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ORIGINAL RESEARCH

Is there any genetic predisposition of MMP-9 gene C1562T and MTHFR gene C677T polymorphisms with essential hypertension?

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Abstract The current study was conducted to determine whether there is a relation between hypertension and two different polymorphisms, including C1562T of the Matrix metalloproteinase-9 (MMP-9) gene and C677T of the methylenetetrahydrofolate reductase (MTHFR) gene. Genomic DNA obtained from 224 persons (125 patients with hypertension and 99 healthy controls) were used in the study. Polymorphisms were determined by using polymerase chain reaction-restriction fragment length polymorphism and electrophoresis. The results were statistically analyzed and were found to be statistically significant. The frequencies of the C1562T genotypes were found to be, in controls CC 75.8 % and CT 24.2 % and in patients CC 71.2 %, and CT 28.8 %. The frequencies of C677T genotype were found to be, in controls CC 56.6 %, CT 38.4 and TT 5.1 % in controls and in patients CC 52 %, CT 30.4 % and TT 17.6 %. In conclusion, we may suggest that there is no relation between the essential hypertension and C1562T polymorphism of MMP-9 gene; on the other hand C677T polymorphism (genotype TT) of MTHFR gene can be regarded as a genetic indicator for the development of essential hypertension.

Keywords Essential hypertension · MMP-9 · MMP-9 C1562T polymorphism · MTHFR · MTHFR C677T polymorphism

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Introduction

Hypertension is a destructive disease, which threatens public and personal health all around the world and may lead to serious health problems such as heart crisis, stroke and renal failure. The higher the blood pressure is, the higher the risk of heart attack, cardiac failure, stroke, eye and renal diseases will be. Therefore, it is the pioneering risk factor among all preventable causes of death (O'Donnell et al. 1998).

Hypertension is a multi-factorial condition and genetic factors play a very important role in its development. However, pathogenesis of hypertension

is not clearly known (Gunes et al. 2004; Bayramoglu et al. 2012). Recently, the application of genetic approaches to this disease has begun to delineate molecular pathways underlying blood pressure variation, defining disease pathogenesis and identifying targets for therapeutic intervention. It is suggested that many genes have influences on the pathogenesis of hypertension (Lifton et al. 2001; Gunes et al. 2004; Bayramoglu et al. 2012). This pathologic process is characterized by structural changes in the arterial wall caused by increased deposition of extracellular matrix (ECM) components, particularly collagen, as well as alterations in ECM architecture or cell-extracellular matrix attachments (Derosa et al. 2006; Bayramoglu et al. 2012). Matrix metalloproteinase (MMP) is a family of zinc-dependent endopeptidase which is capable of destroying all components of the ECM. Matrix metalloproteinase-9 (MMP-9), also known as Gelatinase B or 92 kDa type IV collagenase, plays important roles in the pathogenesis of hypertension (Humphrey 2008; Berg et al. 2011).

MMP-9 was first defined as a neutral protease, which is isolated from human neutrophils. It degrades type IV collagen, proteoglycan, and laminin. MMP-9 is produced by tumoral cells as well as inflammatory cells such as neutrophil, eosinophil, monocyte, lymphocyte and alveolar macrophage (Chintala et al. 1999; Corbel et al. 2000; Apakkan Aksun et al. 2001; Bayramoglu et al. 2009, 2011).

The MMP-9 gene is located on q11.1-13.1 of chromosome 20 (Kleiner and Stetler-Stevenson 1999). The structure of human MMP-9 gene was identified by Huhtala et al. (1990). The human MMP-9 gene contains 13 exons and 7.7 kb of DNA (Chintala et al. 1999). The gene also has TATA box, AP-1 element, SP-1 transcriptional factor, TRE and NF-kB binding region (Chintala et al. 1999; Kleiner and Stetler-Stevenson 1999; Nguyen et al. 2001). Expression of MMP-9 is regulated at the transcriptional level (De Souza et al. 2005).

Due to these features, the MMP-9 gene in patients with hypertension has been studied to understand a possible relationship between hypertension and the MMP-9 gene (Zhou et al. 2007; Palei et al. 2010; Lacchini et al. 2010).

The C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene is found to correlate with hypertension due to its role in catalyzing the formation of 5-methylenetetrahydrofolate (Qian et al. 2007).

MTHFR is an important enzyme of the folate metabolism. The human MTHFR gene is localized to chromosome 1p36.3 and the gene encodes the enzyme MTHFR, which consists of 656 amino acids (Rosenblatt 2001; Dikmen et al. 2004). Some MTHFR gene mutations cause hyperhomocysteinemia and homocystinuia. These are important risk factors for cardio and cerebrovascular diseases (Daly et al. 1999; Homberger et al. 2000; Stern et al. 2000).

The C677T polymorphism of MTHFR involves a point mutation, which occurs due to the conversion of Cytosin (C), localized at nucleotide 677 of the gene encoding the enzyme MTHFR, to Thymine (T). As a result of this point mutation, MTHFR activity is reduced. The reduced MTHFR activity leads to a decrease in the level of 5-methyl tetrahydrofolate and an increase in the plasma level of homocysteine since homocysteine cannot be converted into methionine (Schneider et al. 1998; Lee et al. 1999; Goyette and Rozen 2000). It has been reported that C677T polymorphism of MTHFR is a risk factor for hypertension, cardiovascular diseases, stroke, neural tube defects, Down syndrome and breast and endometrial cancers (Kang et al. 1991; Schmitz et al. 1996; Bova et al. 1999).

In the current study, we envisaged to clarify the relation between hypertension and the C1562T polymorphism of the matrix metalloproteinase-9 gene, as well as between hypertension and the C677T polymorphism of MTHFR. This study was conducted by testing for the prevalence of these polymorphisms in hypertension patients in the Adiyaman region.

Materials and methods

Study population

The study enrolled 99 healthy control subjects and 125 patients with essential hypertension who were admitted to the Cardiology Department of Adiyaman 82. Year State Hospital. The study complies with Declaration of Helsinki and was conducted with the approval of the Ethical Guidelines Committee of the Adiyaman University.

Patients who had greater than mild valve stenosis or regurgitation, aortic coarctation, previous cardiac surgery, chronic kidney disease, hepatic dysfunction, respiratory illness, acute infection, chronic inflammatory

disease, or complex congenital heart disease were excluded from the study.

Blood pressure was measured three times after 5-min rest in the sitting position on both upper limbs with the use of automatic manometer (Omron M4 Plus, Omron Healthcare Europe, Hoofddorp, Holland). The mean value of the second and the third measurements were calculated. The measurements taken on the dominant limb were analyzed. Hypertension was considered if systolic (SBP) >140 mmHg or diastolic (DBP) blood pressure were above 90 mmHg. Ethical approval was obtained from the local research ethics committee and written informed consents were obtained from all of the patients.

Genotype determination

Genomic DNA was extracted from blood samples (10 mL) using salt extraction method (Hulyam et al. 2013). Genotypes for the C1562T polymorphism of MMP-9 were determined by polymerase chain reaction as described previously (Bayramoglu et al. 2009) using the primers 5′-GCCTGGCACATAGTAGGC CC-3′ (sense) and 5′-TTCCTAGCCAGCCGGCATC-3′ (antisense). A 435-bp PCR product was cleaved with 1U SphI restriction enzyme (New England Biolabs, Ontario, Canada). PCR fragments were separated on 2 % agarose gel. The fragments were visualized by a charge coupled device (CCD) camera and evaluated with Labsworks Software (Bio-Rad, Hercules, CA, USA). Following the cleavage with SphI enzyme, three genotypes were determined including CC (435 bp), CT (435-, 247- and 188-bp) and TT (188 bp).

Genotypes for the MTHFR gene C677T polymorphism were determined by polymerase chain reaction amplifigcation using the primers 5′-TGAAGGA-GAAGGTGTCTGCGGGA-3′ (sense) and 5′-AG-GACGGTGCGGTGAGAGTG-3′ (antisense) and the conditions as previously described (Dikmen et al. 2004). Each 15 μL of PCT product was cleaved with 5 units of Hinf I restriction enzyme (New England Biolabs, Ontario, Canada) for C677T polymorphism and the 198-bp DNA fragment was cleaved into 175- and 23-bp fragments. Following the cleavage procedure, DNA fragments were separated on 2 % agarose gel electrophoresis (Sigma Diagnostic, St. Louis, MO, USA) and they were visualized by CCD camera and evaluated using Labsworks Software (BioRad). For the C677T mutation, three different genotypes were determined including 677CC homozygous normal (wild type) (198 bp), 677CT heterozygous (198-, 175- and 23-bp) and 677TT homozygous mutant (175- and 23-bp).

Biochemical analysis

The plasma samples were separated by centrifugation at 1,600 g at 4 °C for 15 min using a cooling centrifuge (Hermle ZK510, Gosheim, Germany) and analyzed for the plasma total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), C reactive protein (CRP) and triglyceride. The plasma total cholesterol, HDL, LDL, CRP and triglyceride levels were immediately measured with a commercial kit (Roche Diagnostics, Mannheim, Germany) using an auto analyzer (Roche/Hitachi Cobas c Systems, Basel, Switzerland). The plasma total cholesterol, HDL, LDL, CRP and triglyceride levels were expressed in mmol/l.

Statistical analysis

Comparison of the categorical variables (such as: gender, genotype, allele…) between groups were performed with Pearson Chi Square test, Yates' Chi Square test, Fisher's Exact test, One Proportion Exact p value and Chi Square Goodness of Fit test analyses. On the other hand, continuous variables (such as: age, height, weight…) were compared between groups with Mann–Whitney U test for the non-normal variables and Student's t test for the normally distributed variables. Shapiro–Wilk test was used for the normality. We used IBM SPSS Statistics 20 for the analyses. The p values <0.05 were accepted as significant.

Results

There was statistical difference between the control group and the all-patients group with respect to the gender distribution ($p < 0.001$), height ($p = 0.001$), weight ($p = 0.001$), body mass index ($p < 0.001$), systolic pressure ($p < 0.001$) and diastolic pressure ($p < 0.001$) and CRP ($p < 0.001$), while there was no significant difference for age ($p = 0.250$), total cholesterol ($p = 0.196$), HDL ($p = 0.090$), LDL ($p = 0.468$) and triglyceride ($p = 0.121$) (Table 1).

Table 1 Clinical characteristics and some individual features of the hypertensive patients and controls

Clinical and individual features		Controls n mean ± SD median (25th–75th) pctl		Hypertension patients n mean ± SD median (25th–75th) pctl		Statistic
Age		99		125		$p = 0.250$*
		55.47 ± 10.68		56.98 ± 10.41		
		55 (47–63)		56 (49–63)		
Gender		36/63		84/41		$p < 0.001$***
(female/male)						
Height (cm)		99		125		$p = 0.001$*
		1.67 ± 0.08		1.64 ± 0.07		
		1.68 (1.60–1.72)		1.65 (1.60–1.68)		
Weight (kg)		99		125		$p = 0.001$**
		75.51 ± 12.74		80.83 ± 10.89		
		75 (66–84.75)		80 (75–90)		
BMI (kg/m^2)		99		125		$p < 0.001$**
		26.91 ± 3.85		30.07 ± 4.40		
		26.53 (24.22–29.34)		29.34 (27.34–33.20)		
Brachial systolic BP (mmHg)		99		125		$p < 0.001$*
		124.60 ± 11.99		144.13 ± 18.02		
		125 (120–130)		140 (130–160)		
Brachial diastolic BP (mmHg)		99		125		$p < 0.001$*
		78.29 ± 10.06		88.10 ± 9.58		
		80 (70–85)		90 (80–97.5)		
Total cholesterol (mmol/l)		99		125		$p = 0.196$*
		194.39 ± 34.95		192.49 ± 42.45		
		198.5 (167.5–216)		183 (168–211)		
HDL cholesterol (mmol/l)		99		125		$p = 0.090$*
		46.06 ± 13.96		42.50 ± 10.76		
		44 (35–56)		40 (35–50)		
LDL cholesterol (mmol/l)		99		125		$p = 0.468$*
		113.55 ± 32.95		111.86 ± 32.04		
		112.5 (93.35–136.90)		109.10 (89.20–127.40)		
Triglycerides (mmol/l)		99		125		$p = 0.121$*
		175.97 ± 114.14		205.96 ± 162.39		
		143.5 (98–223.25)		160 (113–236.25)		
C reactive protein (CRP)		99		125		$p < 0.001$*
		5.38 ± 14.11		5.94 ± 10.47		
		1.13 (0.28–3.50)		2.50 (0.98–6.38)		
Smoking	n/(%)	+	−	+	−	$p = 0.514$****
		9/(9)	90/(91)	14/(11.2)	111/(88.8)	
Alcohol use	n/(%)	7/(7.07)	92/(73.6)	6/(4.8)	119/(95.2)	$p = 0.729$*****
Diabetes	n/(%)	7/(8)	92/(92)	27/(21.6)	98/(78.4)	$p = 0.002$****
Heart D.	n/(%)	0/(0)	99/(100)	23/(18.4)	102/(81.6)	$p < 0.001$****
Stroke	n/(%)	0/(0)	99/(100)	5/(4)	120/(96)	$p = 0.259$*****

Mean: average, median: 25th–75th pctl: (pctl:percentile) *Abbreviations BMI* body mass index, *BSP* brachial systolic blood pressure, *BDP* brachial diastolic blood pressure, *HDL* serum high-density lipoprotein cholesterol, *LDL* serum low-triglycerides, *CRP* serum level of C-reactive protein, *Heart D.* heart disease

* Mann–Whitney U test; ** Student's *t* test; *** Pearson Chi Square test; **** Yates' Chi Square test; ***** Fisher's exact test

Table 2 Distribution of alleles and genotypes of the MMP-9 gene C1562T and the MTHFR gene C677T in controls and patients with hypertension

	n	MMP-9 C1562T genotypes		Alleles		MTHFR C677T genotypes			Alleles	
		CC (n) (%)	CT (n) (%)	C (n) (%)	T (n) (%)	CC (n) (%)	CT (n) (%)	TT (n) (%)	C (n) (%)	T (n) (%)
Control	99	75	24	174	24	56	38	5	150	48
		(75.8)	(24.2)	(87.9)	(12.1)	(56.6)	(38.4)	(5.1)	(75.8)	(24.2)
Hypertensive patients	125	89	36	214	36	65	38	22	168	82
		(71.2)	(28.8)	(85.6)	(14.4)	(52)	(30.4)	(17.6)	(67.2)	(32.8)
Statistics		$p = 0.411^{\dagger}$		$p = 0.448^{\dagger}$		$p = 0.014^{\dagger}$			$p = 0.047^{\dagger}$	

† Pearson Chi Square test

The rate of heart crisis ($p < 0.001$) and diabetes ($p = 0.002$) were statistically higher in the all-patients group in comparison with that of the control group, while there was no difference with respect to the smoking ($p = 0.514$), alcohol ($p = 0.729$) and stroke ($p = 0.259$) (Table 1).

MMP-9 C1562T genotype distribution and allele frequency of controls and patients with essential hypertension are shown in Table 2. No statistically significant difference was found between the control group and the patient group in terms of numbers and percentages of genotypes of MMP-9 C1562T ($p = 0.411$). It was found that allele percentages were not significantly different between the control group and the patient group ($p = 0.448$). MTHFR C677T genotype distribution and allele frequency of controls and patients with essential hypertension are given in Table 2. Statistically significant difference was found between the control group and the patient group in terms of numbers and percentages of genotypes of MTHFR C677T ($p = 0.014$). When intra-group comparisons were made in the control group and all-patients group with respect to the two genotypes, the difference was significant between two genotypes in both groups ($p < 0.001$). It was found that allele percentages were significantly different between the control group and the patient group ($p = 0.047$). The frequency of genotypes observed in the groups is as follows (in descending order): CC > CT > TT.

Discussion

As a result of our study, female gender, body mass index, systolic pressure, diastolic pressure and CRP were found to be significantly higher in all the patient groups compared to the control group, whereas no significant difference was found in terms of age, height, weight, total cholesterol, HDL, LDL, age and triglyceride (Table 1). Heart attack and diabetes were found to be statistically more significant in all patient groups compared to the control group, whereas no significant difference was found by means of cigarette smoking, alcohol consumption and stroke (Table 1). Lacchini et al. (2010) did not find any statistically significant difference in terms of total cholesterol, age and triglyceride, while a difference was seen in HDL, LDL, systolic and diastolic blood pressure, and body mass index in hypertensive patients compared to control. Gai et al. (2009) reported that in terms of smoking, gender distribution, diabetes, systolic and diastolic blood pressure there was no statistically significant difference.

When we examined every patient and control subjects in our study in terms of MMP-9 C1562T genotype distribution and allel frequency, C1562T genotype frequency was determined as CC 76.8 % and CT 23.2 % for control subjects, and as CC 71.9 %, CT 28.1 % for all patients (Table 2). The frequency of 1562T allele was 12.1 % in control subjects and 14.4 % in patients; the frequency of 1562C allele was 87.9 % and 85.6 % in control subjects and patients, respectively. No statistically significant difference was found between control subjects and patients with respect to the frequency of genotype and allele.

Palei et al. (2010) reported that MMP-9 C1562T polymorphism frequencies were CC 81 %, CT 18 %, and TT 1 % in the control group, and CC 68 %, CT 29 %, and TT 3 % in patients with gestational

hypertension. On the contrary to the results of the current study, they reported that C1562T polymorphism may correlate with gestational hypertension. Nevertheless, another study reported that T allele for the C1562T polymorphism is associated with gestational hypertension (Palei et al. 2012).

In a study conducted by Lacchini et al. (2010) the authors determined that the frequency of 1562 CC genotype, CT genotype and TT genotype was 75, 25 and 0 %, respectively, in hypertensive patients, while corresponding frequencies were 80, 18 and 2 % in control subjects. In conclusion, they reported that the genetic polymorphism of the MMP-9 gene may change sensitivity of left ventricular remodeling in hypertensive patients.

Gai et al. reported that MMP-9 C1562T polymorphism frequencies of 1562 CC genotype, CT genotype and TT genotype were 68, 29.7 and 2.3 % for patients with hypertensive heart disease, respectively, and 80.3, 18.4 and 1.3 % for control, respectively. The authors suggested that there is a remarkable relation between Chinese hypertensive heart disease patient population and C1562T polymorphism of the MMP-9 gene (Gai et al. 2009).

In another study, Zhou et al. 2007 reported an increased risk of cardiovascular events for hypertensive patients who carry the T allele. Friese et al. (2009) reported that target organ injury is related with the overexpression of MMPs in hypertension. In a study investigating aortic dissection in hypertensive, the authors reported that for the 1562C/T polymorphism of the MMP-9 gene, the T allele correlates with the aortic dissection in hypertensive patients (Song et al. 2006).

Many studies reported that antihypertensive drugs that down-regulate MMPs may offer advantages in the management of this disease (Martinez et al. 2006; Fontana et al. 2011) .

In our study, MTHFR C677T genotype frequencies were found to be CC 56.6 %, CT 38.4 %, and TT 5.1 % in the control group, and CC 52 %, CT 30.4 %, and TT 17.6 % in the patient group (Table 2). The frequency of 677 T allele was 24.2 % in control subjects and 32.8 % in patients; the frequency of 677 C allele was 75.8 and 67.2 % in control subjects and patients, respectively. A statistically significant difference was found between the control group and the patient group in terms of genotypes and allele frequencies of MTHFR C677T. When comparing control group and overall patient population in itself genotypes showed very significant differences between each other. It was found that allele percentages were significantly different between the control group and the patient group. The frequency of genotypes observed in the groups is as follows (in descending order): CC > CT > TT.

It was reported that MTHFR 677 CT genotype and MTHFR 677T allele are associated with an increased risk of hypertension (Markan et al. 2007). In a meta-analysis, it was stated that the C677T polymorphism is associated with hypertension and this polymorphism is an independent risk factor for hypertension (Qian et al. 2007). In another meta-analysis, it was indicated that the 677T allele may increase the risk of severe diastolic hypertension during pregnancy (Kosmas et al. 2004). In a similar study conducted in the Caucasian population, Heux et al. (2004) concluded that MTHFR C677T gene variant is a risk factor for essential hypertension.

Ilhan et al. have reported 677 CC genotype frequency as 46.2 %, CT genotype frequency as 41.0 % and TT genotype frequency as 12.8 % for hypertension patients. Accordingly, the frequency of CC and TT genotypes is higher, as indicated by our findings. The authors found that for the control subjects, the frequency of CC, CT and TT genotypes was 72.0, 26.0 and 2.0 %, respectively. In our study, the frequency of CT and TT genotypes was higher. Consistent with our results, they reported that the frequency of the C allele of the controls was significantly higher compared with patients with hypertension, and that the MTHFR C677T gene polymorphism is an independent risk factor for essential hypertension (Ilhan et al. 2008).

In another study, it was stated that the determination of the MTHFR genotype, particularly the TT genotype, would be useful in predicting early coronary artery disease in hypertensive adolescents (Koo et al. 2008).

In conclusion, we may suggest that the TT genotype of the MTHFR gene C677T polymorphism may be considered as a genetic indicator in the development of essential hypertension for the population of Adiyaman city.

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