Relationship among angiotensin-converting enzyme polymorphism, cardiovascular risk, and osteoporotic fractures

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Abstract

Objective: Angiotensin-converting enzyme (ACE) has been related to cardiovascular physiology and bone remodeling. Our aim was to assess the relationship among ACE polymorphisms, cardiovascular risk, and osteoporotic fractures.

Material and Methods: We prospectively enrolled 71 patients with hypertension from 2001 to 2014. Sociodemographic and medical data were collected. Comorbidity was evaluated with Charlson index. Densitometric studies on lumbar spine were performed. ACE polymorphism was analyzed by polymerase chain reaction. Data were analyzed using SPSS 15.0 (p value <0.05).

Results: Homozygous deletion (DD) genotype was described in 32.4% of patients, homozygous insertion (II) in 19.7%, and heterozygous insertion/deletion (ID) in 47.9%. On stratifying data by ACE polymorphism, we observed that DD carriers demonstrated neither greater cardiovascular risk factors (30.4% vs. 33.3%, p=0.4) and higher comorbidity (34.8% vs. 22.9%, p=0.3) nor higher osteoporotic fracture incidence (17.4% vs. 16.8%, p=0.9). In women, no significant differences were observed between DD homozygous individuals and ID+II subjects.

Conclusion: It is unclear whether DD genotype is an independent risk factor for cardiovascular disease. In contrast to our expectations, we found no relationship among the DD genotype, cardiovascular risk, and osteoporotic fracture incidence.

Keywords: Angiotensin-converting enzyme polymorphism/genetic, hypertension, cardiovascular diseases, osteoporosis, fractures bone

Introduction

Osteoporosis and hypertension (HT) are two of the great silent pandemics of the 21st century. Both are genetic diseases with polygenic bases. Recently, HT has been linked to bone loss and an increased risk of osteoporotic fractures (1, 2). Renin–angiotensin–aldosterone system (RAAS) controls blood pressure and is the target of antihypertensive drugs. In contrast, both osteoclasts and osteoblasts have adrenergic and neuropeptide receptors modulated by interactions with angiotensin 2 (AT2). AT2 induces RANKL expression in osteoblast, thereby activating osteoclastogenesis via receptor activator of nuclear factor kappaB (RANK)/RANK ligand/osteoprotegerin system and involving bone modeling (3).

Angiotensin-converting enzyme (ACE) is a zinc metallopeptidase that cleaves a wide variety of physiologically relevant substrates, including angiotensin 1 and AT2. ACE serum and cellular levels and ACE activity are genetically determined by insertion/deletion (I/D) ACE polymorphism (4). Thus, D-allele carriers are exposed to a higher level of AT2 and DD homozygous subjects have poor cardiovascular disease prognosis (5, 6).

Despite the role of I/D polymorphism in the incidence of HT and that osteoporosis remains quite controversial, the number of studies focused on genetic factors of these two important diseases is surprisingly low. This study aimed to determine the relationship among ACE I/D polymorphism, cardiovascular disease risk, and osteoporotic fractures in patients with hypertension.

Material and Methods

Between June 2001 and June 2014, we prospectively studied a cohort of 71 patients with systolic or diastolic stage I-II hypertension according to Joint National Committee VI criteria. Exclusion criteria were ethylism, neoplasia, secondary arterial hypertension, chronic renal insufficiency, diabetes, other cardiovascular risk factors (CVRF), hypercalcemia and hypocalcaemia, hyperparathyroidism, and use of modifying...
This study was approved by the hospital’s ethics committee, and patients signed an informed consent form to participate. Data were analyzed using the SPSS 15.0 (SPSS Inc.; Chicago, IL, USA) statistical package. Level of statistical significance was established as p≤0.05.

**Results**

We examined 71 patients of whom 43.7% were men and 56.3% were women. Mean age was 73.3±9 years (range 53–90 years) with no differences by sex (72.5±9 years in males and 74±9 years in females; p=0.5); 48% were aged >75 years. Overall mortality during follow-up was 17% (all of them in last 2 years).

At baseline, no differences between the groups (DD genotype vs ID+II genotype) were observed and neither when analyzing systolic blood pressure (155±24 vs 154±20 mmHg, p=0.841) and diastolic blood pressure (106±33 vs. 93±11 mmHg, p=0.569) nor during lumbar densitometry. At the end of the follow-up, 70.4% of patients had been under antihypertensive treatment with ACE inhibitors. The mean CI score was 1.7±2.7 (range 0–12). Comorbidity was high (>2 points) in 22.5% of cases, and there was no comorbidity in 73.2% of cases. Regardless of concomitant diseases development, 18.3% of cases had diabetes, 32.4% had CVRF that was different from HT, 14% suffered from heart disease, and 12.7% from cerebrovascular disease. In contrast, 17% of patients had at least one fragility fracture (5.6% in hip, 8.5% in vertebrae, and 2.8% in distal radius).

ACE polymorphisms were evaluated in all cases of which 32.4% were DD, 19.7% were ID, and 47.9% were II. The D-allele frequency was 0.57, and I-allele frequency was 0.43. This distribution was in agreement with the Hardy–Weinberg equilibrium (X²=0.05; p=0.8226>0.05). DD genotype subjects did not demonstrate an increase in CVRF (30.4% vs. 33.3%, p=0.4), higher ischemic heart disease (8.7% vs. 16.7%, p=0.3), cerebrovascular disease (8.7% vs. 14.6%, p=0.4), or mortality rate (8.7% vs. 21%, p=0.2). No differences between the groups were determined when analyzing CI comorbidity (35% vs. 23%, p=0.3) and neither in global osteoporotic fractures (17.4% vs. 16.8%, p=0.9) nor specific ones (vertebrae: 8.7% vs. 3%, p=0.9; hip: 8.7% vs. 4.2%, p=0.4).

At baseline, the mean age of women was 59±9.9 years, and all of them were in postmenopausal stage with body mass index of 28±4, systolic blood pressure of 155±22 mmHg, and diastolic blood pressure of 93±10 mmHg. The average time of HT development was 7±8 years.

While analyzing data by sex, females with DD polymorphism resulted in a statistically non-significant increase in the risk of fragility fractures, particularly those involving the hip (25% vs. 6%, p=0.1) as compared with II + ID polymorphism. Analyses adjusted for gender and ACE genotypes are shown in Table 1.

Finally, patients under ACE inhibitors treatment exhibited greater incidence of global osteoporotic fractures compared with subjects under other antihypertensive drugs treatments, with a statistically significant trend (22% vs. 4.8%, p=0.07).

**Discussion**

Cardiovascular disease and osteoporosis are diseases with multifactorial etiology that share pathophysiological mechanisms based on polygenic heritance pattern and both are conditioned by environmental factors.

A recent study compares frequencies of ACE D-allele in different populations, both general and with CVRF (9). ACE polymorphism distribution in our population is in agreement with other studies around the world that were also conducted in patients with hypertension (10-13).

Recent studies have described that the presence of DD polymorphism is associated with an increased ACE activity and bone modeling (4, 5, 14), and several observational studies suggest its association with HT, coronary heart disease, premature heart disease, cerebrovascular disease, and sudden death (5, 6, 15). However, there is contradictory information on the link between I/D polymorphism and CVRF (10). Moreover, there is a lack of studies related to ACE genotypes and osteoporosis (14, 16).

Our findings are in agreement with Bautista et al. (10); therefore, we found no relationship between DD genotype and cardiovascular risk. In contrast to our expectations, we found no association with osteoporotic fracture incidence, although some studies suggest the possible existence of an ACE genotype role in bone mineral density in women (16). Recently, Cakmak et al. (14) described that ACE I/D polymorphism may be a genetic factor related to osteoporosis.

Despite genetic predisposition being probably a determinant in both osteoporosis and HT, our large prospective study that was limited by the relatively small sample did not confirm any role of ACE polymorphism as a marker for cardiovascular risk or fragility fracture in our population.
In conclusion, the relationship among DD polymorphism, cardiovascular risk, and incidence of fragility fractures is hard to establish, and data in literature are contradictory. Hypotheses on the role of I/D genotype in cardiovascular risk remain highly controversial. Current studies are focused on the synergy among different polymorphisms and disease development as a major aim of the pharmacogenomics research.

Ethics Committee Approval: Ethics Committee approval was received for this study from Rio Hortega University Hospital.

Informed Consent: Written informed consent was obtained from patient/patients who participated in this study.

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