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Demographic and Biological Determinants of Hypertension: Insights about ACE I/D Polymorphism in a population from northeastern Brazil

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Abstract- Primary Hypertension is a multifactorial condition and a significant public health concern due to its link with cardiovascular disease. Factors such as obesity, smoking, and genetics contribute to its development. This study examined demographic and biological parameters in hypertensive and normotensive individuals, revealing that ethnicity and family history strongly influence Hypertension risk, particularly among Black participants and those with affected relatives. Hypertensive patients showed higher BMI and waist circumference, with age also contributing to onset. Other parameters, including hip circumference and lipid profiles, were similar between groups. Positive correlations were found among weight-related measures and between total and LDL cholesterol, while HDL cholesterol showed weak negative correlations.

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Demographic and Biological Determinants of Hypertension: Insights about ACE I/D Polymorphism in a population from northeastern Brazil

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Abstract- Primary Hypertension is a multifactorial condition and a significant public health concern due to its link with cardiovascular disease. Factors such as obesity, smoking, and genetics contribute to its development. This study examined demographic and biological parameters in hypertensive and normotensive individuals, revealing that ethnicity and family history strongly influence Hypertension risk, particularly among Black participants and those with affected relatives. Hypertensive patients showed higher BMI and waist circumference, with age also contributing to onset. Other parameters, including hip circumference and lipid profiles, were similar between groups. Positive correlations were found among weight-related measures and between total and LDL cholesterol, while HDL cholesterol showed weak negative correlations. Analysis of 160 genotyped samples showed the D allele as most common in both groups, with no significant genotype differences or association between the ACE I/D polymorphism and Hypertension.

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I. Introduction

Primary Hypertension is a highly heterogeneous disease of multifactorial etiology characterized by persistent elevation of blood pressure (BP) (1–3). Hypertension is defined as a systolic blood pressure (SBP) equal to or exceeding 140 mmHg or a diastolic blood pressure (DBP) equal to or exceeding 90 mmHg (4,5) This condition is a significant risk factor for the development of cardiovascular complications, which are the leading causes of death worldwide, surpassing cancer and infectious diseases, thereby constituting a significant public health issue (6). In Brazil, Hypertension affects 32.5% (36 million) of adult individuals, with over 60% of the elderly population, contributing directly or indirectly to 50% of deaths from cardiovascular disease (CVD) in the country (7).

A range of risk factors has been associated with the development of Hypertension (8), including obesity, smoking, imbalance in the renin-angiotensin-aldosterone system (RAAS), mental stress, ethnicity, among others. The genetic influence on the development of the disease is a consensus within the scientific community; however, its polygenic nature complicates the clear determination of the contribution of each genetic variant in individual patients, rendering each case unique (9,10).

A genome-wide association study (GWAS) comprising over 1,000,000 rigorously phenotyped individuals with measured blood pressure elucidated 901 loci related to blood pressure regulation. Notably, it identified genes encoding proteins of the renin-angiotensin-aldosterone system (RAAS), proteins involved in vascular remodelling, and proteins associated with immune response regulation, such as TGF-β and SMAD. This expands the diversity of therapeutic targets for the treatment of Hypertension(11).

The aberrant action of the renin-angiotensin-aldosterone system (RAAS) is central to the pathogenesis of Hypertension, as it promotes sodium retention, vasoconstriction, endothelial dysfunction, and vascular injury. Renin is released by the kidneys under low-pressure conditions; it cleaves angiotensinogen into angiotensin I, which serves as a substrate for angiotensin-converting enzyme (ACE), converting angiotensin I into its physiologically active form, angiotensin II. This component accelerates sodium reabsorption in the proximal tubule and exhibits pro-fibrotic and pro-inflammatory actions, mechanisms through which angiotensin II is pathological in Hypertension(3,12).

A polymorphism resulting from the insertion/deletion of 287 base pairs in the ACE gene, initially described as hypertensin I (13), has been widely studied in the context of Hypertension (14). The allele frequencies (AF) of the I and D alleles vary significantly

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among populations (15–21). In Brazil, different AF are observed in distinct populations across the country, underscoring the importance of investigating various populations, particularly considering the continental dimensions and the significant ethnic and cultural diversity, as well as the profound social inequality (15,16).

Regarding the physiological relevance of this polymorphism, the D allele appears to be associated with increased expression of ACE in the kidneys (22) and elevated serum levels of angiotensin II (23,24), a pathological component in Hypertension. Furthermore, pharmacological inhibition of ACE is a widely used therapeutic intervention for managing Hypertension (25,26). The convergence of these factors supports the notion that the D allele is a risk factor for Hypertension and a range of cardiovascular complications, highlighting the importance of investigating the allele frequencies of I/D and their association with Hypertension and related pathologies (24), which is the objective driving our research.

II. Methodology

a) Sample Collection

Blood samples were collected at the Municipal Laboratory of Vitória da Conquista (LACEMp), interior of Bahia, Brazil. Patients who attended for blood sampling to undergo laboratory tests were invited to participate in the research, having been initially informed about the study. After clarification and signing the Informed Consent Form (ICF) and self-reported Hypertension (or not), the patients completed a questionnaire, at the time of blood sampling for lab tests, an additional 8 ml blood tube containing EDTA was collected. The tubes were stored and maintained refrigerated for a minimum of 24 hours, after which plasma and cellular fractions were separated in the Genetics Laboratory of UESB. A total of 183 samples were collected, including 95 from hypertensive individuals and 88 from normotensive individuals.

b) DNA Extraction Genomic

DNA was extracted using the QIAGEN DNA extraction kit. Subsequently, the quality of the DNA was assessed by agarose gel electrophoresis at 2%.

i. *Polymerase Chain Reaction Agarose Gel Electrophoresis*

The I/D polymorphism of the ACE gene was identified using the Polymerase Chain Reaction (PCR) technique. To amplify the polymorphic region located in intron 16 of the ACE gene, primers with the following sequences were used: 5′-CTGGAGACCACTCCCATC CTTTCT-3′, 5′-TCGAGACCATCCCGGCTAAAAC-3′, and 5′-GATGTGGGCATCACATTCGTCA-3′(27) Amplifications were conducted in a total volume of 25 μl under the following conditions: 2.5 mM of 10x reaction buffer (Invitrogen), 1.5 mM MgCl2 (Invitrogen), 1.25 mM dNTPs (Invitrogen), 2.5 μM of each primer (Invitrogen), 1 U of Taq polymerase (Invitrogen), 2 μl of genomic DNA, and ultra-pure water. The PCR was initiated with 10 minutes of denaturation at 94°C, followed by 35 cycles as follows: 94°C for 1 minute, 67°C (primer annealing temperature) for 1 minute, and 72°C for 1 minute. The reaction concluded with an extension at 72°C for 5 minutes. The PCR product (fragments of 479 and 277 bp for the I allele and 199 bp for the D allele) was checked on a 3% agarose gel stained with ethidium bromide and visualised under ultraviolet light.

c) Statistical Analyses

Allelic and genotypic frequencies of the ACE I/D polymorphism were estimated by direct counting. Genetic and genotypic differentiation tests were performed using the Genepop software. All other analyses described below were conducted using JASP software (version 0.19.1). The chi-square test was used to assess whether the groups were in Hardy-Weinberg equilibrium (HWE) and to evaluate associations between Hypertension and sociodemographic variables (sex, education level, self-reported race/ethnicity, smoking, alcohol consumption, self-reported family history ofHypertension, self-rated health status, and self-reported kidney disease and/or diabetes), as well as with the ACE I/D polymorphism. For association analyses between Hypertension and anthropometric variables (BMI, waist circumference, and waist-to-height ratio), the t-test was applied. For parameters such as waist-to-hip ratio, age, triglyceride levels, blood glucose, cholesterol, and HDL, the Mann-Whitney U test was used. A p-value < 0.05 was considered statistically significant for all analyses.

III. Resultados

The sociodemographic data of the studied population are presented in *Table 1*. We found an association between hypertention andlower education level, no-whiteethnicity, self-reported family history Hypertension, a poor self-assessment of health and self-reported kidney disease and/or diabetes.

Table 1: Sociodemographic Characteristics of the Study Population

Characteristics	N	HT	NT	X^2	p
Gender (F/M)	183	68/27	56/32	1,319	0,251
Education (1/2/3)	182	66/21/07	37/42/09	15,234	**<0,001**
Smoking (N/Y)	183	65/30	57/31	0,272	0,601
Alcohol consumption (N/Y)	183	62/33	54/34	0,299	0,584
self-declared ethnicity (W/N-W)	182	15/79	30/58	8,030	**0,005**
Reports Family History of Hypertension (+ / -)	183	88/07	69/19	7,581	**0,006**
self-reported kidney disease and/or diabetes (+ / -)	183	73/22	82/06	9,411	**0,002**
Self-assessment of health (4/5)	183	27/68	51/37	16,293	**<0,001**

HT = hipertensive, NT = normotensive, F = female, M = male, 1 = up to elementar school, 2 = until high school, 3 = higher education, N = smokes or has smoked / no drink, Y = smokes / drink, W = white, N-W = no-white, + = yes, - = no, 4 = good to very good, 5 = regular to very bad.

Biological parameters were also evaluated. The analyses of the anthropometric data showed that, on average, hypertensive individuals exhibited higher BMI, WHtR, and WC values (among women) compared to normotensive individuals (Table 2). It was also observed that age, blood glucose levels, and WHR (among men) tended to be higher in the hypertensive group (Fig. 1).

Table 2: Analysis of Anthropometric Parameters of Study Groups

	Mean ± SD	t	*p*	*CI (95%)*
BMI				
Hipertensive (n=95)	28,751 ± 4,656	3,679	**< 0,001**	1,103 – 3,657
Normotensive (n=88)	26,371 ± 4,045			
WHtR				
Hipertensive (n=95)	0,598 ± 0,080	3,683	**< 0,001**	0,019 – 0,062
Normotensive (n=88)	0,558 ± 0,066			
WC - Women				
Hipertensive (n=68)	97,125 ± 10,212	3,229	**0,002**	2,695 – 11,233
Normotensive (n=56)	90,161 ± 13,208			
WC - Men				
Hipertensive (n=27)	98,852 ± 12,287	0,972	0,335	- 3,323 – 9,590
Normotensive (n=32)	95,719 ± 12,382			

Significant difference between both groups, p<0,05. BMI; Body Mass Index, WHtR; Waist-to-height Ratio, WC; waist circunference.

A total of 183 PCR reactions were conducted, including 95 cases and 88 controls (*Fig 2.*). The Hardy-Weinberg equilibrium was assessed, which indicated that the distribution of genotypes in the case and control groups did not differ from what was expected, suggesting that both populations are in equilibrium. As análises também indicaram que não há diferenciação gênica e genotípica entre os grupos, indicando que as os grupos são homogêneos.

Finally, we found no association between the ACE I/D polymorphism and Hypertensionin our study population, nor was there a significant difference in the distribution of genotypes based on the presence or absence of Hypertension. Resultados semelhantes também foram observados considerando os modelos de análise dominante e recessivo. The D allele was the most frequent in our study population, both in normotensives and hypertensives, with the ID genotype also being the most prevalent in both groups, while the I allele and II genotype were the least frequent within the population (*Table 3*).

Table 3: Allelic and Genotypic Frequencies of ACE I/D Polymorphism

ACE I/D	HT (n=95)	NT (n=88)	X^2	p
Genotypes				
II	16	17	0,496	0,708
ID	50	48		
DD	29	23		
Alleles				
I	82	82	1,221	0,543
D	108	94		
Dominant Model				
II	16	17	0,189	0,663
ID + DD	79	71		
Recessive Model				
II + ID	66	65	0,433	0,511
DD	29	23		

Significant difference between both groups, p<0,05

IV. Discussion

The development of cardiovascular complications driven by Hypertensionis responsible for a significant number of deaths in Brazil and worldwide (3,4). As a multifactorial disease, both genetic and environmental factors interact in promoting or protecting against the condition (28). Early identification of genetic factors that predispose an individual to Hypertension may be a key strategy in medical counseling and in promoting lifestyle modifications, such as dietary and behavioral changes, aimed at counterbalancing the altered genetic factor.

In our study, we identified several risk factors that differentially affected normotensive and hypertensive individuals. We found that Hypertension was more prevalent among self-identified Black individuals in our study population. Our findings align with existing literature regarding ethnicity and its relationship with Hypertension (29). It is well established that mortality from cardiovascular diseases is significantly higher in African Americans (30), who, by age 45, exhibit average blood pressure levels comparable to those of 55-year-olds living in the same region, supporting the notion that early primary Hypertension predominantly affects this population (29). This group also shows an increase in blood pressure that positively correlates with salt sensitivity, which may help explain the relationship between ethnicity and blood pressure (31). Other aspects related to Hypertension, such as body weight, appear to be elevated among African American patients (32).

Age is also an extremely relevant factor when discussing Hypertension, as there is a linear relationship between increasing age and elevated blood pressure after the age of 40, which tends to reach a plateau in the later stages of life (5,33,34). This information supports our observations that the hypertensive patient group is older than the normotensive group.

Indicators of obesity, such as BMI and waist-to-hip ratio, are included in the list of classic factors contributing to increased blood pressure (4). It is well established that obesity is associated with the activation of the RAAS through the exaggerated stimulation of renin production by the kidneys in response to signals from the sympathetic nervous system (SNS) observed in overweight patients (35). Abdominal adipocytes also exhibit an aberrant capacity to produce angiotensinogen in these patients (36). Renin and angiotensinogen are precursors and intermediates, respectively, of angiotens in II, a pro-inflammatory component that induces increased blood pressure (37,38). Our data align with the literature and support the concept that age, weight, and ethnicity are key risk factors for blood pressure. We conducted an association analysis between the polymorphism and various anthropometric characteristics in our population; however, no differences were observed (data not shown).

It is estimated that genetics accounts for up to 30% of the variation in blood pressure; thus, the influence of a family history of Hypertensionon the development of the disease is clear (39). In our study, we identified a higher prevalence of Hypertensionin individuals with a positive family history ofHypertension, which is associated with the sharing of a series of genetic variants that may influence blood pressure regulation. Interestingly, it has been demonstrated that the genetic contribution to blood pressure similarity in twins can be as high as 65%. Furthermore, genetic factors are associated with stress, a component that also affects blood pressure (2).

In our study, the D allele and the ID genotype of the ACE gene were found at high frequencies in both groups, consistent with observations in most Western populations where such studies have been conducted (40,41). A strong association was observed between Hypertensionand the combination of the *ACE I/D* polymorphisms and the G8790A polymorphism of the

ACE2 gene, which was not detected when the polymorphisms were assessed individually (40). This finding reinforces the importance of combined analysis of multiple polymorphisms, given that Hypertensionis a multifactorial disease with a polygenic nature (11).

Few studies have aimed to assess the allelic and genotypic frequencies of the *ACE I/D* polymorphism in Brazilian populations (41), and this number is even smaller when considering populations from the state of Bahia (42), which are highly admixed and therefore exhibit a broad genetic diversity that remains largely underexplored in the context of Hypertensiongenetics. This underscores the importance of conducting further studies like this one to fully understand the role of genetic polymorphisms in the development or predisposition to Hypertensionand other diseases, while taking into account the genetic diversity of the Brazilian population (43). It is essential to emphasise that different populations are exposed to distinct environmental conditions and possess unique genetic backgrounds, which helps to explain the varying allele frequencies and the presence or absence of an association between the ACE I/D polymorphism and Hypertension. Similar to our findings and those of other researchers in Brazilian populations, no such association has been observed, mirroring results in specific populations from other continents (21,44), whereas studies in European (45) and some Asian (24,46) populations have reported a significant association. A study conducted with obese children in São Paulo State also found an association between the D allele and Hypertension (47).

V. Conclusion

The absence of an association between the polymorphism and Hypertensiondoes not refute the hypothesis that it may exert an influence on the development ofHypertension. Here, we evaluated only one polymorphism, and it is essential to emphasise that the combination of different polymorphisms, as well as the interplay between genotype, phenotype, and behaviour, may reveal that the cumulative effect of minor influences from various factors, often overlooked when considered in isolation, can robustly contribute to the development of the pathology. Therefore, a comprehensive evaluation of the ACE I/D polymorphism in conjunction with other polymorphisms and non-genetic risk factors is warranted.

Abbreviations

BMI - Body mass index
HDL - High-density lipoprotein
LDL - Low-density lipoprotein
ACE2 - Angiotensin converting enzyme – 2
I/D - Insercion/delection
BP – Blood pressure
SBP - Systolic blood pressure
DBP - Diastolic blood pressure
CVD - Cardiovascular disease
RAAS - Renin-angiotensin-aldosterone system
GWAS - Genome-wide association study
TGF-β - Transforming growth factor beta
SMAD - Suppressor of mothers against decapentaplegic
AF - Allele frequencies
LACEM - Municipal Laboratory of Vitória da Conquista
ICF - Informed Consent Form
EDTA - Ethylenediamine tetraacetic acid
UESB -State University of Southwestern Bahia
DNA - Deoxyribonucleic acid
dNTP - Deoxynucleotide triphosphates
HWE - Hardy-Weinberg equilibrium
WHtR - Waist-to-height Ratio
WC - Waist circunference
SNS - Sympathetic nervous system

Ethics Committee Approval

We declare that this study was approved by the Ethics Committee of UESB (Opinion No. 2,627,076) and the Public Health Foundation Isaú Matos, where LACEM is located (Opinion No. 2,792,660)

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

All patients and healthy donors included in the study agreed to participate and signed the informed consent form.

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Author Contributions

SO: Conceptualization, Investigation, Methodology, Writing – original draft.
MB: Investigation.
PBC: Investigation.
PSZC: Investigation.
DA: Funding acquisition.

WA: Funding acquisition.
MO: Funding acquisition and Writing – original draft.
MT: Methodology and Funding acquisition.
SS: Conceptualization and Funding acquisition.
PL: Conceptualization, Funding acquisition, Supervision, and Writing – original draft

Figure Legends:

Generative AI Statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

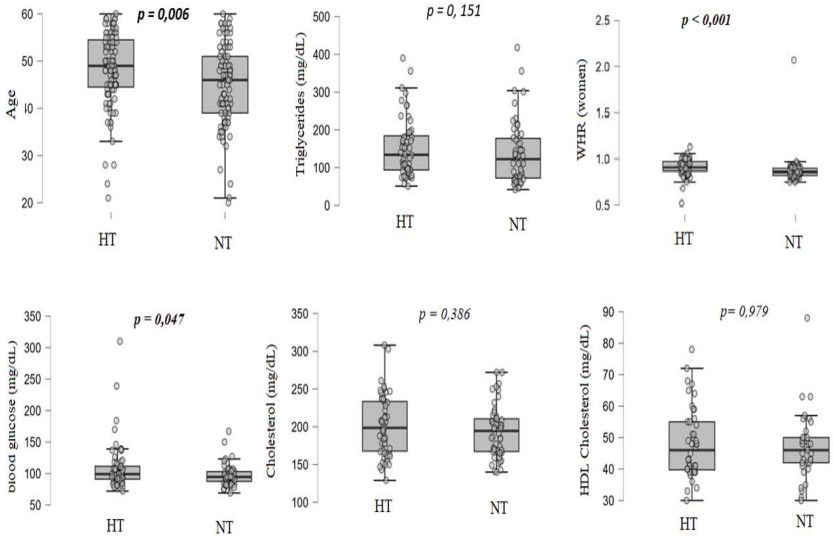

Figure 1: Analysis of anthropometric and clinical of study groups. Significant difference between both groups, p<0,05. BMI; Body Mass Index, WHR; Waist-to-hip Ratio

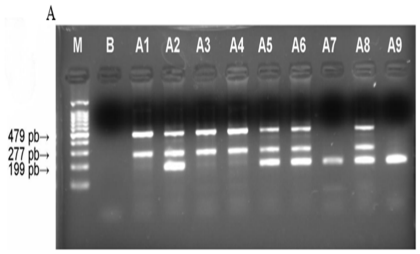

Figure 2: Allelic and genotypic frequencies of I/D ACE in the population: (A) Photograph of the agarose gel after the separation, by electrophoresis, of the fragments generated from the PCR reaction; (B-E) frequency of alleles I and D in normotensive and hypertensive individuals; (F-I) frequency of genotypes DD, ID, and II in normotensive and hypertensive individuals

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