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Original article

Association between angiotensin II type-1 receptor A1166C polymorphism and the presence of angiographically-defined coronary artery disease in an Iranian population

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Background: There are reported associations between a polymorphism of the angiotensin II type 1 receptor (AT_1R/A1166C) gene and coronary artery disease (CAD), hypertension, and myocardial infarction in some populations.

Objective: Investigate the association between A1166C polymorphism and CAD in an Iranian population.

Methods: Four hundred and thirteen patients with suspected CAD were recruited. Based on coronary angiography, the patients were classified into CAD+ (*n*=315) and CAD- (*n*=98) groups defined as >50% and <50% stenosis of any major coronary artery, respectively. One hundred and thirty-five healthy subjects were also recruited as the control group. The AT_1R polymorphism was assessed using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) based method.

Results: A higher frequency of the AC and CC genotypes and lower frequency of the AA genotype was observed in both CAD+ and CAD- groups, compared with the control group ($p < 0.05$). CAD+ and CAD- groups also had a higher frequency of the C allele than controls ($p < 0.01$). There was no significant difference in genotype and allele frequencies between hypertensive and non-hypertensive patients ($p > 0.05$). In addition, the AT_1R genotype frequencies did not differ significantly among different subgroups of CAD+ patients, based on the number of affected coronary vessels ($p > 0.05$).

Conclusion: The frequency AT_1R/A1166C polymorphism was higher among patients with some degrees of coronary stenosis who are candidates of coronary angiography.

Keywords: Angiography, angiotensin receptor, coronary artery disease, hypertension, polymorphism

The renin-angiotensin system (RAS) comprises a cascade of processes leading to the production of angiotensin II from the angiotensinogen. Activation of RAS may play an important role in the pathophysiology of coronary artery disease (CAD). The most likely mechanism by which angiotensin converting enzyme (ACE) affects cardiovascular risk is by increasing the circulating concentrations of

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angiotensin II and by reducing plasma bradykinin levels [1, 2].

Cellular effects of angiotensin II are mediated by two distinct receptor subtypes: angiotensin II type 1 (AT_1) and angiotensin II type 2 (AT_2) receptors [3]. Angiotensin II acts predominantly via the angiotensin II type 1 receptors (AT_1R), which are present on smooth muscle cells of coronary arteries [1, 4, 5].

The AT_1 receptor gene (AF245699) has a chromosomal location of 3q21-q25 extending over a 55kb segment, and comprising five exons. A single nucleotide polymorphism (SNP) in the 3-prime untranslated region (3′-UTR) of this gene (A1166C, rs5186) has been characterized and investigated in relation to hypertension, left ventricular hypertrophy, myocardial infarction (MI), carotid intima medial thickening and stroke in a limited number of patients [6-9]. However, the results have been inconsistent, and previous reports of associations between this SNP and CAD or hypertension have not been confirmed in some studies.

There is little information about the genetic susceptibility to CAD and hypertension in Iranian populations in spite of the high prevalence of these disorders. In this study, we aimed to investigate the A11166C polymorphism of AT_1R gene and the presence of CAD and hypertension in an Iranian population.

Methods

Study population

Five hundred forty eight subjects participated in this study. Four hundred and thirteen patients with suspected CAD who underwent coronary angiography were recruited from Ghaem Medical Center, Mashhad, Iran (245 males, 168 female; mean age 56.3±11.5 years). The presence of CAD was defined as > 50% reduction of coronary artery diameter. Patients were classified according to the number of significant stenotic vessels as follows: angiographically-normal vessel (n = 99), 1-vessel (SVD) (n = 107), 2-vessel (2VD) (n = 106) and 3-vessel (3VD) (n = 101) diseased groups. One hundred thirty-five subjects from a healthy population of volunteers were also recruited from two health centers as the control group (72, males and 63, females; mean age 48.8±9.9 years). These individuals had no personal or family history of cardiovascular disease or diabetes.

The study protocol was approved by the Ethics Committee of the Mashhad University of Medical Sciences (MUMS), and written informed consent was obtained from each participant.

Anthropometric and other measurements

Anthropometric parameters, including weight, height, body mass index (BMI), waist circumference, hip circumference, and waist/hip ratio as well as systolic and diastolic blood pressures were measured [10].

Routine biochemical analysis

A full fasted lipid profile was determined for each subject. Serum lipids and fasting blood glucose (FBS) concentrations were measured using enzymatic methods.

Genetic analysis

Whole blood was collected from the study subjects, and genomic DNA was isolated from peripheral blood leukocytes using a commercial kit (Biogen, Mashhad, Iran). The A1166C variant of AT_1R gene was identified using the polymerase chain reaction (PCR) followed by restriction enzyme digestion of the amplified product, as previously described [11, 12]. The primers used in the PCR reaction were 5′-GCACCA TGTTTTGAGT TG-3′ as the forward and 5′-CGACT ACTGCTTAG CATA-3′ as the reverse primer under the conditions described by Behravan et al [12, 13]. The PCR products were digested with the *Dde*I restriction enzyme (MBI Fermentas, EU). Digested products were separated using electrophoresis on a 1.5% agarose gel, and visualized directly under UV light after staining with ethidium bromide. Undigested 540 bp fragment indicated the presence of the A allele and, appearance of two bands at 110 and 430 bp represented the C allele [12].

Statistical analysis

All statistical analyses were performed using the SPSS for Windows (version 11.5) (SPSS, Chicago, IL USA). Data were expressed as mean±SD or median and interquartile range. The statistical difference in genotype and allele frequencies between the CAD+, CAD- and control groups were assessed by the χ^2 test. Other variables were compared using one-way ANOVA or Kruskall-Wallis test. Compliance of genotypes with the Hardy-Weinberg equilibrium in each group was assessed by χ^2 test with one degree of freedom. A two-sided p-value <0.05 was considered statistically significant.

Results

Demographic characteristics

Among the individuals who underwent coronary angiography, 59.3% were male. According to the results of coronary angiography, 58.9% of males and 88.2% of females had coronary artery disease. The prevalence of coronary artery disease among those undergoing angiography was significantly higher in females compared with males.

Table 1 shows the general characteristics (clinical and biochemical) of patient and control subjects. There was a significant difference between the three groups in their age and gender. Smoking habit and diabetes mellitus were more frequent in CAD+ and CAD- groups than control subjects. The family history of coronary heart disease (CHD), diabetes mellitus, stroke, and peripheral vascular disease were also higher in CAD+ and CAD- groups compared to the controls. Waist to hip ratio was significantly higher in both CAD+ and CAD- subjects compared to the controls whereas the difference among groups in their BMI did not reach statistical significance. In regard to the lipid profile, CAD+ and CAD- groups had significantly higher levels of high-density lipoprotein cholesterol (HDL-C) and triglycerides, and lower levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) compared to the control group. This favourable status of lipid profile in CAD+ and CAD- subjects may be attributed to the consumption of lipid lowering drugs. CAD+ and CAD- patients had a significantly higher systolic blood pressure and FBS. Among patients, CAD+ subjects were older than CAD- subjects, and had significantly higher levels of FBS and triglycerides. Other biochemical parameters were not significantly different between CAD+ and CAD- groups.

Table 1. Clinical and biochemical characteristics of patients and control subjects. (BMI: body mass index; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FBS: fasting blood sugar; SBP: systolic blood pressure; DBP: diastolic blood pressure; CHD: coronary heart disease; PVD: peripheral vascular disease).

		Control	CAD-	CAD+
Number		135	98	315
Gender (female/male)		63/72	69/29***	99/216$^{**\spadesuit\spadesuit\spadesuit}$
Age (years)		48.0±9.5	52.8±12.2**	57.4±11.1$^{***\spadesuit\spadesuit}$
Height (cm)		161.0±10.8	153.1±29.2*	159.0±23.5
Weight (kg)		71.0±13.6	67.4±12.9	70.6±12.8
BMI (kg/m^2)		27.8±5.6	27.1±5.7	27.1±5.8
Waist (cm)		87.1±21.7	87.8±12.7	88.6±12.3
Hip (cm)		102.1±9.3	94.9±13.0***	94.0±13.1***
Smoker (%)		15.6	28.6*	38.4***
FBS (mg/dL)		85.6±14.5	103.2±37.7*	119.2±55.0$^{***\spadesuit}$
Diabetes mellitus		0	20.4***	28.9***
TC (mg/dL)		183.8±39.2	167.5±46.7*	178.5±49.6
LDL-C (mg/dL)		121.9±34.5	97.7±33.1***	102.2±36.8***
HDL-C (mg/dL)		39.8±8.4	45.9±13.3*	45.5±23.8*
TG (mg/dL)		101.0 (71.0-142.0)	109.0 (83.0-156.0)*	135.5 (95.0-192.2)$^{***\spadesuit\spadesuit}$
SBP (mmHg)		117.3±22.6	141.0±28.0***	137.9±29.4***
DBP (mmHg)		78.8 ± 11.5	77.1 ± 14.2	78.5 ± 14.2
Family history of	**CHD (%)**	0	17.3***	14.9***
	Stroke (%)	0	10.2***	7.2**
	Diabetes (%)	0	9.2***	14.1***
	PVD (%)	0	1	3.2*

Values are expressed as mean ± SD or median and interquartile range. Comparisons were made using the χ^2 test, one-way ANOVA and Kruskal-Wallis test. $^{*}p < 0.05$, $^{**}p < 0.001$, $^{***}p < 0.001$, compared with the control group; $^{\spadesuit}p < 0.05$, $^{\spadesuit\spadesuit}p < 0.001$, $^{\spadesuit\spadesuit\spadesuit}p < 0.001$, compared with the CAD- group.

Association between AT_1R/A1166C polymorphism and presence of CAD

In vitro DNA amplification of the AT_1R gene using the specific primers resulted in a 540 bp DNA product. On digestion of the amplified fragment (amplicon) with *Dde*I restriction endonuclease, DNA fragments of 540 (AA), 430 (CC) or 540 and 430 (AC) bp length were observed. Thus, each sample revealed one of three different electrophoretic patterns.

Table 2 shows genotype and allele frequencies of AT_1R/A1166C polymorphism in CAD+, CAD- and control subjects. Overally, among a total of 413 patients, the frequencies of AA, AC, and CC genotypes were 66.0% (208 cases), 25.1% (79 cases), and 8.9% (28 cases) in the CAD+ and 69.4% (68 cases), 24.5% (24 cases), and 6.1% (6 cases) in the CAD- group, respectively. Likewise, among 135 control subjects, the frequencies of AA, AC, and CC genotypes were 86.7% (117 cases), 11.8% (16 cases), and 1.5% (2 cases), respectively. The genotype distribution in the CAD- and control groups was consistent with the Hardy-Weinburg equilibrium ($p > 0.05$). However, a significant deviation from the equilibrium was observed in the CAD+ group ($p < 0.001$). The frequency of A and C alleles 0.786 and 0.214 in the CAD+ patients, 0.816 and 0.184 in the CAD- patients, and 0.926 and 0.074 in the control group, respectively. A higher frequency of the AC and CC genotypes was observed in both CAD+ and CAD- patients when compared with the control group ($p \leq 0.05$). On the other hand, the frequency of AA homozoygotes was significantly higher in the control subjects compared to the CAD+ and CAD- subjects ($p < 0.01$). In regard to the allele frequencies, a significantly higher frequency of the C allele was observed in the CAD+ and CAD- groups compared to the control group ($p < 0.01$). Notably, there was no significant difference between CAD+ and CAD- groups, neither in the genotype distribution nor in their allele frequencies ($p > 0.05$).

In regard to the number of stenosed coronary vessels, no significant difference in the genotype distribution or allele frequencies was detected between subgroups with one (SVD), two (2VD), and three (3VD) affected vessels except for a significant difference in allele frequencies between SVD and 3VD groups ($p < 0.05$, **Table 3**).

Table 2. Genotype and allele frequencies of AT_1R/A1166C polymorphism in CAD+, CAD- and control subjects.

	Control	CAD-	CAD+
Genotype frequency			
AA	117 (86.7)	68 (69.4)**	208 (66.0)***
AC	16 (11.9)	24 (24.5)*	79 (25.1)**
CC	2 (1.5)	6 (6.1)‡	28 (8.9)**
Allele frequency			
A	250 (92.6)	160 (81.6)**	495 (78.6)***
C	20 (7.4)	36 (18.4)**	135 (21.4)***

Values are expressed as number (%). Comparisons were made by the χ^2 test. $^{*}p < 0.05$, $^{**}p < 0.001$, $^{***}p < 0.001$, compared with the control group; $^{\ddagger}p = 0.05$, compared with the control group.

Table 3. Genotype and allele frequencies of AT_1R/A1166C polymorphism in the CAD-patients and subgroups of CAD+ patients based on the number of affected coronary vessels.

	CAD-	SVD	2VD	3VD
Genotype frequency				
AA	68 (69.4)	67 (62.6)	68 (64.2)	73 (72.3)
AC	24 (24.5)	27 (25.2)	28 (26.4)	23 (22.8)
CC	6 (6.1)	13 (12.2)	10 (9.4)	5 (4.9)
Allele frequency				
A	160 (81.6)	161 (75.2)	164 (77.4)	169 (83.7)*
C	36 (18.4)	53 (24.8)	48 (22.6)	33 (16.3)*

Values are expressed as number (%). Comparisons were made using the χ^2 test. $^{*}p < 0.001$, compared with the SVD group. SVD: single vessel disease; 2VD: two-vessel disease; 3VD: three-vessel disease.

Association between AT_1R/A1166C polymorphism and hypertension

In our study, the prevalence of hypertension was significantly higher in females (50.0%) compared to males (31.0%) ($p < 0.05$). The genotype and allele frequencies did not differ significantly between hypertensive and non-hypertensive subjects (**Table 4**).

Discussion

CAD is the most common underlying cause of the heart disease [14, 15]. The involvement of an inherited genetic component is supported by strong familial tendency to CAD [16]. Therefore, identification of susceptibility genes for this prevalent and multifactorial disease is of high importance to public health. There have been few studies concerning the identification of genetic determinants of CAD in Iranian population.

In a previous study, Alvarez et al. [17] did not find a significant difference in the frequency of AT_1R genotypes between Caucasian patients with early CAD and healthy control subjects. However, they reported a synergistic contribution of ACE and AT_1R polymorphisms to the risk of coronary artery disease. The lack of significant difference in the genotype distribution and allele frequencies of the A1166C SNP was also confirmed in other studies performed in patients with CHD and coronary artery bypass grafting [18, 19]. However, Gardemann et al. [1] failed to observe any significant difference in A1166C genotypes between patients with and without CAD or MI. This latter finding is consistent with that of some other studies [4, 20-23]. In addition, in another investigation, the AT_1R genotypes were not found to be significantly associated with cardiovascular outcomes in neither African American subjects nor whites [24].

Despite the findings of aforementioned reports, the AA genotype of AT_1R gene was associated with decreased risk of premature CHD in Turkish subjects [25]. On the other hand, in Italian subjects, Fatini et al. [27] reported a significant association between AT_1R CC genotype and the presence of CHD [26]. This finding was also confirmed in a later study on male subjects with CHD [27]. Moreover, the C allele of the AT_1R gene was previously reported to be associated with the severity of CHD in Japanese patients [23] and development of the stenosis of coronary artery in Chinese patients [18]. The higher prevalence of the CC genotype and C allele of the AT_1R gene have also been reported in cases with MI, which jointly support a plausible role for the C allele in the pathogenesis of CHD [28-30]. It was hypothesized that the adverse effects of the 1166 C allele is due to the increased responsiveness to angiotensin II [31], and complications such as vasoconstriction [32] as well as cardiac and vascular hypertrophy [33]. In the present study, we did not observe any significant difference in genotype or allele frequencies between CAD+ and CAD- groups. However, it is worth noting that the CAD- subjects with <50% stenosis might have degrees of CAD that may progress to overt CAD over time. Moreover, CAD- subjects were significantly younger than CAD+ patients (about five years) and had relatively high frequency of diabetes mellitus and family history of CHD. Therefore, the probability that some of these subjects may become CAD+ within five years should be considered.

Table 4. Genotype and allele frequencies of AT_1R/A1166C polymorphism in hypertensive and non-hypertensive subgroups patients.

	Hypertensive	Non-hypertensive
Genotype frequency		
AA	117 (66.8)	159 (66.8)
AC	43 (24.6)	60 (25.2)
CC	15 (8.6)	19 (8.0)
Allele frequency		
A	277 (79.1)	378 (79.4)
C	73 (20.9)	100 (20.6)

Values are expressed as number (%). No significant difference in genotype or allele frequencies was observed ($p > 0.05$).

In the present study, we did not observe any significant difference between hypertensive and non-hypertensive patients in genotypes nor in their allele frequencies. Previously, several studies have reported an association between A1166C polymorphism and hypertension, and higher frequencies of this SNP have been observed in hypertensive patients [6, 34, 35]. However, these results have not been well consistent. In some studies, subjects with CC genotype have been reported with lower blood pressure and cardiovascular risk [36, 37], while others have shown higher frequency of C allele or CC genotype among hypertensive subjects [4, 35, 38]. Concerning the Iranian population, Behravan et al. [13] reported no significant difference in genotype distribution or allele frequencies between hypertensive and normo-tensive subjects when the combined males and females were analyzed. Their result is consistent with our findings [13]. Furthermore, some other studies also failed to report any significant difference in genotype distribution between hypertensive and normo-tensive subjects or any significant association between A1166C polymorphism and hypertension [11, 39-41].

Conclusion

We observed significant differences in the frequency of AA, AC, and CC genotypes between patients with suspected CAD and controls. The frequency of polymorphic genotypes (AC and CC) was higher between CAD+ and CAD- patients compared with the control subjects. The carriers of the C allele were also significantly higher in CAD+ and CAD- groups compared with the control group. The main reason for the discrepant findings on the association between A1166C polymorphism and CAD or hypertension, may be the complex nature of gene-environment interactions in the pathophysiology of these diseases. Therefore, conflicting results in different populations could be attributed to the differences in lifestyle or diet that affect the genetic predisposition to CAD. Together with environmental factors, the involvement of multiple genes in the pathophysiology of CAD is another factor responsible for the uncertainties in correct risk assessment of the disease. Indeed, it is difficult to identify a single polymorphism as a risk factor for a polygenic and multifactorial disease. To obtain more reliable results, it may be better to study the association between different polymorphisms and CAD jointly (e.g. by linkage studies).

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