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

Muntadher Abdulateef Alhasan*, Manal Badi Salih

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 we evaluated and compared 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* status was determined by serum (IgG/IgA). HSP60 levels were determined using enzyme-linked immunosorbent assay.

Results: HSP60 levels differed significantly among the study groups (overall $p < 0.001$; least significant difference (LSD) = 1.86), with Group 1 showing higher concentrations than Group 2, and both Groups 1 and 2 showing significantly higher levels than the control group (Group 3).

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 because 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 pneumoniae*, 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 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 [13-20]. 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 [13-19]. 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]. Anticardiolipine (aCL) autoantibodies are among the anti-phospholipid autoantibodies that have been proven to have the most significant pathogenic impact [18].The cofactor of CL is β2-Glycoprotein I, and autoantibodies against (β2GPI) have been linked to the pathophysiology of accelerated atherosclerosis and the antiphospholipid syndrome (APS) [19]

Heat shock proteins (HSPs) are expressed in the human body when internal cellular defects occur or when infections are caused by pathogens such as viruses or bacteria. Excessive expression of HSPs can lead to their accumulation in atherosclerotic plaques. This accumulation may promote the development of atherosclerosis through interactions with immune components [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. The study period was September 2022 to March 2023.

Cases: The study included 100 patients, 50 with coronary artery disease and those 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 HSP60

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 permission to that effect was obtained from the ethical committee of the hospitals.

Determination of CRP

The test employs a sandwich immune detection 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.

The AFIAS CRP kit includes: cartridge, pipette tip, ID chip, and instructions for use.

Statistical analysis

Data were statistically analyzed using SPSS version 26 (Statistical Package for the Social Sciences). One-way ANOVA was applied to compare mean values, and post-hoc comparisons were performed with the least significant difference (LSD) test, with statistical significance set at $p<0.05$. Independent t-tests and chi-square tests were also used where appropriate. Assumptions were checked with Shapiro–Wilk and Levene's tests.

Results

The study included 150 individuals, who were divided into three groups: The first group included 50 patients with *H. pylori* infection and coronary artery disease, and the second group included 50 patients who did not have *H. 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%). Hypertension was observed in 36 individuals (72%) in Group 1 and 21 individuals (42%) in Group 2, while no cases were reported in the control group (Group 3). Diabetes was present in 28 individuals (56%) in Group 1 and 23 individuals (46%) in Group 2, while no cases were reported in the control group (Group 3) as shown in table 1.

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	P < 0.001
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%	0.002*
	No	14 (28%)	29 (58%)	0%	
Diabetes	Yes	28 (56%)	23 (46%)	0%	0.317
	No	22 (44%)	27 (54%)	0%	

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

* P-values: Age compared using one-way ANOVA; categorical variables compared using χ^2 test. Asterisks (*) indicate statistical significance at $p < 0.05$.

HSP60 Levels in the Study Groups

HSP60 levels varied markedly among the study groups. Group 1 demonstrated the highest concentrations (42.91 ± 6.18 ng/mL), followed by Group 2 (32.45 ± 6.64 ng/mL), while the control group (Group 3) had the lowest values (12.83 ± 1.73 ng/mL). Statistical analysis revealed that both Group 1 and Group 2 had significantly higher HSP60 levels compared with the control group (p<0.001). In addition, Group 1 exhibited significantly elevated levels compared with Group 2, indicating a gradient pattern across the three groups as shown in table 2.

Group	HSP60 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: HSP60 levels in the study group.

Estimation of HSP60 Levels According to Age and Gender

Among males, HSP60 concentrations in Group 1 were slightly higher in the ⩽ 60-year subgroup (45.22 ± 5.72 ng/mL) compared with the ⩾ 60-year subgroup (43.77 ± 5.18 ng/mL), but this difference was not statistically significant (p=0.791). In Group 2 males, the ⩾ 60-year subgroup (36.18 ± 6.14 ng/mL) showed significantly higher HSP60 levels than the ⩽60-year subgroup (35.11 ± 2.90 ng/mL, p=0.043). In Group 3 males, the ⩾ 60-year subgroup (13.63 ± 1.28 ng/mL) had slightly higher levels compared with the ⩽60-year subgroup (12.82 ± 1.74 ng/mL), but the difference was not statistically significant (p=0.189). Among females, Group 1 showed no significant difference between those ⩽60 years (46.93 ± 6.13 ng/mL) and ⩾60 years (44.13 ± 6.56 ng/mL, p=0.913). Similarly, in Group 2 females, the values were 33.76 ± 2.85 ng/mL in the ⩽60-year subgroup and 34.37 ± 2.22 ng/mL in the ⩾60-year subgroup, with no significant difference (p=0.493). However, in Group 3 females, those ⩾60 years had significantly lower HSP60 levels (13.14 ± 2.30 ng/mL) compared with those ⩽60 years (15.18 ± 5.07 ng/mL, p=0.019) as in table 3.

Estimation of C-Reactive Protein Levels According to Study Group

As indicated in Table 4, C-reactive protein values (CRP) showed no significant difference between Group 1 and Group 2; however, both groups had significantly higher values compared with the control group (Group 3, $p < 0.001$).

Male Male Age	HSP60 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	HSP60 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: HSP60 levels by age group and sex in study groups

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 (CRP) Levels by Age Group and Gender

As shown in table 5, age-related variations in CRP levels were observed within both male and female subgroups. Among males, Group 1 participants aged ⩾ 60 years had significantly higher CRP concentrations compared with those ⩽ 60 years (7.84 ± 1.98 vs 6.88 ± 1.09 mg/dL, p = 0.025). In contrast, no significant age-related differences were detected in Group 2 (6.24 ± 0.99 vs 5.42 ± 0.89 mg/dL, p = 0.906) or Group 3 (3.32 ± 0.86 vs 2.85 ± 0.94 mg/dL, p = 0.729). Among females, CRP levels also showed significant age-related increases in Group 1 (8.43 ± 2.34 vs 6.17 ± 1.53 mg/dL, p = 0.034) and Group 2 (7.34 ± 2.42 vs 6.36 ± 0.44 mg/dL, p = 0.045), whereas Group 3 females demonstrated no significant difference between the two age categories (2.83 ± 0.73 vs 2.57 ± 0.75 mg/dL, p = 0.883).

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	21	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	9	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. *H. 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 *H. pylori*, which leads to acute infections or cellular stress, and thus HSP60 is released 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 develop as a result of inflammation [38] Inflammation's origins are still unknown, though. The increase in the level of HSP60 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, serum HSP60 levels were elevated in CAD patients, particularly those seropositive for *H. pylori*. These findings suggest that HSP60 may be involved in inflammatory pathways linked to CAD. However, whether immune responses to HSP60 (e.g., autoantibodies) contribute causally to disease development requires further investigation.

Author Contributions

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Competing Interests

The authors declared that there were no conflicts of interest.

References

1. Adler SP, Hur JK, Wang J, Vetrovec GW. Prior infection with cytomegalovirus is not a major risk factor for angiographically demonstrated coronary artery atherosclerosis. Journal of Infectious Diseases, (1998); 177(1), 209–212.
2. Benjamin IJ, McMillan DR. Stress (heat shock) proteins molecular chaperones in cardiovascular biology and disease. Circulation Research, (1998); 83(2), 117–132.
3. Berk BC, Weintraub WS, Alexander RW. Elevation of C-reactive protein in "active" coronary artery disease. The American Journal of Cardiology, (1990); 65(3), 168–172.
4. Billack B, Heck DE, Mariano TM, Gardner, CR, Sur R, Laskin DL, Laskin JD. Induction of cyclooxygenase-2 by heat shock protein 60 in macrophages and endothelial cells. American Journal of Physiology - Cell Physiology, (2002); 283(4 52-4), 1267–1277.
5. Birnie DH, Holme ER, McKay IC, Hood S, McColl KEL, Hillis WS. Association between antibodies to heat shock protein 65 and coronary atherosclerosis. Possible mechanism of action of Helicobacter pylori and other bacterial infections in increasing cardiovascular risk. European Heart Journal, (1998); 19(3), 387–394.
6. Businaro R, Profumo E, Tagliani A, Buttari B, Leone S, D'Amati G, Ippoliti F, Leopizzi M, D'Arcangelo D, Capoano R, Fumagalli L, Salvati B, Riganò R. Heat-shock protein 90: A novel autoantigen in human carotid atherosclerosis. Atherosclerosis, (2009); 207(1), 74–83.
7. Chmiela M, Gajewski A, Rudnicka K. Helicobacter pylori vs coronary heart disease - searching for connections. World Journal of Cardiology, (2015); 7(4), 187.
8. de Graaf R, Kloppenburg G, Kitslaar PJHM, Bruggeman CA, Stassen F. Human heat shock protein 60 stimulates vascular smooth muscle cell proliferation through Toll-like receptors 2 and 4. Microbes and Infection, (2006); 8(7), 1859–1865.
9. De Nardin E. The role of inflammatory and immunological mediators in periodontitis and cardiovascular disease. Annals of Periodontology / the American Academy of Periodontology, (2001); 6(1), 30–40.
10. Epstein SE. The multiple mechanisms by which infection may contribute to atherosclerosis development and course. Circulation Research, (2002); 90(1), 2–4.
11. Epstein SE, Zhu J, Najafi AH, Burnett MS. Insights into the role of infection in atherogenesis and in plaque rupture. Circulation, (2009); 119(24), 3133–3141.
12. Haghighat N, Mohammadshahi M, Shayanpour S. The Relationship of Serum Heat Shock Protein 70 Antibody Levels with the Inflammatory Factors and Serum Uric Acid Levels in Hemodialysis Patients. Iranian Red Crescent Medical Journal, (2019); 21(6).
13. Hansson G K. Regulation of immune mechanisms in atherosclerosis. Annals of the New York Academy of Sciences, (2001); 947, 157–166.
14. Hoppichler F, Lechleitner M, Traweger C, Schett G, Dzien A, Sturm W, Qingbo X. Changes of serum antibodies to heat-shock protein 65 in coronary heart disease and acute myocardial infarction. Atherosclerosis, (1996); 126(2), 333–338.
15. Huang WS, Tseng CH, Lin CL, Tsai CH, Kao CH. Helicobacter pylori infection increases subsequent ischemic stroke risk: A nationwide population-based retrospective cohort study. Qjm, (2014); 107(12), 969–975.
16. Induce FT, Atherogenesis IOR. Inflammation or Atherogenesis. Health (San Francisco), (2008); 115–126.
17. Kocsis J, Veres A, Vatay A, Duba J, Karádi I, Füst G, Prohászka Z. Antibodies against the human heat shock protein hsp70 in patients with severe coronary artery disease. Immunological Investigations, (2002); 31(3–4), 219–231.
18. Lebherz-Eichinger D, Ankersmit HJ, Hacker S, Hetz H, Kimberger O, Schmidt EM, Reiter T, Hörl WH, Haas M, Krenn CG, Roth GA. HSP27 and HSP70 serum and urine levels in patients suffering from chronic kidney disease. Clinica Chimica Acta, (2012);413(1–2), 282–286.
19. Lopez LR, Dier KJ, Lopez D, Merrill JT, Fink CA. Anti-β2-Glycoprotein I and Antiphosphatidylserine Antibodies Are Predictors of Arterial Thrombosis in Patients with Antiphospholipid Syndrome. American Journal of Clinical Pathology, (2004); 121(1), 142–149.
20. Markus HS, Mendall MA. Helicobacter pylori infection: A risk factor for ischaemic cerebrovascular disease and carotid atheroma. Journal of Neurology Neurosurgery and Psychiatry, (1998); 64(1), 104–107.
21. Mohammed H, Alyasiri F. HbA1c as indicator for dyslipidaemia, cardiovascular and atherosclerotic events in patients with metabolic syndrome. University of Thi-Qar Journal of Science, (2019); 5(3).
22. Musiał K, Szprynger K, Szczepańska M, Zwolińska D. Heat shock proteins in children and young adults on chronic hemodialysis. Pediatric Nephrology, (2009); 24(10), 2029–2034.
23. Ohashi R, Mu H, Yao Q, Chen C. Atherosclerosis: Immunopathogenesis and immunotherapy. Medical Science Monitor, (2004); 10(11).
24. Ouchi K, Fujii B, Kanamoto Y, Karita M, Shirai M, Nakazawa T. Chlamydia pneumoniae in coronary and iliac arteries of Japanese patients with atherosclerotic cardiovascular diseases. Journal of Medical Microbiology, (1998); 47(10), 907–913.
25. Pencina MJ, Navar AM, Wojdyla D, Sanchez RJ, Khan I, Elassal J, D'agostino RB, Peterson ED, Sniderman AD. Quantifying Importance of Major Risk Factors for Coronary Heart Disease. Circulation, (2019); 139(13), 1603–1611.
26. Pockley AG. Heat shock proteins, inflammation, and cardiovascular disease. Circulation, (2002); 105(8), 1012–1017.
27. Prasad A, Zhu J, Halcox JPJ, Waclawiw MA, Epstein SE, Quyyumi AA. Predisposition to atherosclerosis by infections: Role of endothelial dysfunction. Circulation, (2002)106(2), 184–190.
28. Ridker PM. Evaluating novel cardiovascular risk factors: Can we better predict heart attacks? Annals of Internal Medicine, (1999); 130(11), 933–937.
29. Roger VL, Go AS, Lloyd-Jones, DM, Adams RJ, Berry JD, Brown TM, Carnethon MR., Dai S, De Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Michael Ho P, Howard VJ, Kissela BM, Wylie-Rosett J. Heart disease and stroke statistics-2011 update: A report from the American Heart Association. Circulation, (2011); 123(4).
30. Rosenfeld ME. Inflammation and atherosclerosis: Direct versus indirect mechanisms. Current Opinion in Pharmacology, (2013); 13(2), 154–160.
31. Schett G, Xu Q, Amberger A, Van Der Zee R, Recheis H, Willeit J, Wick G. Autoantibodies against heat shock protein 60 mediate endothelial cytotoxicity. Journal of Clinical Investigation, (1995); 96(6), 2569–2577.
32. Shoenfeld Y, Gerli R, Doria A, Matsuura E, Cerinic MM, Ronda N, Jara LJ, Abu-Shakra M, Meroni PL, Sherer Y. Accelerated atherosclerosis in autoimmune rheumatic diseases. Circulation, (2005); 112(21), 3337–3347.
33. Shoenfeld Y, Sherer Y, Harats D. Atherosclerosis as an infectious, inflammatory and autoimmune disease. Trends in Immunology, (2001); 22(6), 293–295.
34. Soehnlein O, Libby P. Targeting inflammation in atherosclerosis — from experimental insights to the clinic. Nature Reviews Drug Discovery, (2021); 20(8), 589–610.
35. Szodoray P, Timar O, Veres K, Der H, Szomjak E, Lakos G, Aleksza M, Nakken B, Szegedi G, Soltesz P. Th1/Th2 imbalance, measured by circulating and intracytoplasmic inflammatory cytokines - Immunological alterations in acute coronary syndrome and stable coronary artery disease. Scandinavian Journal of Immunology, (2006); 64(3), 336–344.
36. Vaughan CJ. Chronic infections and coronary heart disease. Lancet, (1997); 350(9083), 1029–1030.
37. Veres K, Lakos G, Kerényi A, Szekanecz Z, Szegedi G, Shoenfeld Y, Soltész P. Antiphospholipid antibodies in acute coronary syndrome. Lupus, (2004); 13(6), 423–427.
38. Visseren FLJ, MacH F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, DI Angelantonio E, Franco O. H, Halvorsen S, Hobbs FDR, Hollander M, Williams B. 2021

ESC Guidelines on cardiovascular disease prevention in clinical practice. European Heart Journal, (2021); 42(34), 3227–3337.
39. Wick G, Jakic B, Buszko M, Wick MC, Grundtman C. The role of heat shock proteins in atherosclerosis. Nature Reviews Cardiology, (2014) 11(9), 516–529.
40. Xu Q, Wick G. The role of heat shock proteins in protection and pathophysiology of the arterial wall. Molecular Medicine Today, (1996); 2(9), 372–379.
41. Zhao Y, Zhang C, Wei X, Li P, Cui Y, Qin Y, Wei X, Jin M, Kohama K, Gao Y. Heat shock protein 60 stimulates the migration of vascular smooth muscle cells via Toll-like receptor 4 and ERK MAPK activation. Scientific Reports, (2015); 5(September), 1–11.