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Original Article

HSP27 expression in the human peripheral blood mononuclear cells as an early prognostic biomarker in coronary artery disease patients

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ABSTRACT

Background: Coronary artery disease (CAD), is one of the leading causes of death globally. CAD risk factors, such as smoking, dyslipidemia, and obesity, are mainly associated with increased oxidative stress. Heat Shock Protein-27 (HSP27) has a protective role in conditions of oxidative stress. The aim of the current study was to investigate the relationship between HSP27 mRNA copy numbers in the peripheral blood mononuclear cell (PBMCs) and the degree of CAD progression.
Methods: A total of 103 subjects aged 49–71 years were recruited; Patients with CAD were categorized into two groups: patients having <50% stenosis (Angio$^-$) and ≥50% stenosis (Angio$^+$). The mRNA copy numbers of HSP-27 in PBMCs, anthropometric-parameters, fasting blood glucose (FBG), and the fasted serum lipid profile were evaluated.
Results: Angio$^+$ patients had a significantly higher level of TC and LDL-C values compared with Angio$^-$ patients and the control group ($p < 0.05$). The HSP27 expression in PBMCs was significantly increased in Angio$^+$ and Angio$^-$ subjects, compared to the control group. Moreover, there was a significant association between the FBG, TC, LDL-C and TG among the groups ($p < 0.05$).
Conclusion: It was shown that the increased expression of HSP27 in PBMCs of CAD patients is significantly correlated with CAD severity in Angio$^+$ subjects, which can be used as an early prognostic biomarker, indicating the degree of overall oxidative stress in patients. In order to verify this statement, it is suggested to measure Pro-oxidant- Antioxidant Balance (PAB) test by the same design in subsequent studies.

1. Introduction

The Heat Shock Proteins (HSPs) are often the first line of defense against the accumulate tendency of protein or polypeptide denaturation and misfolding associated with environmental stressors that include oxidative stress, heat, and toxins [1]. and act as chaperone molecules in response to stress [2]. sHSPs have 80 to 100 evolutionary conserved amino acids within an α-crystalline domain (ACD) which is essential for its function [3]. HSP27 is a member of the small HSP family and is typically expressed in cardiovascular cells including endothelial cells and cardiomyocytes [4] as a molecular chaperone to facilitate the misfolded proteins

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refolding and modulate F-actin role in cell movement [5].

In addition, HSP27 plays an important role in cell protection against various stresses, including ischemic stress [6]. HSP27 increases the intracellular glutathione concentration and prevents cytoskeleton fragmentation to reduce cardiomyocyte susceptibility to ischemic oxidative stress [7]. Several studies suggest that HSP27 acts as a protective factor in the cardiovascular system. In this regard, HSP27 overexpression leads to cardiac myocytes protection following ischemic injury [8]. Any disruption in the functioning of this defensive mechanism, including mutations in its component encoding genes, has been reported to be associated with several disorders such as skeletal and cardiac myopathies, neurological disorders [9] and, myocardial ischemia [10].

Cardiovascular disease (CAD), one of the most common causes of death worldwide, is often preventable [11]. CAD refers to a group of diseases including stable and unstable angina, myocardial infarction and heart failure [12]. In fact, CAD is the most common type of cardiovascular disease [13]. Several risk factors for CAD development have been reported, including high blood pressure, obesity, cigarette smoking, loss of exercise, diabetes, high cholesterol, depression, and alcohol consumption [14]. Because of the protective role of HSP27 in ischemic oxidative stresses reduction [7], and its high level of endogenous expression in the human myocardial tissues [15], it seems that HSP27, a functional protective chaperone, plays an important role to reduce CAD development. The aim of the current study is to find the relationship between the levels of HSP27 mRNA in the peripheral blood and serum of CAD patients with their clinicopathological symptoms, which is considered as a useful prognostic biomarker for CAD patients.

2. Material and methods

2.1. Ethics statement

Informed written consent was obtained from all subjects with protocols approved by the Research Ethics Committee of the Tarbiat Modares University.

2.2. Study design and population

The study was performed on a sample of 62 patients (32 males and 32 females) and 41 healthy volunteers (20 males and 21 females). Sex and age were matched in both groups (age, 37–82 years) who underwent these tests and the angiograms at the Ghaem Medical Education Hospital, Mashhad, Iran. All patients without a prior history of coronary angioplasty or coronary artery bypass graft (CABG), clinical infection or chronic inflammatory disease, HBS antigen, anti-HCV antibody, and anti-HIV antibody were selected to participate in this study. Patients who were on lipid-lowering medication, oral contraceptives, or hormone replacement therapy, as well as pregnant women, were excluded from the study.

2.3. CAD patients grading or classification

Patients with the angiogram indicating one or more vessel stenoses≥50% in diameter of at least one major coronary artery (Left main, right coronary artery, left anterior descending, circumflex) were defined as Angio^{+}, and CAD subjects those had stenoses≤50%. Were defined as Angio^{-} participants. Coronary angiograms were carried out using routine techniques [29]. An expert cardiologist performed an off-line examination of all angiograms. Evaluation of stable angina in these subjects was carried out by usual coronary angiography and was positive for at least one objective test of myocardial ischemia (for example an exercise stress test, Dobutamine stress echocardiography, and Thallium SPECT).

2.4. Anthropometric measurements

For all individuals, anthropometric parameters including weight (Kg), height (cm), and waist circumference (cm) were measured. In order to measure the systolic and diastolic blood pressure standard mercury sphygmomanometer was used three times over a period of 45 min, and the average of measurements was applied to the blood pressure. The BP ≥ 140/90 is defined as High Blood Pressure.

Collection of peripheral blood samples, RNA extraction, and cDNA synthesis:

Blood samples centrifuged (at 2500 rpm for 15 min at 4 °C temperature). Hemolyzed samples were excluded from the study. The QIAamp Circulating Nucleic Acid Kit (Qiagen, Hilden, Germany) was used to isolate mRNA from peripheral blood mononuclear cell (PBMCs) using the manufacturer's instructions. The RNA concentration was estimated by measuring UV light absorbance at 260 nm using a Nanodrop device (Nanodrop Technology-1000, USA). In order to eliminate the possibility of remaining DNA fragments in the samples, 10 ng of the total RNA of each sample was amplified in the thermocycler. There was no PCR product in water or the total RNA samples. cDNA was synthesized using the QuantiTect Reverse Transcription Kit (Qiagen, Hilden, Germany), according to the manufacturer's protocol.

2.5. Real-time RT-PCR for expression analyses

We have assessed the stability of various housekeeping genes expression and found the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene, an endogenous control, to normalize the values [16]. After cDNA synthesis, the HSP27 and GAPDH fragments were amplified using the designed primer sets showed in Table 1. SYBR green master mixed (Takara, Japan) was used to detect the PCR product. Real-time PCR was performed by using SYBR green PCR Master Mix (Takara, Japan) in a total volume of 20 μl employing the ΔCt method [17]. The thermal cycling program for HSP27 was performed followed by denaturation at 95 °C for 4′, annealing at 60 °C for 35″, extension at 72 °C for 20″ for 40 cycles. The final extension was at 72 °C for 5'. Absolute quantitative real-time PCR for HSP27 and GAPDH genes was accomplished using A melting curve analysis and gel electrophoresis. HSP27 mRNA fragments were quantified and serially diluted to supply the standard curve. Copy numbers were estimated for all standards formulas as described by Bustin in 2000 [18]. All samples were analysed in duplicate. The PCR efficiencies verification for HSP27 and GAPDH were carried out by generating their standard curves.

2.6. Measurement of lipids and lipoproteins

Standard enzymatic methods were used to determine the lipid profile including total cholesterol (TC), HDL, LDL and TG, and FBG levels as well as the method of polyethylene glycol-enhanced immune-turbidimetry to detect C-reactive protein (CRP) level, as described previously [19].

Table 1
Primers used for amplification. GAPDH: glyceraldehyde-3-phosphate dehydrogenase, HSP27: heat shock proteins 27, F: forward primer, R: reverse primer.

Gene	Forward/Reverse	Primer
GAPDH	F	5'- GACAACAGCCTCAAGATCATCAG-3'
GAPDH	R	5'-ATGGCATGGACTGTGGTCATGAG-3'
HSP27	F	5'-GCGTGTCCCTGGATGTCAAC-3'
HSP27	R	5'-ATCTCCACCACGCCATCCT-3'

2.7. Statistical analysis

All statistical analyses were performed with SPSS software (version 16). All data were expressed as the mean ± standard deviation (SD) when normally distributed if no as the median and IQR (interquartile range) is displayed. Differences were considered statistically significant at p-values <0.05. Reproducibility of the Real-time PCR data was evaluated by performing the intra-assay (the average coefficient of variation between duplicates) and inter-assay (the average coefficient of variation from the control means in each run) variability.

3. Results

3.1. Baseline characteristics of the population

The three subject groups (Angio$^+$, Angio$^-$, and control) were well-matched for age and gender. No significant difference was observed for BMI and hip circumference between the groups, while there was a significant difference in waist circumference, waist/hip ratio, systolic blood pressure and diastolic blood pressure ($p < 0.05$, Table 2) between the groups. One-way analysis of variance showed significant differences in FBG, TC, LDL-C and TG between the groups ($p < 0.05$). Moreover, patients with Angio$^+$ had a significantly higher level of TC and LDL-C values compared with Angio$^-$ and control groups ($p < 0.05$).

3.2. HSP27 mRNA copy numbers in our population

The expression of HSP27 in the PBMCs of Angio+and Angio$^-$ subjects were significantly higher than for the control group ($p < 0.01$ and $p < 0.05$ respectively, Fig. 1-a), while no differences were detected in the Angio$^+$ group, compared to Angio−group. In addition, the level of HSP27 mRNA was higher in the Angio$^+$ subjects with more than one vessel affected, compared to the other groups (Fig. 1-b).

4. Discussion

We have assessed the HSP27 mRNA copy numbers in peripheral blood mononuclear cells (PBMCs) with coronary artery disease (CAD) severity in Iranian patients with the abnormal coronary angiogram. A high HSP27 mRNA value in the peripheral blood nuclear cells of CAD patients was significantly associated with the Angio$^+$ subjects, those with more than one vessel affected, compared to the other groups. Moreover, there was a significant difference in waist circumference, waist/hip ratio, systolic blood pressure and diastolic blood pressure between the groups. As expected, high values of TC and LDL-C were strongly associated with Angio$^+$ CAD patients compared with Angio$^-$ and control groups, which are in agreement with previous studies [10,20,21].

The presence of at least 50% of the stenosis is used to detect meaningful CAD [22]. It has been indicated that various types of dyslipidemia are associated with coronary artery disease (CAD) [23]. Interestingly, Ibrahim et al. showed a higher prevalence of dyslipidemia among young CAD patients and a gradual reduction in the prevalence of lipid abnormalities over time [24]. Dyslipidemia is generally known as a major risk factor for CAD [25].

Oxidative stress may be induced by several CAD risk factors, including smoking, dyslipidemia and diabetes mellitus [26]. An imbalance between reactive oxygen species and antioxidant defense leads to oxidative stress. It has been shown to play an important role in cardiovascular disease initiation [27]. The relationship between oxidative stress and CAD has long been considered. CAD may arise in the presence of increased oxidative stress and not compensated antioxidant defense [28]. sHSPs are expressed during cellular stress responses and play a protecting important role in the various harmful conditions such as heat, hypoxia, and ischemia [7]. As a highly protected chaperone protein, sHsps interactions with other proteins to improve the normal cellular function, such as translation regulation, cytoskeletal maintenance and normal redox conditions [29].

Recruitment and activation of HSPs are due to the signals from the hydrophobic residues of nascent or misfolded proteins, which classify HSPs as a potent environmental (heat, oxidative) and physiological (infection, inflammation) stress sensors [30]. HSP27's intracellular function, in addition to maintaining cell homeostasis, by refolding misfolded proteins, includes its key role in the cytoskeletal structure dynamics, mRNA stabilization, antioxidant defense and anti-apoptosis [31]. According to previous studies, extracellular HSP27 is involved in immune signaling [32], cell migration [33], and cell proliferation [34]. Extracellular HSP27 through the exosomal carriers, depending on the external or internal status of HSP27, can interact with target cells with or without

Table 2
Demographic and clinical characteristics of the population. Values are presented as mean ± SD. *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBS* fasting blood sugar, TC total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides. Compared with the control group: $^{a}p < 0.05$, $^{b}p < 0.01$, $^{c}p < 0.001$; compared with the Angio−group: $^{d}p < 0.05$, $^{e}p < 0.01$, $^{f}p < 0.001$; comparison between all groups: $^{g}p < 0.05$, $^{h}p < 0.01$, $^{i}p < 0.001$.

	Angio $^+$	Angio $^-$	Control
Number of subjects	36	26	41
Gender (F/M)	19/17	13/13	21/20
Age (year)	60.6 ± 10.7	58.8 ± 9.9	59.6 ± 10.6
Height (cm)	160.25 ± 9.28	162.04 ± 8.78	161.68 ± 7.94
Weight (kg)	71.19 ± 11.68	69.73 ± 13	67.97 ± 11.97
BMI	27.85 ± 4.77	26.53 ± 4.66	25.96 ± 3.8
Waist circumference (cm)	93.36 ± 11.48	92.77 ± 13.53	86.05 ± 12.17^{g}
Hip circumference (cm)	93.58 ± 9.7	93.50 ± 13.05	91.61 ± 10.5
Waist/hip ratio	0.996 ± 0.05^{c}	0.992 ± 0.06^{b}	0.938 ± 0.08^{i}
SBP (mmHg)	138.47 ± 16.25^{b}	131.92 ± 17.27	125.53fx114.08^{h}
DBP (mmHg)	79.31 ± 9.79^{c}	78.27 ± 11.04^{b}	71.05 ± 7.98^{i}
Smoking n (%)	9 (25%)	4 (15.4%)	5 (12.2%)
FBS (mg/dl)	135.92 ± 74.68^{b}	115.04 ± 64.46	96.79 ± 14.9^{g}
TC (mg/dl)	182.56 ± 38.12^{a}	159.77 ± 37.11^{a}	158.74 ± 35.91^{g}
LDL-C (mg/dl)	113.08 ± 31.27^{a,e}	90.19 ± 31.54	92.13fx128.28 ^{h}
HDL-C (mg/dl)	42.83 ± 6.96	41.65 ± 16.67	39.37 ± 8.08
TG (mg/dl)	132.50 ± 54.02^{a}	141.81 ± 68.29^{b}	102.32 ± 34.95 ^{h}

related receptor respectively [35]. The HSP27 affection modality on target cells is unknown. However, it may stimulate various effects based on the exosomal source and target cells. In this regard, the expression of HSP70 has been shown at exosomal surfaces, which is responsible for TLR-4 signaling, leading to cardiomyocytes protection [36] and increases natural killer cell (NK) cytolytic activity against HSP70 positive tumour cells [37].

The abnormal expression of heat shock proteins in the vascular diseases such as CAD, peripheral arterial disease (PAD) and abdominal aortic aneurysm (AAA) have introduced these proteins as an emerging therapeutic factor in vascular disease treatment [38,39]. According to the previous studies, the protective role of HSP27 in pathophysiological oxidative stresses reduction, increased intracellular HSP27 expression in cardiomyocytes, and high levels of circulatory HSP27 in 2VD or 3VD CAD patients compared with 1VD CAD or healthy control subjects [10], altogether suggest a rational correlation among cellular and circulatory levels of HSP27 with such oxidative stress disorders progression.

Since HSP27 is involved in glutathione activity regulation, glutathione peroxidase and apoptotic death conception of blood lymphocytes, the upregulation of HSP27 seems to be necessary for cell protection [40]. As expected, in the present study we showed the HSP27 upregulation in PBMCs of CAD patients is significantly correlated with the degree of CAD progression (Fig. 1). Therefore, there may be an indirectly logical relationship among the increased expression of HSP27 and the degree of the antioxidants activity against oxidative stress in CAD patients. In fact, this compensatory system gives rise to improve cell redox status. In order to define whether the HSP27 protein participates in exosomes and how does the extracellular HSP27 affect the myocardial tissues, certainly further researches are required.

Measurement of HSP27 mRNA copy number in Human PBMCs might be used as a novel prognostic biomarker for every disorder which is correlated with the degree of oxidative stress. However, more experimental studies are required to verify this statement.

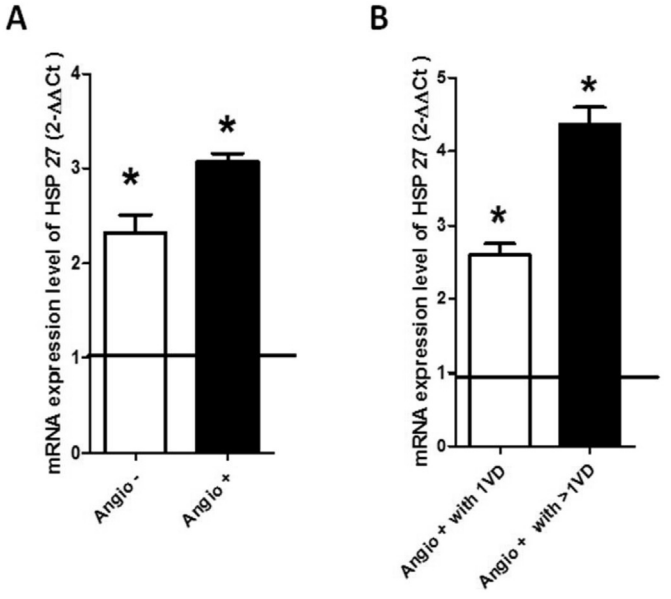

Fig. 1. The expression levels of HSP27 expression in CAD subjects. A. a comparative diagram indicating the abundance of HSP27 mRNA levels in CAD groups without any vessel disease (VD). B. The diagram indicates a significant difference among the Angio + groups with 1VD and more than a single vessel stenosis. CAD: coronary artery disease; HSP27: heat shock protein 27; *: p-value <0.05.

5. Conclusion

HSP27, an important component of the oxidative stress response, acts as an exclusive compensator agent in environmental and pathophysiological stresses. It was shown that the increased expression of HSP27 in PBMCs of CAD patients is significantly correlated with in CAD severity in Angio^{+} subjects, which can be used as an early prognostic biomarker, indirectly indicating the degree of overall oxidative stress in patients. In order to verify this statement, it is suggested to measure Pro-oxidant- Antioxidant Balance (PAB) test by the same design in subsequent studies.

Conflicts of interest

The authors have no conflict of interest to disclose.

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