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Association between diabetes mellitus and rs2868371; a polymorphism of HSPB1

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ABSTRACT

Introduction: Diabetes (DM) is a type of metabolic disorder that its types are generated by collectingof genetic and environmental risk agents. Here, the association between HSPB1 polymorphism as a genetic risk factor and DM was investigated.
Methods: Total 690 participants from MASHAD cohort study population were recruited into the study.Anti-HSP-27level was assessed followed by genotyping using Taqman®-probes-based assay. Anthropometric, demographic and hematological/ biochemical characteristics were evaluated. Kaplan-Meier curves were utilized, while logistic regression models were used to assess the association of the genetic variant with clinical characteristics of population.
Results: Finds was shown there are meaningful differences among groups of age, height, waist circumference, systolic blood pressure, FBG,TG, HDL-C, and hs-CRP, and was no big -significant difference between theexists in different HSP27 SNP in the two studied groups (with and without DM), also was no remarkable relation between genetic forms of HSPB1and T2DM. This investigation was the first research that analyzed the relationship between the genetic type of the HSPB1 gene (rs2868371) and Type 2 diabetes (DM2). In our population, the CC genotype (%68.1) had a higher prevalence versus GC (%26.6) and GG (%5.3) genotypes and the data shown that no genetic difference of HSPB1 gene polymorphism (rs2868371) was related with DM2.
Conclusion: HSPB1 polymorphism, rs2868371, was not associated with type 2 diabetes mellitus.

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Introduction

Diabetes mellitus (DM) is a distinct class of disorders discerned by persistent hyperglycemia. It is the most common non-communicable disease, distinguished as a metabolic disorder (1,2). Hyperglycemia occurs due to decreased insulin production or insulin resistance(3-5). Diabetic patients may reveal symptoms like constant thirst, polyuria, weight loss, blurred vision, microvascular disease, and macrovascular critical complications that affect life quality and lead to death(6, 7). Cardiovascular diseases are important causes of morbidity and mortality for individuals with diabetes (DM). Even though their essential mechanisms are not understood, ahead glycated end products (AGEs), oxidative stress, and low-scale inflammation are thought to show principal roles in mediating hyperglycemia-induced cell dysfunction and destruction (8).

Thus, there is a requirement to identify treatments either blocking cascades leading to cells' injury or improving the efficacy of endogenous cytoprotective systems. All diabetes types are created through a combination of environmental and genetic risk factors. First-degree relatives have a higher risk of developing diabetes than unrelated individuals from the general people (almost 6% vs. <1%, respectively),(9) that suggests genetic factors are associated with the growth of the disease(10).

Hspsare usually expressed at a paltry amount and can be activated by various physiological or environmental stresses, including cytotoxic, heat shock, oxidative stress, and apoptotic stimuli(12, 13). Besides helping protein refolding and regulating proteostasis under stressful conditions, Hsps also administer a principal role in protecting cells versus inflammation, oxidative stress, and apoptosis. They decrease oxidative stress by raising both glyceraldehyde 3-phosphate dehydrogenase (GAPDH) activity and glutathione levels. Hence, Hsps are essential in neutralizing the harmful hyperglycemia effects of complications targeting organs of diabetes vascular. Modifications in expression have been proven in diabetic complications and functionally associated with cell injury induced by hyperglycemia. Thus, Hsps portrays an exciting therapeutic opportunity and might be helpful as clinical and biological markers. They are pervasive proteins divided into different families. One of them is HspB that is classified into two groups: HspB1 and HspB2.

HspB1 (known as Hsp25 in mice and Hsp27 in both humans and rats are a large group of proteins extremely conserved during evolution for their unique cytoprotective properties.HspB1 group also includes the Hsp27, CMT2F, HMN2B, Hsp28, Hsp25, HS.76067, and DKFZp586P1322 (14).There was a rise in glomerular expression of phosphorylating or total HspB1 in experimental DM (15-18).

Additionally, significant to small HspB1 oligomers were transferred into separate diabetic glomeruli in experimental DM(19). Possibly, phosphorylation/ induction of HspB1is a cytoprotective mechanism with the target limiting both apoptosis and oxidative stress(20). HspB1 is coded by the heat shock protein beta-1 gene (HSPB1), mapped to chromosome 7 at q11.23, containing three exons and two introns; the HspB1 protein expression level may be related to the HSPB1 genotype which was associated with various disease pathogenesis (21).In this study, we investigated HSPB1 polymorphism (rs2868371) on diabetes disease. This research field is still at its start, and additional investigations in both humans and experimental diabetes are required to get a full awareness of HspB1 relevancy.

Material and Methods

1.Study population

Total 690 individuals were divided into two groups of with DM (142) and without DM (548) according to past medical history, fasting blood glucose and consuming glucose lowering agents.

2.Demographic data and anthropometric parameters

Demographic data, including gender, age, smoking status, physical activity level (PAL), and social class, including educational and economic levels, were collected using a questionnaire. Anthropometric variables, including weight, height, hip and waist circumference, BMI, and blood pressure, were evaluated using standard procedures.

At baseline, a fasted blood sample (after 12 hours fast) was taken from all subjects. Biochemical parameters such as serum total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), and serum High-sensitivity C-Reactive Protein (hsCRP) were assessed by using Alycon auto analyzer and Pars Azmoon kits (mg/ dl). Friedewald formula was used to estimate Low-density lipoprotein cholesterol (LDL-C) value.

3.DNA extraction and genotyping

DNA extraction was done from whole blood using YTA Mini-Kit (Yekta Tajhiz Azma, Tehran, Iran). The purity and concentration of DNA were tested with NanoDrop.Analysis of HSPB1-rs2868371 genotype was done by Taqman ®-probes-based assay; PCR reactions were set up in 12.5 µl total volume using 20 ng of DNA in TaqMan® Universal Master Mix (C-4364338) and predesign probes and primers (C-16146175-10; StepOne, Applied Biosystems, USA). We used the ABI PRISM-7500 instrument equipped (Foster City, USA) for evaluating the allelic content.

4.Statistical analysis

SPSS version 16.0 was implemented for the entire statistical analyses (SPSS Inc. Chicago, IL, USA). The normality of the data was determined. For comparing parameters between groups, parametric and nonparametric statistical analysis was applied for normal and non-normally distributed data, respectively.

Also, Logistic regression analysis was assessed to demonstrate the relationship between genotypes and event incidence in the presence of confounding variables. The data values were stated as median(first and third Quartiles) and mean ± SD for non-normally and normally distributed data.

Results

1.Clinical specifications of the population

The population's clinical and baseline characteristics are reported in Table 1. A total of 690 participants, 400 females and 290 males were joined in the current project. The results represented that age, height, waist circumference, systolic blood pressure, FBG, TG, HDL-C and hs-CRP (P-value<0.05) had a significant difference between groups (Table1). HSP27.

Table 1: Baseline clinical and biochemical characteristics of the study population

Variables		With DM (N=142)			Without DM (N=548)			P value[1]
		Male (N=58)	Female (N=84)	Total (N=142)	Male (N=232)	Female (N=316)	Total (N=548)	
Age (year)		56.00(10.00)	53.00(9.00)	54.00(8.00)	50.00(11.75)	48.00(12.00)	49.00(12.00)	<0.001
Weight (kg)		76.80(15.23)	70.35(13.80)	72.95(15.25)	76.60(17.20)	70.70(14.30)	73.25(16.75)	0.95
Height (cm)		1.67(0.10)	1.54(0.06)	1.59(0.13)	1.69(0.09)	1.56(0.07)	1.60(0.14)	0.04
BMI (kg/m2)		27.51(4.22)	29.74(5.56)	28.68(5.44)	26.72(5.70)	29.37(6.16)	28.01(5.85)	0.16
WC (cm)		98.0(10.0)	98.50(15.68)	98.0(13.0)	96.0(15.0)	97.0(16.88)	96.75(16.0)	0.01
HC (cm)		101.0(8.03)	104.25(11.50)	102.0(10.50)	101.50(9.50)	105.50(12.0)	103.50(10.23)	0.34
SBP (mmHg)		129.0(24.17)	130.0(22.50)	130.0(22.33)	120.33(24.67)	120.0(24.42)	120.0(26.67)	<0.001
DBP (mmHg)		80.66(14.17)	80.0(11.25)	80.0(12.33)	80.0(15.0)	80.0(19.33)	80.0(18.58)	0.15
FBG (mg/dl)		156.0(105.0)	138.0(100.0)	143.0(106)	82.0(15.0)	82.0(16.0)	82.0(16.0)	<0.001
TC (mg/dl)		190.0(59.0)	198.0(66.0)	192.0(64.0)	180.0(51.0)	193.0(54.0)	187.0(54.0)	0.44
TG (mg/dl)		206.0(105.0)	191.50(119.0)	194.50(114.0)	152.50(117.0)	130.50(98.0)	140.0(109.0)	<0.001
HDL-C (mg/dl)		34.0(10.45)	37.50(14.13)	35.0(13.33)	35.05(11.83)	42.0(17.50)	39.0(16.0)	0.01
LDL-C (mg/dl)		106.70(47.83)	102.80(55.76)	105.45(50.65)	103.90(52.59)	113.45(46.54)	109.95(49.77)	0.22
hsCRP (mg/L)		1.96(3.32)	2.51(4.48)	2.19(3.50)	1.39(1.80)	1.96(3.03)	1.66(2.49)	0.01
BUN (mg/dl)		14.0(7.0)	11.0(4.50)	12.0(6.0)	13.0(4.50)	13.0(5.0)	13.0(5.0)	0.25
Cr (mg/dl)		0.90(0.40)	0.70(0.30)	0.80(0.30)	0.90(0.30)	0.80(0.30)	0.90(0.30)	0.09
PAL		1.33(0.32)	1.64(0.25)	1.55(0.36)	1.34(0.36)	1.66(0.25)	1.58(0.36)	0.45
Smoking status	Non smoker	28(48.35)	62(73.8%)	90(63.4%)	133(57.3%)	240(75.9%)	373(68.1%)	0.08
	Ex-smoker	16(27.6%)	8(9.5%)	24(16.9%)	31(13.4%)	25(7.95)	56(10.2%)	
	Current smoker	14(24.1%)	14(16.7%)	28(19.7%)	68(29.3%)	51(16.1%)	119(21.7%)	
Genotype	GG	2(3.4%)	3(3.6%)	5(3.5%)	17(7.3%)	12(3.8%)	29(5.3%)	0.38
	GC	22(37.9%)	23(27.4%)	45(31.7%)	58(25.0%)	88(27.8%)	146(26.6%)	
	CC	34(58.6%)	58(69.0%)	92(64.8%)	157(67.7%)	216(68.4%)	373(68.1%)	

[1]Comparison between two groups with and without DM

Data are shown as mean (SD) or number (%). IFG impaired fasting glucose, BMI, body mass index; WC, waist circumferences; HC, hip circumferences; SBP, systolic blood pressure, DBP, diastolic blood pressure, FBG, fasting blood glucose, TC, total cholesterol, TG, triglycerides, HDL-C, high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, Hs-CRP high sensitivity C-reactive, BUN, blood urea nitrogen, Cr, creatinine; PAL, physical activity level. Mann-Whitney test was used to examine the difference in the mean of groups.

2.Association between T2DM with HSPB1 genetic variants in follow up cases

The genetic polymorphism was in Hardy–Weinberg equilibrium (p>0.05). The frequency of CC genotype was 68.1%, whereas the frequency of CG and GG genotypes were 26.6% and 5.3%, respectively, as presented in table2. The association of HSPB1 genetic variants and T2DM has been explained in Table 2. There was no significant relation between HSPB1 genetic variants and T2DM (Table 2).

Table 2: Association between HSPB1 genetic variant and Diabetes

Variables	SNP	Without DM (n%)	With DM (n%)	Uni-variate regression OR(95%CI)	P-value	Multivariate regression1 OR(95%CI)	P-value
Co-dominant	CC	373(68.1%)	92(64.8%)	Ref.	Ref.	Ref.	Ref.
	GC	146(26.6%)	45(31.7%)	1.25(0.83-1.87)	0.28	1.23(0.65-2.33)	0.51
	GG	29(5.3%)	5(3.5%)	0.70(0.26-1.85)	0.47	0.37(0.07-1.98)	0.24
Dominant	CC	373(68.1%)	92(64.8%)	Ref.	Ref.	Ref.	Ref.
	GG/GC	175(31.9%)	50(35.2%)	1.16(0.78-1.71)	0.46	1.07(0.58-1.98)	0.83
Recessive	GC/CC	519(94.7%)	137(96.5%)	Ref.	Ref.	Ref.	Ref.
	GG	29(5.3%)	5(3.5%)	0.65(0.25-1.72)	0.39	0.34(0.06-1.83)	0.21
Over dominant	GG/CC	402(73.4%)	97(68.3%)	Ref.	Ref.	Ref.	Ref.
	GC	146(26.6%)	45(31.7%)	1.28(0.85-1.91)	0.23	1.31(0.69-2.46)	0.41
Allele	C	892(81.4%)	229(80.6%)	Ref.	Ref.	Ref.	Ref.
		204(18.6%)	55(19.4%)	1.05(0.75-1.46)	0.77	-	-

[1]Adjusted for WC, SBP, FBG, TG, HDL, HS-CRP, Smoking, age.

Discussion

To best our knowledge, our project was the only study that investigated the relationship between the genetic variant of HSPB1 gene (rs2868371) and Type 2 diabetes mellitus (T2DM). The data revealed that no genetic variant of HSPB1 gene polymorphism (rs2868371) was associated with T2DM, implying the genetic variant of HSPB1 gene (rs2868371) may not increase or decrease the risk of T2DM.

DM is a chronic condition resulting from insulin resistance or impaired insulin secretion that leads to hyperglycemia(31). Diabetes is a chronic condition with increased oxidative stress and inflammation(32).

Heat shock proteins (Hsps) have a crucial role in cytoprotection against various stressors classified into several groups according to their molecular mass (33). Hsps are ubiquitous, highly evolutionary conserved intracellular proteins (22). Thermal, oxidative, hemodynamic, osmotic, and hypoxic stresses induce Hsps expression, and this stress response results in cytoprotection (22). Specifically, Hsps prevent non-specific protein assembly, assist in denatured protein refolding, and interfere with pro-apoptotic pathways (23).

HspB1 belongs to the group of the small Hsps that are over-expressed during stressful conditions (34). Several studies have been established the relation between DM complications and Hsp27. To investigate whether Hsp25expression is modulated by diabetes, R. Mastrocola et al. studied Hsp25 protein expression in total hippocampus from both diabetic and control mice by western blotting. Total Hsp25 protein expression was remarkable in diabetic mice and densitometric analysis, a significant increase of Hsp25 expression in diabetic animals compared to controls (24). Moreover, Hsp27 has a crucial role in photoprotection through increased expression in human diabetic neuropathy (DN)(26 ,25).Furthermore, Sanchez-Nino et al. showed that HspB1 mRNA and protein expression is enhanced in vivo and cultured podocytes through high glucose and Ang II. It may be a compensatory mechanism that allows podocytes to tolerate the stressors and reduce apoptosis caused by high glucose or Ang II (45 ,44). Hsp27 knockdown or overexpression are respectively associated with attenuated or improved axon regeneration in adult sensory neurons. Hsp27 expression promotes survival of adult sensory and motor neurons after axonal injury, and its expression is elevated in sensory neurons of diabetic rodent models(27).

Reports suggest that overexpression of Hsp27 has a beneficial effect in diabetic polyneuropathy in the type 1 diabetic rat model (28 ,27). Furthermore, Andrew et al. have determined the expression of Hsp27 in ischemic retinas by establishing ischemia retinae rat models and found that Hsp27 induces its protective effect by increasing its expression (29).

Joachim et al. also investigated the role of Hsp27 in different oxidative damages to the retina, and the results showed that the expression of Hsp27 significantly increased under the action of oxidative damage (30). These results show that retinal tissue ischemia and anoxia in diabetic retinopathy (DR) could lead to the expression of Hsp27 to be up regulated through stress response, which might play a protective effect in DR.

The question of why hyperglycemia does induce downregulation of Hsp27 remains unknown. Indeed, altered expression of Hsp27 is detected in different pathophysiological states (35).A proposed pathway is AMP-activated protein kinase (AMPK) activation which has been known as a significant target to treat insulin resistance. Yuan et al. observed that activation of AMPKa through acute or chronic exercise enhanced expression of HSPB1

gene in the skeletal muscle.The downregulation of HSPB1expression was reportedinthequadricepsmu sclesofAMPKa2/mice.

Furthermore, HSPB1 overexpression increased insulin sensitivity in palmitate-induced insulin-resistant cells and repaired metabolic phenotypes related to defective AMPK (43). In turn, compromised Hsp expression may related to diabetic complications (41 ,40), resulting in a vicious cycle. The effect of diabetes on Hsps is tissue-specific. Expression of Hsps is altered in diabetes in a tissue-specific manner because of differing susceptibility of the tissues to injury (42).

Contrary to expectations, this study did not find a significant association between HSPB1 gene polymorphism (rs2868371) and T2DM. This discrepancy could be attributed to variations in different races, limited case numbers. Moreover, this inconsistencymay be associated with the fact that most of the available studies on DM and Hsp27 investigate the link of Hsp27 to microvascular complications of DM not affected by DM.

Conclusion

Our finding did not show any association between HSPB1 polymorphism, rs2868371, and DM , therefore, more investigation was needed to assess this association.

Conflict of interest

Authors declare that have no competing interest.

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