

Lack of association between angiotensin-converting enzyme (ACE) genotype and essential hypertension in Peruvian older people

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Abstract

Background: Epidemiological studies have shown an association between the ACE gene I/D polymorphism with arterial hypertension, specifically the DD genotype, in different populations. The objective of this study is to evaluate the association between ACE polymorphisms (Insertion, Deletion or I/D) and essential hypertension in a population of Lima, Peru.

Material and methods: This is a study of cases (essential arterial hypertension) and controls, with determination of the ACE I/D genotype.

Results: Cases (65) and controls (39) had a mean age (standard deviation) of 74.3 (7.9) and 72.6 (6.5) ($p = 0.24$). In cases, the genotype frequencies DD, ID, and II were 6 (9.2%), 28 (43.1%) and 31 (47.7%), respectively. In controls, the genotype frequencies DD, ID, and II were 6 (15.4%), 14 (35.9%) and 19 (48.7%). The Hardy-Weinberg equilibrium analysis in cases and controls was $p = 0.93$ and $p = 0.23$, respectively. No significant associations between genotype DD *vs.* ID + II (OR = 0.56, 95% CI: 0.17–1.87, $p = 0.34$) or II *vs.* DD + ID (OR = 0.95, 95% CI: 0.43–2.12, $p = 0.92$) and essential hypertension were found.

Conclusions: The ACE I/D polymorphism was not associated with hypertension in our sample.

Key words: hypertension; renin–angiotensin system; genetic polymorphism; angiotensin converting enzyme; Peru

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Introduction

Hypertension is one of the most common non-communicable diseases in the world, with a prevalence of 22% [1] and in Peru 23.7% [2]. Essential hypertension refers to primary hypertension where an aetiology has not been clearly identified. Arterial hypertension has been associated with various risk factors including age, sex, demographic, lifestyle, environmental and genetic. The heritability of hypertension ranges from 48 to 60% for systolic hypertension and 34 to 67% for systo-diastolic [3], although it should be noted that heritability does not identify which genetic difference is more significant or the mechanism by which it exerts its effect on blood pressure [3].

Currently, 2129 genes associated with hypertension have been reported, among which is the angiotensin-converting enzyme (ACE) gene [4]. The ACE enzyme converts inactive angiotensin I into active angiotensin II and also degrades bradykinin to maintain homeostasis of blood pressure. ACE is a membrane-bound dipeptidyl carboxypeptidase ectoenzyme, located in the endothelium of blood vessels and is the main component of the renin-angiotensin and kallikrein-kinin system. The ACE gene is encoded on the long arm of chromosome 17 (17q23), consists of 26 exons and 25 introns. The presence or absence of a 287bp element in the ACE gene gives rise to three genotypes: insertion (II), insertion/deletion (I/D) and deletion (DD). Epidemiological studies have shown an association between the ACE gene I/D polymorphism with arterial hypertension, specifically the DD genotype in different populations [5]. On the other hand, certain differences in response have been evidenced in the antihypertensive inhibitors of the angiotensin converting enzyme (ACEI) or angiotensin II receptor blockers (ARBs), according to ACE polymorphism and the study population [5].

The present study aims to evaluate the association between ECA polymorphisms (Insertion/Deletion or I/D) and hypertension essentially in a population of Lima, Peru.

Material and methods

An observational, retrospective case-control study was carried out. 104 patients (65 cases and 39 controls) equal to or older than 60 years were included. Patients with a diagnosis of essential hypertension verified in clinical history and receiving treatment with antihypertensives for more than 3 months were called cases; and controls were those with a clinical

history and evaluation without criteria of arterial hypertension or taking antihypertensives. The study was conducted at the Hospital de Geriátrico of the Almenara Hospital in Lima, Peru, between January 2016 and December 2018. The 104 people of mestizo ancestry, from Lima, who entered the study, were part of an investigation on the use of angiotensin II antagonists, memory performance and its relationship with ACE polymorphisms. The research project was approved by the Almenara Hospital Ethics Committee, and all participants signed an informed consent. The method of patient selection was not probabilistic.

Genomic analysis

After signing the informed consent, whole blood samples were collected in EDTA tubes of each patient. The DNA was extracted from the leukocytes using the standard phenol/chloroform method and amplified by PCR (polymerase chain reaction). ACE I/D polymorphism (rs1799752) was detected using the method described by Franken et al [6].

Statistical analysis

Descriptive statistical data were presented as a percentage (%), mean with standard deviation (SD) and range. The Chi-square analysis was used for the Hardy-Weinberg equilibrium deviation evaluation. The genotype distribution and allele frequencies of each polymorphism were compared between cases and control subjects by the χ^2 test. In establishing the association between hypertension and ACE I/D genotypes, the odds ratio (OR) and 95% confidence intervals (CI) were used. It was considered statistically significant if $p < 0.05$. The SPSS statistical package was used to analyse the data.

Results

The population studied consisted of 46 men (44.2%) and 58 women (55.8%), with a mean age and standard deviation (SD) of 73.7 (7.4) years, range between 60–90 years. In the population studied the frequency of D/D, I/D and I/I genotypes was 12.65%, 43.66% and 43.66% respectively, with allelic D and I frequency of 34.5% and 65.5% respectively. The analysis of the distribution of genotype frequencies showed that it was consistent with a population in Hardy-Weinberg equilibrium ($\chi^2 = 0.1051$; $p = 0.746$) (Tab. 1).

The mean and standard deviation (SD) of age of the cases and controls were 74.34 (7.87) and 72.56 (6.60) years ($p = 0.24$). The cases were male 32

Table 1. Characteristics of the population studied

Characteristics	Controls (n = 39)	Cases (n = 65)	p value
Age (\pm SD)	72.56 (6.60)	74.34 (7.87)	0.24
Sex			
Male (%)	14 (35.90%)	32 (49.23%)	0.19
Female (%)	25 (64.10%)	33 (50.77%)	0.19
Body mass index	27.28 (4.21)	28.02 (3.89)	0.37
Smoking	3 (7.69%)	2 (3.13%)	0.30
Dyslipidaemia	9 (23.08%)	27 (41.54%)	0.07
Diabetes mellitus type 2	7 (17.95%)	14 (21.54%)	0.66
Genotype			
D/D n (%)	6 (15.38%)	6 (9.23%)	0.42
I/D n (%)	14 (35.90%)	28 (43.08%)	0.47
I/I n (%)	19 (48.72%)	31 (47.69%)	0.92

SD — standard deviation

Table 2. Relationship between angiotensin convertase enzyme (ACE) polymorphisms and essential hypertension in a population of Lima, Peru

Genotype ACE	Controls (n = 39)	Cases (n = 65)	OR	95% CI	p value
DD vs. ID + II n (%)	6 (15.38)	6 (9.23%)	0.56	0.17–1.87	0.34
ID vs. II + DD n (%)	14 (35.9%)	28 (43.08)	1.35	0.60–3.06	0.47
II vs. DD + ID n (%)	19 (48.72)	31 (47.9%)	0.95	0.43–2.12	0.92
D vs. I n (%)	26 (33)	40 (31%)	0.89	0.49–1.62	0.70
The Hardy-Weinberg equilibrium (p value)	0.23	0.93			

OR — odds ratio; CI — confidence interval

(49%) and female 33 (51%), while controls were male 14 (36%) and female 25 (64%). In the cases the genotype frequency DD, ID, and II were 6 (9.23%), 28 (43.08%), 31 (47.69%) respectively. In the controls the genotype frequency DD, ID, and II were 6 (15.38%), 14 (35.90%), 19 (48.72%). The Hardy-Weinberg equilibrium analysis in cases and controls was $p = 0.93$ and $p = 0.23$ respectively. No significant association of genotype DD vs. ID + II (OR = 0.56, 95% CI: 0.17–1.87, $p = 0.34$) or II vs. DD + ID (OR = 0.95, 95% CI: 0.43–2.12, $p = 0.92$) with essential hypertension was found (Tab. 2).

Discussion

The present study did not find an association between ACE polymorphisms and essential hypertension in a population of Lima, Peru.

The results of studies on the relationship between ECA polymorphisms and essential hypertension differ significantly depending on the geographic location and population studied. The main study with positive results is the meta-analysis conducted by Mengesha et al. in the African continent, which included 6 studies, finding that patients with the D allele were 1.49 times more likely to develop essential hypertension compared to the carriers of the I allele (OR: 1.49; CI: 1.07–2.07), additionally found that those from sub-Saharan Africa were more susceptible than those from North Africa [5]. A study conducted in the USA with Mexican-Americans found an association between the D allele and essential arterial hypertension [7]. Studies in India have also reported an association between the ACE/(D/D) genotype and essential hypertension [8–11].

On the other hand, the negative results are reported by Agerholm et al. [12], the meta-analytical

study included 45 studies in white people in Europe and the US, finding no relationship between the ACE gene and essential hypertension. In addition, two studies have been published with the same negative results between Hawaiian Americans and African Americans [13, 14].

In Latin America, a study in Colombia (Bucaramanga) found that DD genotype was 1.56 times more frequent in hypertensive patients, compared to allele I [15]. Bonfim-Silva et al. [16] in their study with Afro-Brazilian and Caucasian population found no association; neither did the study conducted in Cuba in a multi-ethnic sample [17]. A recent study in Brazil also found no relationship; however, this relationship became significant only when ACE and ACE2 polymorphisms were combined [18]. Prior to this study, the only study conducted in Peru (Lima and Chincha), was that of Lizaraso et al. and found no relationship between these polymorphisms and essential hypertension [9].

The importance of knowing the association of ACE gene and essential hypertension is to know if there is a genetic basis in the effectiveness of antihypertensive pharmacotherapy with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). It has been described that the effectiveness of ACEIs is diminished in the African and African-American population and these antihypertensives are not of first choice in that population [20, 21]. Coincidentally the ACE D/D genotype is related to essential hypertension in this population [5]. It has been described that the rate of early responses to ramipril is more frequent in patients with genotypes ID and II, compared to DD, in patients from India; once again it is compatible with the finding of the association of DD with HT in that country [22]. Another study in Malaysia, found that DD carriers respond better to enalapril or lisinopril than ID and II [23]. On the other hand, genotypes II respond better than DD or ID to ARB such as ibersartan [24]. One of the practical objectives of this type of pharmacogenetic studies is to convert the ACE polymorphism determination into a marker of individualized antihypertensive response to ACEIs and ARBs.

The present study has some limitations. The main one is the number of patients is relatively small. However, it provided genetic data that can be used to initiate other studies designed to know the pharmacogenetics of ACEIs and ARBs in the Peruvian population, having ACE genotypes as markers.

In conclusion, the present study did not find an association between ACE polymorphisms (Insertion/Deletion or I/D) and essential hypertension in the

study population. More research is required in different populations of the country, adding other candidate genes.

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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