Interplay between glycemia and the genetics of *eNOS* and *ACE* genes for the susceptibility to the onset and development of hypertension on the Portuguese population

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Introduction

Arterial hypertension is a very prevalent cardiovascular risk factor in Portugal (1). This pathology is a multifactorial condition of anthropometric, physiologic, metabolic, genetic and environmental nature (2). Insulin resistance and hypertension are components of the metabolic syndrome and often coexist. Increased blood glucose levels associated with hypertension significantly increase the risk of cardiovascular disease (3).

The aim of this study is to evaluate the contribution of anthropometric, physiological and genetic factors (*eNOS* and *ACE* genes) to the development of hypertension in a Portuguese population.

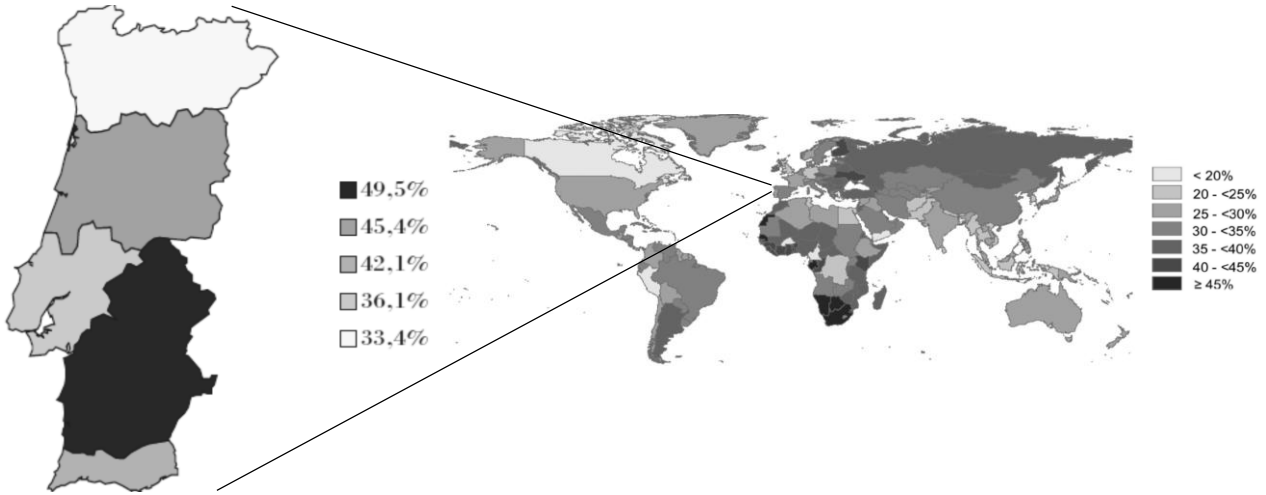

Figure 1 - Prevalence of Hypertension [adapted from (4,5)].

Material and methods

A case-control study was conducted in a sample of 377 individuals, 243 hypertensives and 134 normotensives. The polymorphic analyses of intron 4 VNTR in the *eNOS* gene and the insertion/deletion (I/D) in *ACE* gene were performed by polymerase chain reaction (PCR). Anthropometric (body mass index - BMI) and biochemical parameters (uricemia, cholesterol, triglycerides, glycemia, glycosylated haemoglobin - HbA1c and homeostasis model assessment - HOMA) were also studied. All statistical analyzes were performed using the SPSS software, version 24.0, with the level of statistical significance set at $p < 0.05$.

Results

The following statistically significant results were observed:

- High BMI values, high glycemia levels and high HOMA were associated with hypertension (p=0.004, p=0.0036 and p=0.016, respectively) (Table 1).

Table 1 – Comparison of BMI and biochemical parameters between Hypertensive and Normotensive individuals

Parameter	Normotensive	Hypertensive	p-value
BMI (kg/m²)	28.34; 17.26 - 44.49 (134)	31.41; 21.46 - 44.60 (90)	0.004
Glycemia (mg/dl)	82.50; 60 - 178 (112)	91.00; 63.00 - 215.00 (85)	0.036
HOMA	1.73; 0.24 - 7.95 (100)	1.97; 0.39 – 15.98 (82)	0.016

*Mann-Whitney test - the statistical measures considered are: median; min-max (n)

- An association was found between the presence of the 4a allele of the *eNOS* gene and hypertension (OR = 2.227; CI (95%) = 1.391 – 3.563; p = 0.001) (Table 2), even after adjusting for age (OR = 2.297; CI (95%) = 1.206 – 4.376, p = 0.011).
- The presence of the 4a allele of the *eNOS* gene in hypertensive individuals was associated with higher HbA1c values (p = 0.031) (Table 3).
- The presence of the D allele of the *ACE* gene in hypertensive individuals was associated with higher blood glucose levels (p = 0.017) and high HOMA (p = 0 0.043) (Table 4).

Table 2 - Comparison of the genotype distribution of the 4 a/b (*eNOS*) polymorphism between the Normotensive and Hypertensive groups

Genotype	Normotensive	Hypertensive	p-value*	OR (95% CI)
4a/4a or 4a/b	34 (26.4)	102 (44.3)	0.001	2.227 (1.391 – 3.563)
4 b/b	95 (73.6)	128 (55.7)		

*Pearson's χ^2 test, n (%)

Table 3 – Comparison of HbA1c (%) between the presence and the absence of the 4a allele among hypertensive individuals

Parameter	Presence of allele 4a	Absence of allele 4a	p-value*
HbA1c (%)	6.1; 3.8-8.6 (12)	4.5; 3.1-9.2 (20)	0.031

*Mann-Whitney test - the statistical measures considered are: median; min-max (n)

Table 4 - Comparison of glycemia (mg/dl) between the presence and the absence of the D allele among hypertensive individuals

Parameter	Presence of allele D	Absence of allele D	p-value*
Glycemia (mg/dl)	90; 63-208 (49)	77; 74-103 (7)	0.017
HOMA	1.95; 0.39-12.42 (47)	1.08; 0.69-2.39 (7)	0.043

*Mann-Whitney test - the statistical measures considered are: median; min-max (n)

Conclusion

Our study reinforces the importance of the clinical control of the anthropomorphic, physiological, metabolic and genetic parameters in the onset and development of hypertension. These parameters should not be analyzed independently, but instead, as interacting factors that may lead to different phenotypes, depending on their background. We believe that a combinatory clinical approach including the traditional anthropomorphic and physiological parameters together with genetic studies from genes with known physiological interplay, such as *eNOS* and *ACE* can be more elucidative in establishing a susceptibility profile on multifactorial conditions as hypertension.

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Interest conflict

The authors declare that they have no conflict of interest.

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