these organisms does not necessarily prove causation, as they could be "innocent bystanders" trapped within the compromised vessel wall [9]. Additionally, it is well known that some germs, particularly *Helicobacter pylori*, can cause cerebrovascular illness in addition to digestive system disorders such as peptic ulcer disease and coronary artery disease [10]. *H. pylori* seropositivity has a tendency to be positively correlated with coronary artery disease (CAD) or cerebrovascular disease [11-12].

More and more experts believe that atherosclerosis is an immune system-mediated disease of the vascular system. The idea that atherosclerosis is an inflammatory condition caused by the immune system is supported by the discovery of macrophages and activated lymphocytes within atherosclerotic plaques [13]. Atherosclerotic plaques include immune system cells, which may indicate that the immune system is involved in the atherogenic process. Numerous triggers may be secondary to their migration and activation inside the plaques [14]. According to recent research, inflammation is the primary factor accelerating atherosclerosis[15]. Even in the very early stages of the illness, inflammatory cells such macrophages, T cells, and B cells have been shown infiltrating early fatty streaks of atherosclerotic plaque [13]. Numerous pathogenic autoantigens, including heat shock proteins (HSP), oxidized low-density lipoprotein, and ß2-glycoprotein I, have been linked to the development of atherosclerosis [16]. Antigen-presenting cells (APC), such as dendritic cells, B cells, monocytes/macrophages, and vascular smooth muscle cells that express the HLA-DR, present to T cells during antigen-specific immune responses in the vasculature[17].Macrophages and T cells release cytokines, which are important regulators of inflammation,Cytotoxic T cells and pathogenic autoantibodies made by plasma cells powered by B cells also have a role in the formation of atherosclerotic plaques [18]. There are many activated T cells, which generate IL-2 and other cytokines, in the plaques[19].In atherosclerotic lesions, a large number of cytotoxic CD8 T cells have been identified [20-13]. B cells and natural killer (NK) cells have also been discovered in atherosclerotic plaques, but to a lesser extent. Surprisingly, these plaques include plasma cells that produce IgG [19]. As we have already seen, B cells and plasma cells that produce antibodies have been linked to the development of atherosclerosis [19-13]. It's interesting to note that HLA-DR is required for CD4+ T cells to identify oxLDL. As a result, cellular and

humoral immune responses are focused towards oxLDL[21]. Acute coronary syndrome (ACS), stroke, and anti-phospholipid autoantibodies have all been linked to atherosclerosis [15-18]. Anti-cardiolipine (a-CL) autoantibodies are among the anti-phospholipid autoantibodies that have been proven to have the most significant pathogenic impact [18].The cofactor of CL is b2-Glycoprotein I, and autoantibodies against b2GPI have been linked to the pathophysiology of accelerated atherosclerosis and the antiphospholipid syndrome (APS) [19]

It is known that heat shock proteins are expressed within the human body when a defect occurs in the internal cells or when infections are caused by pathological factors such as a virus, bacteria, or any other pathological factor, when heat shock protein is expressed in large quantities, it may lead to accumulation in atherosclerotic plaques. It was stated that this may promote the development of atherosclerosis through the interaction between immune reactants [22].

There is mounting evidence that autoimmunity promotes atherogenesis, and heat-shock protein (HSP) may be one of the factors that determine autoantigenic development [23-24]. When cells are subjected to stressful stimuli such inflammation, infection, and exposure to oxidizing agents, highly conserved proteins, or HSPs, are created in enormous numbers. Notably, human atherosclerotic lesions show higher expression of human HSP60 on endothelial cells, macrophages, and smooth muscle cells [25]. Heat shock proteins are A group of intracellularly situated, functionally related proteins. Their expression is elevated in response to environmental stress, such as exposure to inflammation, infection, and oxidizing chemicals, and they are then visible on the cell surface [26-27]. It has been hypothesized that the human immune system detects these typically intracellular molecules as foreign via surface expression, which makes them seem like cryptic antigens [28]. Given how highly conserved HSPs are throughout all eukaryotes and prokaryotes, it has been hypothesized that immune responses to microbial HSPs may interact with homologous host proteins in a way known as molecular mimicry [29-30-27].

Methods

The study was conducted at Al Nasiriyah Heart Center and Al Nasiriyah Teaching Hospital. From September 2022 to March 2023.

Cases: The study included 100 patients, 50 of with coronary artery disease and infected with *H. pylori*, 50 patients with coronary artery disease and without *H. pylori*.

Controls: The control group consisted of 50 people with no history or presence of identified or suspected vascular disease identified by clinical examination. They were obtained from the Medical Consultation Department at Al-Nasiriyah Heart Center who were referred for examination from Al-Nasiriyah Teaching Hospital.

Determination of HSP-60

The level of HSP60 in the serum of the study group and the control group, was determined by ELISA (enzyme-linked immunosorbent assay) using a prepared kit for HSP60 provided by Biomatik (USA). Blood samples were obtained with the informed consent of the subjects participating used for this study and the permission to that effect was obtained from the ethical committee of the hospitals.

Determination of CRP

The test employs a sandwich immunedetection technique, in which the detector antibody in the buffer binds to the antigen in the sample to produce antigen-antibody complexes, which then migrate onto the nitrocellulose matrix and are picked up by the other immobilized antibody on the test strip. As more antigen is present in the sample, more antigen-antibody complexes are formed. This results in a brighter fluorescence signal on the detector antibody, which the equipment processes for the AFIAS tests to determine the sample's CRP content.

AFIAS CRP consists of: Cartridge, Pipette tip, ID chip, Instruction for use-tip (On demand).

Statistical analysis

The data of the current study was statically analyzed using SPSS (Statistical Package of Sociot Science version 26) using one-way (ANOVA) for mean variation, least significant difference(LSD) p. value less than 0.05., independent t-test and chi square.

Results

The study included 150 individuals, who were divided into three groups: The first group included 50 patients with *Helicobacter pylori* infection and coronary artery disease, and the second group included 50 patients who did not have *Helicobacter pylori* infection but had coronary artery disease. The third group, the control group, included 50 individuals.

There were 28 (56%) men and 22 (44%) women with an average age of 72.60 ± 18.97 in the first group. As for the second group, there were 33 (66%) men and 17 (34%) women, with an average age of 71.70 ± 21.06, while in the control group, there were 28 (56%) men and 22 (44%) women, with an average age of 55.44 ± 18.53.

The number of smokers in the first group was 29 (58%), while in the second group 26 (52%). The number of smokers in the third group and the control group was 0 (0%). The number of people with blood pressure reached 14 (28%) in the first group, while the second group had a number of 29 (58%), while in the third group there was none. The number of people with diabetes was 28 (56%) for the first group, while for the second group the number of people with diabetes was 23 (46%) and the third group did not exist.

Group		G1 (N = 50)	G2 (N = 50)	G3 (N=50)	*P.value*
Age		72.60±18.97	71.70±21.06	55.44±18.53	
Gender	Male	28 (56%)	33 (66%)	28 (56%)	0.50
	Female	22 (44%)	17 (34%)	22 (44%)	
Smoking	Smoker	29 (58%)	26 (52%)	0 (0%)	0.000*
	Non-smoker	21 (42%)	24 (48%)	50 (100%)	
Hypertension	Yes	36 (72%)	21(42%)	-	0.002*
	No	14 (28%)	29 (58%)	-	
Diabetes	Yes	28 (56%)	23 (46%)	-	0.317
	No	22 (44%)	27 (54%)	-	

Table 1: Characteristics of the study groups according to age, gender, smoking habit, Hypertension, and diabetes.

Estimate of Heat shock protein-60 According of the study group

The current study recorded a significant increase in the concentration of heat shock protein -60 in the first and second groups compared to the third group at p. value <0.05, as shown in Table 2

Group	HSP-60 ng/ml Mean ± SD
G1(N=50)	42.91 [a] ± 6.18
G2(N=50)	32.45 [b] ± 6.64
G3(N=50)	12.83 [c] ± 1.73
p-Value	<0.001*
LSD	1.86

Table 2: HSP-60 levels in the study group.

Estimation of Heat Shock Protein-60 According to Age Groups and Gender

According to the current findings, there was no statistically significant difference in the concentration of heat shock protein-60 in the first group of male age groups, but there was a difference in the second group (p value <0.05), and there was an increase in the third group (p value <0.05), but it was not statistically significant.

As shown in Table 3, the current findings revealed that there was no statistically significant difference in the concentration of heat shock protein -60 in the first group of female age groups, no significant difference in the second group, and a statistically significant increase in the third group.

Estimation of C-Reactive Protein Level According to Study Group

As indicated in Table 4, the current study discovered a substantial rise in C-reactive protein concentration for the first group when compared to the second group, but there was no significant difference between the two groups. However, when compared to the third group, the increase was significant at p. value <0.05.

Male Male Age	HSP-60 ng/ml Mean ± SD					
	No.	G1	No.	G2	No.	G3
⩽ 60 years	5	45.22±3.72	12	35.11±2.90	22	12.82±1.74
> 60 years	23	43.77±5.18	21	36.18±6.14	7	13.63±1.28
P-value	0.791		0.043		0.189	
Female Age	HSP-60 **ng/ml** Mean ± SD					
	No.	G1	No.	G2	No.	G3
⩽ 60 years	6	46.93±6.13	4	33.76±2.85	8	15.18±5.07
> 60 years	16	44.13±6.56	13	34.37±2.22	13	13.14±2.30
P-value	0.913		0.493		0.019	

Table 3: The HSP-60 in study groups according to age and gender.

Group	CRP mg/dl Mean ± SD
G1(N=50)	5.65 [a] ± 1.02
G2(N=50)	5.51 [a] ±1.17
G3(N=50)	3.59 [b] ± 1.80
p - value	<0.001*
LSD	0.79

Table 4: C-Reactive Protein of the study group.

Estimation of C-Reactive Protein Level According to Age Groups and Gender

According to the current findings, the first age group of men in the first group had a significantly lower concentration of C-reactive protein than the second age group, whereas the first age group increased in the second group although this rise was not statistically significant at p. value <0.05. In the third group, the second category increased relative to the first category, but this difference was not statistically significant. value <0.05. According to the current findings, there was a significant difference between the levels of C-reactive protein in the females in the first age group of the first group and those in the second age group. Additionally, in the second group, the second age group showed a statistically significant rise (p value <0.05). In the third group, the second category increased relative to the first category, but this difference was not statistically significant. value 0.05, as seen in table 4.

Male Age	CRP mg/dl Mean ± SD					
	No.	G1	No.	G2	No.	G3
⩽ 60 years	5	6.88±1.09	12	6.24±0.99	22	2.85±0.94
> 60 years	23	7.84±1.98	21	5.42±0.89	7	3.32±0.86
p-value	0.025		0.906		0.729	
Female Age	CRP mg/dl Mean ± SD					
	No.	G1	No.	G2	No.	G3
⩽ 60 years	6	6.17±1.53	4	6.36±0.44	8	2.57±0.75
> 60 years	16	8.43±2.34	13	7.34±2.42	13	2.83±0.73
p-value	0.034		0.045		0.883	

Table 5: The C-Reactive Protein in study groups according to age and gender.

Discussion

The development of coronary heart disease may be influenced by infections brought on by different bacteria. *Helicobacter pylori* is one of these microorganisms, and it has the potential to lead to blood vessel lining inflammation [31].

Chronic infections may influence the development of CHD by a variety of pathways, including autoimmune reactions, chronic inflammatory responses, and modifications to established CHD risk factors [10-32]. They may cause the production of foam cells, which would have a direct impact on the vessel wall [33]. Therefore, bacteria and viruses such as *H. pylori*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, *Porphyromonas gingivalis*, *Streptococcus mutans*, and Herpes simplex and Hepatitis C viruses have been thought to play a role in the development of CHD [34].

According to the current study, levels of heat shock protein -60 were significantly higher in the first group than in the second group, but there was also a rise in both the first and second groups as compared to the third group (the control). High levels in the first group may be due to infection with *Helicobacter pylori*, which leads to acute infections or cellular stress, and thus HSP-60 is secreted in larger quantities than normal.

It is not known exactly how Hsp60 confers a higher cardiovascular risk, but it may be that increases in Hsp60 levels in the circulation could stimulate organs and distant cells such as endothelial cells and other cells in the vascular wall and heart muscle. Because Hsp60 has been shown to stimulate inflammation in endothelial cells [35] as well as smooth muscle cell proliferation and migration as critical steps in arterial wall thickening [36-37]. Atherosclerosis is believed to be developed as a result of inflammation [38] Inflammation's origins are still unknown, though. The increase in the level of heat shock protein-60 in the first group is only evidence that the response of heat shock proteins increases in expression in the case of inflammation, stress on the cell, or damage to the cell due to pathological factors, even though the systemic inflammatory response could be a result of the disease process or present a mediator in the pathogenic chain [39]. High levels of inflammation and stress could trigger intracellular HSP release, which helped increase extracellular HSP content and stimulate an innate immune response [40-41].

The current study recorded an increase in the level of C-reactive protein concentration in the first group compared to the second group, but it is not statistically significant, but in both the first and second groups there is an increase in the level of C-reactive protein concentration compared to the third group (the control), the resulting increase in the concentration of C-reactive protein for the first group, it may be due to systemic infections or myocardial ischemia. CRP has been reported to be elevated in patients with acute ischemia [42].

In conclusion, it appears that heat shock proteins-60 produced due to infection with some pathogens, especially *Helicobacter pylori*, stimulate the production of antibodies against human HSP-60, which leads to the development of the condition.

Author Contributions

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Competing Interests

The authors declared that there were no conflictsof interest.

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