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Research Paper

Serum Anti-heat Shock Protein 27 Antibody Titers in Patients With Dyslipidemia: A Population-based Case-control Study

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ABSTRACT

Background: Heat shock protein 27 (HSP27) is found in several cell types of adults, such as cardiomyocytes, and endothelial cells. It is expressed in response to different cellular stress conditions. HSP27 decreases the levels of reactive oxygen species (ROS) and dyslipidemia is closely associated with increased endothelial production of reactive oxygen species (ROS).

Objective: Higher serum HSP27 antigen and anti-HSP27 antibodies have been reported in patients with unstable angina and myocardial infarction

Methods: This population-based case-control study was conducted in 2018. We investigated serum anti-HSP27 antibody titers in all participants with dyslipidemia from the Mashhad stroke and heart atherosclerotic disorder (MASHAD) study (n=8141) and those who were healthy in terms of dyslipidemia (n=1637) using an in-house enzyme-linked immune sorbent assay (ELISA) in individuals with dyslipidemia.

Findings: Anti-HSP27 titers were significantly lower in individuals with dyslipidemia compared to people without dyslipidemia (P=0.036).

Conclusion: Our results revealed that the anti-HSP27 antibody titer was lower in the participants with dyslipidemia than in the negative group. However, there may be a confounding effect of drug therapy. In a subgroup of dyslipidemic subjects, we observed lower anti-HSP27 antibody titers in patients treated with some drugs (statins or corticosteroids, non-steroidal anti-inflammatory drugs [NSAIDs], or anti-diabetic and anti-hypertensive) compared to subjects untreated with these drugs.

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1. Introduction

Dyslipidemia has long been recognized as a risk factor for cardiovascular disease [1], and atherogenic dyslipidemia may increase metabolic risk [2, 3]. The main features of dyslipidemia are defined by hypertriglyceridemia, low level of high-density lipoprotein cholesterol (HDL-C), and elevated or normal level of low-density lipoprotein cholesterol (LDL-C) [4]. We defined dyslipidemia as increased triglyceride (TG≥150 mg/dL) and or increased LDL-C (LDL-C≥130 mg/dL), and or decreased HDL-C (HDL-C≤40 mg/dL) in men and (HDL-C≤50 mg/dL) in women [5].

Several HSPs protect cells against stress, such as UV light and oxidative stress. Heat shock protein 27 (HSP27) decreases the levels of reactive oxygen species (ROS) [6-10]. On the other hand, dyslipidemia is closely associated with increased endothelial production of reactive oxygen species (ROS) [1].

Various pathological conditions, such as dyslipidemia are categorized by the deficiency of heat shock response, which plays a key role in the onset or worsening of the disease [11-13]. HSP27 is expressed in response to different cellular stress conditions. HSP27 is found in several cell types of adults, such as breasts, uterus, platelets, cardiomyocytes, and endothelial cells [14, 15].

It has been reported that HSP27 expression is lower in atherosclerotic plaques compared to control arteries, and therefore it was proposed that reduced HSP27 expression may be related to the plaque complexity [16]. However, Park et al. have reported that serum levels of HSP27 are higher in patients with acute coronary syndrome compared to healthy controls; nevertheless, they found that the level of HSP27 was undetectable in the core of atherosclerotic plaques [17]. Serum antibody titers against this protein (anti-HSP27) have been reported in a small number of studies. Higher serum HSP27 antigen and anti-HSP27 antibodies have been reported in patients with unstable angina and myocardial infarction [18]. It has been found that increased antibody titers against HSP27 are related to increased cardiovascular morbidity and mortality [19]. In our previous study, we found high serum anti-HSP27 titers in individuals with high fasting serum triglycerides and low HDL-C [20].

However, serum anti-HSP27 has not been fully explored in dyslipidemic patients. In this study, we evaluated serum levels of anti-HSP27 antibody in dyslipidemic subjects recruited into the Mashhad stroke and heart atherosclerotic disorder (MASHAD) Study cohort.

2. Material and Methods

In the present study, all samples were obtained from individuals recruited to the MASHAD study population. The MASHAD study, one of the first cohorts of cardiovascular disease (CVD) in the Middle East, aimed to assess the influence of environmental, nutritional, psychosocial, and genetic risk factors on the prevalence of cardiovascular events started in 2007. Participants aged 35-65 years were selected from the urban population of Mashhad City, the northeastern region of Iran. This research has been approved by the Ethics Committee of Mashhad University of Medical Sciences. All individuals included in this study signed written consent. In the present research, all participants with dyslipidemia from the MASHAD study (n=8141) and healthy people in terms of dyslipidemia (n=1637) were investigated. The seven different dyslipidemic statuses studied in this study are as follows:

TG↑, HDL-C↓, LDLC↑, TG↑ & HDL-C↓, TG↑ & LDL-C↑, TG↑ & HDL-C ↓ & LDL-C ↑, HDL-C↓ & LDL-C ↑.

Individuals who suffered from cardiovascular disease before entering the study or were pregnant or breastfeeding women were excluded from the study.

Initially, blood samples were collected from volunteers after a 12- hour fasting. The assessment of anthropometric, demographic, and biochemical parameters is described in detail previously [21]. Biochemical tests were performed on serum samples using commercial kits by an Alcyon analyzer (ABBOTT, Chicago, IL, USA).

The serum HSP27 antibody levels were assessed using an in-house enzyme-linked immune sorbent assay (ELISA), as previously described [20].

Statistical analysis

All statistical analyses were performed using SPSS software, version 18. The variable with normal and non-normal distribution was shown as Mean±SD and median and interquartile range respectively. All groups were compared using analysis of variance (ANOVA) and Kruskal-Wallis tests with a Bonferroni correction.

Multivariate regression analyses were performed to evaluate the independent effects of age, gender, smoking, and drug use on anti-HSP27 levels in patients with dyslipidemia. Data about taking drugs was collected us ing a questionnaire. The level of statistical significance was set at P<0.05.

3. Results

Baseline biochemical, anthropometric, and demographic characteristics in dyslipidemic and non-dyslipidemic participants

This study was conducted on 9759 patients. Approximately 40% of them were men and 60% were women.

Table 1. Comparison of the baseline biochemical, anthropometric and demographic characteristics of participant with or without dyslipidemia

Variables		Mean±SD/% (No.)		P
		Dyslipidemia+(n=8141)	Dyslipidemia-(n=1637)	
Age (y)		48.22±8.19	47.30±8.55	<0.001
Height (m)		1.60±0.09	1.62±0.09	<0.001
Weight (kg)		72.55±12.81	67.92±12.47	<0.001
Waist circumference (cm)		96.4±11.84	91.19±12.15	<0.001
Hip circumference (cm)		104.22±9.26	101.28±9.29	<0.001
BMI (kg/m^2)		28.28±4.65	25.96±4.68	<0.001
Systolic blood pressure (mm Hg)		122.11±18.81	120.37±20.48	0.002
Diastolic blood pressure (mm Hg)		79.34±11.96	78.18±10.82	<0.001
Triglycerides (mg/dL)		131 (93-184)a	83 (63-108)a	<0.001
Cholesterol (mg/dL)		194.61±40.81	175.18±23.49	<0.001
HDL-C (mg/dL)		40.78±8.77	53.12±8.95	<0.001
LDL-C (mg/dL)		120.10±36.47	99.09±21.10	<0.001
FBG (mg/dL)		94.02±41.09	86.04±28.15	<0.001
Hs-CRP (mg/dL)		1.7 (1.02-3.66)[a]	1.33 (0.89-2.81)[a]	0.07
Gender	Male	37.6 (3057)	52.1 (848)	<0.001
	Female	62.4 (5073)	47.9 (781)	
Smoking	Never	58.4	69.3	0.384
	Past	9.8	10.4	
	Current	21.7	20.3	
Diabetes		15.3	8.7	<0.001
Hypertension		32.7	26.1	<0.001
Anti-HSP27 (OD)		0.208 (0.105-0.345)[a]	0.213 (0.113-0.356)[a]	0.036

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BMI: Body mass index; FBG: Fasting blood glucose; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; Hs-CRP: High sensitivity C-reactive protein; OD: Optical density; HSP: Heat shock protein; [a]Median (interquartile range) due to skewed distribution.

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Table 2. Comparison of serum anti-heat shock protein (HSP27) antibody titers in patients with dyslipidemia and healthy subjects

Variable	Normal (n: 1689)	TG↑ (n: 404)	HDL-C ↓ (n: 2840)	LDL-C ↑ (n: 913)	P
Anti-HSP27 (OD)	0.213 (0.112-0.357)	0.219 (0.109-0.361)	0.208 (0.104-0.348)	0.190 (0.108-0.334)	0.114

HSP: Heat shock protein; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; OD: Optical density.

Data are presented as the median and interquartile range for non-normally distributed data and differences in variables among study groups assessed using the Kruskal-Wallis H test.

Table 1 presents the baseline biochemical, anthropometric, and demographic characteristics of participants. All parameters showed a significant difference in individuals with dyslipidemia and subjects without dyslipidemia, except for smoking and high-sensitivity C-reactive protein (Hs-CRP). In the dyslipidemic group, the rates of hypertension (32.7%) and diabetes mellitus (15.3%) were significantly higher than those without dyslipidemia (P<0.001). Age, weight, waist circumference, hip circumference, Body Mass Index (BMI), systolic and diastolic blood pressure, TG, Cholesterol, LDL-C, and Glucose were also significantly higher in the dyslipidemic group compared to participants without dyslipidemia (P<0.002 for systolic blood pressure and P<0.001 for other parameters).

Serum anti-heat shock protein (HSP27) levels in dyslipidemic and non-dyslipidemic participants

Anti-HSP27 levels were significantly lower in participants with dyslipidemia compared to those without dyslipidemia (P=0.036; Table 1).

The comparison of the serum anti-HSP27 antibody titers in dyslipidemic patients suffering from high TG or only low HDL-C or high LDL-C (individuals with two or three characteristics were not dyslipidemia) with healthy subjects was reviewed and no significant difference was observed (Table 2).

Serum anti-HSP27 antibody titers in three dyslipidemic statuses of dyslipidemia (TG↑, HDL-C↓, LDLC↑) and healthy subjects were compared between males and females, and no significant differences were observed between the two genders were detected (Figure 1).

A comparison of serum anti-HSP27 antibody titers was evaluated among different combined dyslipidemia status and normal participants and no significant differences were seen between the groups (Table 3).

The levels of serum anti-HSP27 antibodies were compared between men and women in patients with combined dyslipidemia and normal subjects were compared, but no significant difference was observed between the groups (Table 4).

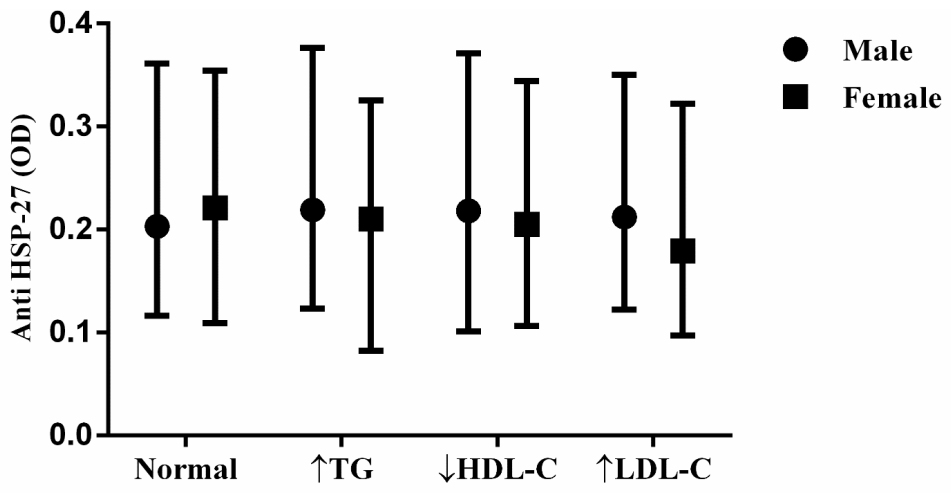

Figure 1. Comparison of serum anti-heat shock protein (HSP27) antibody titers between males and females in 2 groups of dyslipidemia and healthy

Table 3. Comparison of serum anti-heat shock protein (HSP27) antibody titers in patients with combined dyslipidemia and normal subjects

Variable	Normal (n: 1689)	TG↑ & HDL-C↓ (n: 1670)	TG↑ & HDL-C ↓ & LDL-C ↑ (n: 882)	HDL-C↓ & LDL-C ↑ (n: 1055)	TG↑ & LDL-C↑ (n: 379)	P
Anti-HSP27 (OD)	0.210 (0.112-0.354)	0.206 (0.103-0.338)	0.200 (0.097-0.332)	0.221 (0.110-0.358)	0.188 (0.088-0.331)	0.164

HSP: Heat shock protein; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; OD: Optical density.

Data are presented as the median and interquartile range for non-normally distributed data and differences in variables among study groups assessed using the Kruskal-Wallis H test.

Multivariate regression analysis of anti-heat shock protein (HSP27) in participants with dyslipidemia

Different multivariate regression models were conducted to assess the effect of age, gender, smoking, and drug use on anti-HSP27 levels in participants with dyslipidemia (Table 5).

Dyslipidemia was regarded as a dependent factor and anti-HSP27 as a covariate in model 1. Model 1 showed that people with a higher level of anti-HSP27 had a 68% lower risk of dyslipidemia (P=0.022). Also, in model 2 (age and gender were adjusted) and in model 3 (age, gender, and cigarette smoking were adjusted). In model 4, age, gender, cigarette smoking, and drug use (corticosteroids, non-steroidal anti-inflammatory drugs [NSAIDs], and statins) were adjusted. In model 4, the relationship between anti-HSP27 level and dyslipidemia was not significant.

4. Discussion

In the present study, anti-HSP27 levels were found to be significantly lower in participants with dyslipidemia compared to those without dyslipidemia (P=0.036).

HSP and anti-HSP immune complexes can lead to the destabilization of atherosclerotic plaque. Activation of the complement system may be an imperative factor in the chronic inflammatory process associated with atherosclerosis. The particular role of anti-HSP immunity in vascular disease is controversial [22]. Several studies have shown that higher levels of CVD risk factors are directly related to higher levels of anti-HSP antibodies and have concluded that anti-HSP antibodies may have a pathologic role in atherosclerosis. Anti-HSP27 antibody levels are related to cardio/cerebrovascular events [23, 24]. Since HSP27 has a vital role in myocardial protection in CVD [13], maybe the presence and increasing the anti-HSP27 level causes the formation of HSP and anti-HSP immune complexes and reduces the protective effect of HSP in patients with cardiovascular disease.

Table 4. Comparison of serum anti-Heat Shock Protein (HSP27) antibody titers between males and females in patients with combined dyslipidemia and normal subjects

Sub-Groups	Anti-HSP27 (OD)		P
	Male	Female	
Normal (Male:836, female:765)	0.197 (0.115-0.354)	0.220 (0.109-0.354)	0.98
TG↑ and HDL-C ↓ (Male:723, female:942)	0.208 (0.105-0.340)	0.206 (0.102-0.336)	0.53
TG↑ and HDL-C ↓ and LDL-C ↑ (Male:280, female:599)	0.210 (0.108-0.336)	0.197 (0.097-0.331)	0.66
HDL-C↓ and LDL-C ↑ (Male:266, female:789)	0.235 (0.107-0.426)	0.220 (0.110-0.337)	0.11
TG↑ and LDL-C ↑ (Male:209, female:169)	0.178 (0.088-0.311)	0.193 (0.086-0.350)	0.66

HSP: Heat shock protein; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; OD: Optical density. Data are presented the median and interquartile ranges for non-normally distributed data and differences in variables combined dyslipidemia subjects assessed using the Mann-Whitney test.

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Table 5. Different model of multivariate regression for anti-heat shock protein (HSP27) and dyslipidemia

Models		OR (CI 95%)	P
Anti-HSP27 (OD)	Model 1	0.68 (0.49-0.95)	0.022
	Model 2	0.71 (0.51-0.99)	0.044
	Model 3	0.68 (0.51-0.99)	0.049
	Model 4	0.72 (0.52-1)	0.055

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Model 1, unadjusted; Model 2, adjusted for age, and gender; Model 3, adjusted for age, gender and smoking; Model 4, adjusted for age, gender, smoking, and using the drug.

HSP: Heat shock protein; OD: Optical density; CI: Confidence interval.

In the previous study, we conducted for acute coronary syndrome in our lab, it was revealed that anti-HSP27 increased in the first 12 hours but decreased in the next 12 hours. This finding was concluded to suggest that the formation of immune complexes between anti-HSP27 and HSP27 antigens rapidly clears this complex via Fc-receptor [25].

Pourghadamyari et al. contrary to our results showed that CAD+ patients had significantly higher anti-HSP27 titers compared to both CAD− and control groups [26].

In another study on CAD patients, consistent with our results, lower levels of serum anti-HSP27 and HSP27 were observed in the CAD group compared to the healthy control, and after 6 months, this result did not change [27].

In contrast to our finding, Azarpazhooh et al. found that the serum level of anti-HSP27 antibodies of patients with stroke was significantly higher than the control group in the first 24 hours after the onset of stroke [28].

In contrast to our findings, Shams et al. found a higher level of anti-HSP27 in patients with chest pain both at admission time and 12 hours later compared to healthy control. According to the Shams and the results of our study, patients with acute cardiac chest pain with hypertension and hyperlipidemia had lower anti-HSP27 IgG antibody levels than patients without hypertension and hyperlipidemia [29]. Maybe the level of anti-HSP27 in people with dyslipidemia is different from other diseases, furthermore using some drugs affects the anti-HSP27 antibody titer in patients with dyslipidemia.

5. Conclusion

In multivariate regression that adjusted age, gender, and smoking, no effect was observed on anti-HSP27 in dyslipidemic patients. However, when taking statins, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and anti-diabetic and anti-hypertensive drugs were adjusted for this test, the relationship between anti-HSP27 level and dyslipidemia was not significant. These results showed that using these drugs can affect the level of anti-HSP27 antibodies in dyslipidemic patients. In our previous study, we showed that statin therapy in dyslipidemic subjects can reduce heat shock protein antibody titers and concluded that reduction in HSP antibody titers following statin treatment may be related to the other immunomodulatory properties of this class of drugs [30].

We concluded that maybe using different drugs in dyslipidemic patients reduced the level of anti-HSP27 in dyslipidemic patients compared to subjects without dylipidemia. The next study could be to follow anti-HSP27 levels in dyslipidemic patients with cardiovascular disease at the admission time and 12 hours later compared to patients without cardiovascular disease.

Ethical Considerations

Compliance with ethical guidelines

This research was approved by the Ethics Committee of Mashhad University of Medical Sciences by the Declaration of Helsinki (Code: IR.MUMS.REC.1386.250). Informed consent was obtained from all individuals recruited for the study.

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Authors' contributions

Conceptualization, methodology, software, and, writing–review & editing: Fatemeh Sadabadi, Maryam Shahi, and Sousan Darroudi; Measurement of anti-HSP27 antibody: Azam Rastgar Moghadam, Sahar Heidari-Bakavoli, and Asma Porsa; Data analysis: Sara Saffar Soflaei and Habibollah Esmaeili; Supervision: Mohsen Mouhebati. Visualization and investigation, resources: Ghodratollah Salehi Sangani, and Bibi Razieh Hoseini farash; Review & editing: Gordon A. Ferns. Project administration, funding acquisition: Majid Ghayour-Mobarhan; All authors reviewed the manuscript.

Conflict of interest

The authors declared no conflict of interest.

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