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GENETIC AND CARDIO-METABOLIC RISK FACTORS OF ESSENTIAL HYPERTENSION: A STUDY IN A CENTRAL ARGENTINEAN POPULATION

FACTORES DE RIESGO GENÉTICOS Y CARDIOMETABÓLICOS EN LA HIPERTENSIÓN ESENCIAL: ESTUDIO EN UNA POBLACIÓN DEL CENTRO ARGENTINO

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ABSTRACT

Essential hypertension is a multifactorial disease influenced by both genetic and cardiometabolic factors, with variable prevalence and risk profiles among different populations. Polymorphisms in genes of the renin-angiotensin-aldosterone system (RAAS) and endothelial function have been widely studied for their role in blood pressure regulation and the development of cardiovascular complications. The aim of this study was to investigate the ACE I/D, AT1R A1166C, AGT M235T and eNOS Glu298Asp polymorphisms, together with traditional risk factors, in relation to essential hypertension in a population from San Luis, Argentina. A total of 208 hypertensive patients and 150 normotensive subjects were included. Demographic, anthropometric and biochemical data were collected and analyzed. Genotypic and allelic frequencies of the polymorphisms were determined by PCR-RFLP. Significant differences were found in body mass index (BMI), age, fasting glucose, total cholesterol, HDL-C, triglycerides, and dyslipidemia, with higher levels in hypertensive subjects. Advancing age, overweight, elevated fasting glucose and triglyceride levels were identified as metabolic risk factors. Genotypic and allelic frequencies of the studied polymorphisms did not differ significantly between hypertensive and control groups. No association was found between the studied polymorphisms and hypertension in our population. Age, overweight, elevated fasting glucose, and elevated triglycerides were identified as significant predictors of hypertension in this population.

Key words: endothelial nitric oxide synthase, genetic polymorphisms, hypertension, renin–angiotensin-aldosterone system, risk factors

RESUMEN

La hipertensión arterial esencial es una enfermedad multifactorial influenciada por factores genéticos y cardiometabolicos, con una prevalencia y perfiles de riesgo variables entre diferentes poblaciones. Los polimorfismos en genes del sistema renina-angiotensina-aldosterona (RAAS) y de la función endotelial han sido ampliamente estudiados por su rol en la regulación de la presión arterial y en el desarrollo de complicaciones cardiovasculares. El objetivo de este estudio fue investigar los polimorfismos ACE I/D, AT1R A1166C, AGT M235T y eNOS Glu298Asp, junto con los factores de riesgo tradicionales de hipertensión arterial esencial, en una población de San Luis, Argentina. Se incluyeron 208 pacientes hipertensos y 150 sujetos normotensos. Se recolectaron y analizaron datos demográficos, antropométricos y bioquímicos. Las frecuencias genotípicas y alélicas de los polimorfismos se determinaron mediante la técnica de PCR-RFLP. Se observaron diferencias significativas en índice de masa corporal (IMC), edad, glucosa en ayunas, colesterol total, HDL-C, triglicéridos y dislipidemia, con valores más elevados en los sujetos hipertensos. La edad avanzada, el sobrepeso, la glucemia en ayunas elevada y los niveles aumentados de triglicéridos fueron identificados como factores de riesgo metabólicos. Las frecuencias genotípicas y alélicas de los polimorfismos estudiados no mostraron diferencias significativas entre los grupos hipertensos y control. No se encontró asociación entre los polimorfismos analizados y la hipertensión en esta población. La edad, el sobrepeso, la glucemia en ayunas elevada y los triglicéridos aumentados se identificaron como predictores significativos de hipertensión arterial esencial en esta muestra.

Palabras clave: factores de riesgo, hipertensión, óxido nítrico sintasa endotelial, polimorfismos genéticos, sistema renina–angiotensina-aldosterona

INTRODUCTION

Arterial hypertension (HT) is a common chronic condition that affects approximately one in three adults worldwide, as reported by the World Health Organization (WHO). Nearly half of adults with HT are unaware of their condition (NCD Risk Factor Collaboration, 2021). This non-communicable disease is the primary risk factor for cardiovascular disease and a major cause of premature death worldwide.

While age and genetic factors contribute to HT occurrence, other modifiable factors such as high salt intake, physical inactivity, and harmful habits (smoking and alcohol consumption) also increase HT risk (Mills *et al.*, 2020; Zhou *et al.*, 2021).

Globally, HT prevalence doubled between 1999 and 2019, with a higher incidence in low- and middle-income countries. In the Americas, HT prevalence is around 35%, though it varies widely by region due to genetic and environmental differences (Delucchi *et al.*, 2017; Zhou *et al.*, 2021; Ordunez *et al.*, 2022).

The RENATA 2 study, which surveyed 5,931 adults in 25 cities across Argentina, found a hypertension prevalence of 36.3% (Delucchi *et al.*, 2017). More recent data showed a combined HT prevalence of 46.6%, whereas only 34.7% of individuals self-reported HT. In San Luis province, prevalence reached 40.9%, the highest in its region (Lamelas *et al.*, 2019; Ministerio de Salud de la Nación, 2019; Giunta *et al.*, 2023).

HT is considered a complex trait, with disease predisposition resulting from interactions among multiple genes (Lind and Chiu, 2013; Horani *et al.*, 2015). In 90% of patients, HT etiology is unknown, and genetic factors are significant, with heritability estimated at 30–50% (Agarwal *et al.*, 2005; Padmanabhan and Dominiczak, 2021).

The renin–angiotensin system (RAAS) plays a key role in cardiovascular homeostasis and HT pathogenesis. Extensive evidence links single nucleotide polymorphisms (SNPs) in RAAS genes with HT (Agarwal *et al.*, 2005; Singh *et al.*, 2010). These polymorphisms can alter gene function and predispose individuals to HT. Among the most studied are the angiotensin-converting enzyme (ACE) insertion/deletion (I/D), angiotensinogen (AGT) M235T, and angiotensin II type 1 receptor (AT1R) A1166C polymorphisms. Although RAAS genetic variants have been widely studied, results across different populations are inconsistent and sometimes contradictory (Agachan *et al.*, 2003; Companioni Nápoles *et al.*, 2007; Bautista *et al.*, 2008; Bonfim-Silva *et al.*, 2016; Isordia-Salas *et al.*, 2023; Al-Eitan *et al.*, 2024).

The vascular endothelium is structurally simple but functionally complex, regulating blood flow and vascular homeostasis. In HT, endothelial dysfunction promotes pathological vascular changes. Evidence associates eNOS polymorphisms with HT, coronary disease, stroke, and preeclampsia (Moe *et al.*, 2006; Oliveira-Paula *et al.*, 2017; Gallo *et al.*, 2022). The clinically relevant eNOS variants include the Glu298Asp (G894T) polymorphism, the T-186C polymorphism and the 27 bp VNTR (variable number of tandem repeats) in intron 4 (Oliveira-Paula *et al.*, 2017). Understanding genetic and molecular mechanisms in HT pathophysiology is essential to improve prevention, diagnosis, and treatment strategies (Franks, 2009).

Genetic variability among human populations significantly influences disease pathogenesis, posing challenges for the development of tailored therapies. The aim of the present study is to investigate the association of the ACE I/D, AT1R A1166C, AGT M235T and eNOS Glu298Asp polymorphisms with essential hypertension and risk factors, in a population from the central region of Argentina.

The research is justified by the existing knowledge gap regarding HT genetics in our region. We seek to determine whether these polymorphisms are more prevalent in hypertensive patients, with the intent to draw conclusions applicable to the general population, provide data, and unify diagnostic criteria.

MATERIALS AND METHODS

Study design

A case-control study was conducted at Hospital *Juan Gregorio Vivas* in San Luis, Argentina. The sample comprised 358 individuals: 208 hypertensive patients (HT group) and 150 normotensive subjects (control group).

The study was approved by the Institutional Ethics Committee of the Faculty, and adhered to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Demographic and clinical data were collected from both hypertensive patients and controls subjects.

Inclusion criteria: hypertensive patients were aged 18–75 years old with systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg. All patients had a diagnosis of essential hypertension and were receiving antihypertensive treatment. The control group comprised healthy individuals aged 18–75 years with no history of hypertension and normal physical and mental health.

Exclusion criteria: individuals outside the specified age range were excluded. Pregnant women and patients with secondary HT were also excluded.

Blood pressure measurement

Blood pressure was measured using a validated arm cuff sphygmomanometer. Three consecutive readings

were averaged. Hypertension was defined as a mean SBP ≥140 mmHg or DBP ≥90 mmHg, measured on three separate occasions, or as a reported diagnosis. The diagnosis of hypertension was based on the Seventh Joint National Committee criteria (Chobanian *et al.*, 2003) and in accordance with the Argentine Consensus of Hypertension 2025. Although threshold values for defining hypertension have been revised in recent years, it is recommended to reserve the definition of hypertension for office-measured SBP values ≥140 mmHg and/or DBP ≥90 mmHg, as from these levels onward the clinical benefit of hypertension treatment is undeniable (Aquieri *et al.*, 2025).

Body mass index (BMI)

Height and weight were measured to calculate BMI (kg/m²) according to the World Health Organization guidelines. Patients were categorized as underweight (<18.5 kg/m²), normal weight (18.5 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), obese I (30 to 34.9 kg/m²), obese II (35 to 39.9 kg/m²), and obese III (≥40.0 kg/m²).

Biochemical parameters

The biochemical parameters determined were fasting plasma glucose (Glu) and lipid profile components including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). All measurements were performed using standardized enzymatic methods.

Genetic analysis

Genomic DNA was extracted from leukocytes using DNAzol™ (Invitrogen), quantified by spectrophotometry (Epoch Biotek), and stored at -20 °C. Polymorphisms were genotyped by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) on a Smart Gradient PCR T960C thermocycler (Hangzhou Jingle Sci Int, China). Amplicons or digested fragments were separated on 2–3% agarose gels with GelRed™ and visualized under UV.

Amplification of the Insertion/Deletion (I/D) polymorphism in the ACE gene (rs4646994)

Genotyping for I/D polymorphism was performed using the PCR protocol (Rigat *et al.*, 1992); with the following primers: forward (*fw*): 5′-CTGGAGACCACTCCCATCCTTTCT-3′ and reverse (*rv*): 5′-GATGTGGCCATCACATTCGTCAGAT-3′. The cycling conditions were as follows: initial denaturation at 94°C for 1 min, followed by 30 cycles of annealing at 58°C for 1 min, extension at 72°C for 2 min, denaturation at 94°C for 1 min, and final extension at 72°C for 10 min. PCR amplified products were I allele: 490bp and D allele: 190 bp.

Samples identified as DD homozygotes on the gel required a second PCR due to preferential amplification of the D allele and inefficient amplification of the I allele. Primers used were *fw:* 5′-TGGGACCACAGCGCCCGCCACTAC-3′ and *rv:* 5′-TCGCCAGCCCTCCCATGCCCATAA-3′ (Lindpaintner *et al.*, 1995). The thermal conditions were: initial denaturation at 94 °C for 5 min; 30 cycles of denaturation at 94 °C for 1 min, annealing at 55 °C for 1 min, and extension at 72 °C for 1.5 min; followed by a final extension at 72 °C for 10 min. Only the I allele produced a 335 bp fragment; DD homozygote samples showed no amplification.

Amplification of the A1166C polymorphism in the AT1 receptor gene (rs5186)

The A1166C polymorphism was detected by PCR-RFLP as described previously (Frishberg *et al.*, 1998). The following primers were used: *fw* 5'-AATGCTTGTAGCCAAAGTCACCT-3' and *rv* 5'-GGCTTTGCTTTGTCTTGTTG-3'. The cycling conditions were: initial denaturation at 94 °C for 2 min; 35 cycles of denaturation at 94 °C for 1 min, annealing at 60 °C for 1 min, and extension at 72 °C for 2 min; followed by a final extension at 72 °C for 10 min. The PCR products of 850 bp were digested with the restriction endonuclease *DdeI* (Promega, USA) overnight at 37°C. The enzyme generated two fragments (600 and 250 bp) and recognizes an additional site at nucleotide 1166 in the C allele, that cuts the 250 bp fragment into two smaller bands. Digested products were: A allele-600 and 250 bp; C allele-600, 140 and 110 bp.

Amplification of the M235T polymorphism in the AGT gene (rs699)

The M235T polymorphism was detected by PCR-RFLP (Yuan *et al.*, 2009). The following primers were used: *fw*5'-CCGTTTGTGCAGGGCCTGGCTCTCT-3' and *rv*5'-CAGGGTGCTGTCCACACTGGACCCC-3'. The thermal conditions were an initial denaturation at 94°C for 1 min, followed by 30 cycles of denaturation at 94°C for 30 s, annealing at 65 °C for 30 s, and extension at 72 °C for 30 s, with a final extension at 72 °C for 5 min. The PCR products of 162 bp were digested with the restriction endonuclease *Tth111I* (Thermo Scientific™) for 6 h at 37°C. The M allele remained uncut (162bp) and the T allele produced fragments of 141 and 21 bp.

Amplification of the Glu298Asp polymorphism in the eNOS gene (rs1799983)

Determination of Glu298Asp polymorphism was performed by PCR–RFLP as described by Pereira *et al.* (2006). The following primers were using:

fw 5′-AAGGCAGGAGACAGTGGATGGA-3′ and *rv* 5′-CCCAGTCAATCCCTTTGGTGCTCA-3′. The cycling conditions were: initial denaturation at 94 °C for 3 min; 35 cycles of 94 °C for 1 min, 63 °C for 1 min and 72 °C for 30 s; and a final extension at 72 °C for 5 min. The resulting 248 bp product was digested overnight at 37 °C with Mbo I (Promega, USA). The G allele remained uncut (248 bp), whereas the T allele produced fragments of 158 bp and 90 bp.

Statistical Analysis

All data were expressed as means ± standard deviation (SD), frequency, or percentage as appropriate. Distribution of genotype and allele frequencies of ACE I/D, AT1R A1166C, AGT M235T and eNOS Glu298Asp polymorphisms among hypertensive and normotensive patients were assessed by the Chi square ($\chi 2$) test. Intergroup comparisons were made using Student's t-test. For continuous variables with normal distribution, ANOVA was used to evaluate differences among groups, followed by Tukey post-test. Odds ratio (OR) was used as a measure of association. All data were analyzed using SPSS software version 27.0 (SPSS Inc., Chicago, IL). A p-value <0.05 was considered statistically significant.

RESULTS

A total of 358 subjects (208 hypertensive patients and 150 controls) were examined in the present case-control study. The demographic, anthropometric, and biochemical characteristics of all the participants are described in Table 1. Among the hypertensive group (HT), 52.4% were male and 47.6% were female. The mean BMI values were significantly higher in HT than in controls (p<0.0001), exceeding the normal range in both groups. Hypertensive and normotensive subjects showed significant differences in age, fasting glucose, total cholesterol, HDL-C, and triglycerides, which were higher in the HT group. In addition, dyslipidemia values were significantly higher in the HT group than in the control group (p<0.01).

The results of the OR analysis for traditional hypertension risk factors are shown in Table 2. The main risk factors for hypertension were overweight/obesity (BMI≥25kg/m²; OR9.44; 95%CI4.81–18.50; p<0.001) and age ≥50 years (p<0.001). Fasting glucose (≥100mg/dl) and elevated TG (≥150mg/dl) were also associated with an increased risk of hypertension.

The distribution of RAAS polymorphisms was investigated in order to find possible associations with the development of HT. Table 3 details the distribution of genotypes and allelic frequencies of RAAS polymorphisms. No significant genotypic and allelic differences were found between hypertensive patients and control subjects.

Genotypic and allelic frequencies of eNOS Glu298Asp polymorphism are also shown in Table 3. No significant genotypic or allelic differences were found between the HT and control groups. The ORs for all polymorphisms were non-significant.

The analyses of BMI, glucose, and lipid profiles according to the genotypes of RAAS polymorphisms in hypertensive and control subjects, stratified by sex, are summarized in Table 4.

Regarding the ACE I/D polymorphism, hypertensive individuals exhibited significantly higher BMI and triglyceride levels across genotypes. The ID genotype was associated with elevated glucose levels in hypertensive subjects, while the DD genotype was linked to lower HDL-C, particularly among women.

Table 1. Baseline characteristics and clinical data in hypertensive (HT) and normotensive (control) patients

	HT (n=208)	Control (150)	*p* value
Sex (% Male/Female)	52.4 / 47.6	31.3 / 68.7	—
Age (years)	54.3 ± 9.6	39.75 ± 13.56	<0.001
BMI (kg/m²)	31.3 ± 5.9	26.8 ± 4.7	<0.001
SBP (mm Hg)	153.2 ± 16.3	117.9 ± 11.7	<0.001
DBP (mm Hg)	90.5 ± 10.2	71.1 ± 9.7	<0.001
Glucose (mg/dl)	91.3 ± 14.3	84.7 ± 11.6	<0.001
Total cholesterol (mg/dl)	199.6 ± 36.3	189.1 ± 40.3	<0.02
HDL-C (mg/dl)	48.3 ± 14.5	51.7 ± 11.8	<0.04
LDL-C (mg/dl)	119.9 ± 34.5	115.7 ± 38.7	NS
Triglycerides (mg/dl)	179.4 ± 96.8	126.1 ± 60.5	<0.001
Dyslipidemia (%)	59.13	44.91	<0.01

Presentation of values: mean ± standard deviation (SD). BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol. NS: non significant (p > 0.05).

Table 2. Odds ratio (OR) analysis for classic risk factors for hypertension

Risk factor	OR (95% CI)	*p* value
Age ≥50 years	7.45 (4.75 – 11.68)	<0.001
BMI ≥25 kg/m²	9.44 (4.81 – 18.50)	<0.001
Glucose ≥100 mg/dl	3.77 (1.40 – 10.11)	0.005
Total cholesterol ≥200 mg/dl	1.20 (0.73 – 1.97)	NS
LDL-C ≥130 mg/dl	1.15 (0.68 – 1.93)	NS
Triglycerides ≥150 mg/dl	2.76 (1.61 – 4.74)	<0.001

OR: odds ratio, CI: confidence interval. BMI: body mass index, LDL-C: low-density lipoprotein cholesterol. NS: non significant (p > 0.05).

Table 3. Distribution of genotypic and allelic frequencies of the ACE I/D, AT1R A1166C, AGT M235T, and eNOS Glu298Asp polymorphisms in the hypertensive group (HT) and normotensive group (Control)

Polymorphism	Genotype/ allele	HT (n=208)		Control (n=150)		*p* value	OR (95% CI)		*p* value
		n	%	n	%				
AT1R A1166C	AA	110	52.88	81	54		AA vs. AC+CC	0.95 (0.62–1.45)	NS
	AC	78	37.50	55	36.6	NS	AC vs. AA+CC	1.03 (0.67–1.6)	NS
	CC	20	9.62	14	9.3		CC vs. AA+AC	1.03 (0.5–2.11)	NS
	Allele A	298	71.63	217	72.3	NS	C vs. A	0.96 (0.74–1.44)	NS
	Allele C	118	28.36	83	27.6				
ACE I/D	II	57	27.40	38	25.3		II vs. ID+DD	1.11 (0.69–1.79)	NS
	ID	120	57.70	79	52.6	NS	ID vs. II+DD	1.22 (0.8–1.86)	NS
	DD	31	14.9	33	22		DD vs. II+ID	0.62 (0.36–1.06)	NS
	Allele I	234	56.3	155	51.6	NS	D vs. I	0.83 (0.60–1.15)	NS
	Allele D	182	43.8	145	48.4				
AGT M235T	MM	31	14.90	26	17.3		MM vs. MT+TT	0.83 (0.47–1.47)	NS
	MT	100	48.08	79	52.6	NS	MT vs. MM+TT	0.83 (0.54–1.26)	NS
	TT	77	37.02	45	30		TT vs. MM+MT	1.37 (0.87–2.14)	NS
	Allele M	162	38.94	131	43.6	NS	T vs. M	0.82 (0.60–1.11)	NS
	Allele T	254	61.06	169	56.4				
eNOS Glu298Asp	GG	106	50.96	78	52		GG vs. GT+TT	0.95 (0.63–1.46)	NS
	GT	85	40.86	61	40.6	NS	GT vs. GG+TT	1.00 (0.65–1.54)	NS
	TT	17	8.18	11	7.3		TT vs. GG+GT	1.12 (0.51–2.47)	NS
	Allele G	297	71.39	217	72.3	NS	G vs. T	0.95 (0.68–1.32)	NS
	Allele T	119	28.61	83	27.7				

OR: odds ratio, CI: confidence interval. NS: non significant ($p > 0.05$).

In the AT1R A1166C polymorphism, the AA and AC genotypes were associated with increased BMI, glucose, and triglyceride levels in hypertensives; additionally, AA carriers showed higher total cholesterol and HDL-C, especially in women.

For the AGT M235T polymorphism, hypertensive individuals with the MM genotype had higher BMI and total cholesterol levels; those with the MT genotype had higher BMI, glucose, total cholesterol, LDL-C, and triglycerides levels; and TT carriers displayed higher BMI, glucose, and triglyceride levels, compared with the control group.

Considering the NOS Glu298Asp polymorphism (Table 4), the GG genotype was significantly associated with most parameters, especially in women. While the TT genotype was linked to higher glucose level.

Since BMI values exceeded the normal range in both study groups (hypertensive and normotensive) the relationship between BMI and the genotypes was evaluated in the whole population (Table 5).

DISCUSSION

HT is a major public health issue in Argentina and globally. We examined demographic, anthropometric, biochemical, and genetic factors in a central Argentine population.

Hypertension is a complex polygenic disease, and identifying the genes involved in its etiology can contribute to a better understanding of the main pathogenic mechanisms, target organ complications, and interactions with environmental factors.

Recent Genome-Wide Association Studies (GWAS) have identified a large number of loci related to HT by examining common genetic variations. However, it is important to note that a major limitation has been the difficulty in linking SNPs to causal gene and function. GWAS identify genetic regions linked to HT but do not pinpoint the exact causal gene or mechanism (Padmanabhan and Dominiczak, 2021).

Although polygenic risk scores have been used to predict hypertension, their utility in the clinical setting remains uncertain (Kauko *et al.*, 2021).

The renin-angiotensin-aldosterone system is one of the most relevant systems in the regulation of blood pressure. Several studies have reported different components of this system as candidates for the genetic basis of essential hypertension (Bautista *et al.*, 2008; Singh *et al.*, 2010; Lind and Chiu, 2013).

In the present study, we investigated the possible association of RAAS genes polymorphisms with HT.

Table 4. Anthropometric and biochemical parameters according to genotypes of the ACE I/D, AT1R A1166C, AGT M235T, and eNOS Glu298Asp polymorphisms in the whole population (hipertensive and normotensive groups)

Anthropometric/ biochemical parameters	Polymorphism	Genotype	Whole population (n=358)			Male (n=157)	Female (n=201)
			HT (n=208)	Control (n=150)	*p* value	*p* value	*p* value
BMI (kg/m²)	ACE I/D	II	30.85 ± 4.79	26.02 ± 4.91	0.001	0.059	0.001
		ID	31.79 ± 5.08	27.59 ± 5.03	0.001	NS	0.001
		DD	31.04 ± 4.86	26.00 ± 3.79	0.001	0.04	0.001
	AT1R A1166C	AA	31.64 ± 4.56	26.47 ± 4.54	0.001	0.005	0.001
		AC	30.77 ± 5.25	26.47 ± 4.25	0.001	0.02	0.001
		CC	32.83 ± 5.80	30.27 ± 6.65	NS	NS	0.07
	AGT M235T	MM	31.01 ± 4.53	26.03 ± 4.83	0.001	NS	0.02
		MT	30.94 ± 4.54	26.68 ± 4.22	0.001	0.04	0.001
		TT	32.29 ± 5.63	27.50 ± 5.54	0.001	NS	0.001
	eNOS Glu298Asp	GG	32.28 ± 5.36	27.13 ± 4.90	0.001	NS	0.001
		GT	30.54 ± 4.26	26.42 ± 4.30	0.001	0.03	0.001
		TT	31.43 ± 4.97	27.03 ± 6.84	NS	NS	NS
Glucose (mg/dl)	ACE I/D	II	89.45 ± 15.98	84.35 ± 8.67	NS	NS	NS
		ID	92.67 ± 13.26	84.55 ± 12.60	0.001	NS	0.001
		DD	89.77 ± 14.78	85.32 ± 12.42	NS	NS	NS
	AT1R A1166C	AA	91.51 ± 14.62	82.54 ± 10.76	0.001	NS	0.002
		AC	91.08 ± 13.40	85.18 ± 10.49	0.02	NS	0.07
		CC	91.44 ± 16.49	95.56 ± 16.19	NS	NS	NS
	AGT M235T	MM	95.44 ± 21.21	81.50 ± 10.80	0.01	NS	NS
		MT	89.76 ± 12.74	86.60 ± 12.60	NS	NS	0.06
		TT	91.67 ± 12.41	83.40 ± 10.41	0.001	NS	0.003
	eNOS Glu298Asp	GG	92.45 ± 13.66	84.21 ± 12.45	0.001	NS	0.004
		GT	89.80 ± 15.50	86.26 ± 10.72	NS	NS	NS
		TT	90.92 ± 12.67	78.86 ± 10.46	0.04	NS	0.04
Total cholesterol (mg/dl)	ACE I/D	II	202.10 ± 28.98	190.04 ± 43.75	NS	NS	0.01
		ID	198.65 ± 39.27	189.64 ± 38.78	NS	NS	NS
		DD	198.54 ± 37.70	187.08 ± 41.84	NS	NS	NS
	AT1R A1166C	AA	199.57 ± 35.20	187.25 ± 41.95	0.06	NS	0.07
		AC	200.23 ± 37.00	191.92 ± 41.44	NS	NS	0.07
		CC	197.33 ± 41.08	188.33 ± 25.48	NS	NS	NS
	AGT M235T	MM	200.11 ± 38.91	179.82 ± 37.79	0.09	NS	0.09
		MT	198.11 ± 33.46	187.59 ± 37.51	NS	NS	0.02
		TT	201.33 ± 39.23	195.97 ± 45.11	NS	NS	NS
	eNOS Glu298Asp	GG	200.84 ± 34.69	189.12 ± 33.29	0.05	NS	0.08
		GT	196.58 ± 37.93	186.43 ± 43.24	NS	NS	0.04
		TT	205.69 ± 41.04	208.83 ± 68.35	NS	NS	NS
HDL-C (mg/dl)	ACE I/D	II	49.96 ± 21.04	52.87 ± 12.89	NS	NS	NS
		ID	48.15 ± 11.32	50.67 ± 11.86	NS	NS	NS
		DD	46.17 ± 10.11	53.08 ± 10.91	0.02	NS	0.02
	AT1R A1166C	AA	47.66 ± 11.75	53.60 ± 10.18	0.003	NS	0.009
		AC	49.18 ± 18.12	50.95 ± 11.63	NS	NS	NS
		CC	49.00 ± 13.07	44.33 ± 18.52	NS	NS	NS
	AGT M235T	MM	47.89 ± 10.94	49.88 ± 10.37	NS	NS	NS
		MT	46.63 ± 11.68	52.40 ± 12.70	0.01	NS	NS
		TT	50.91 ± 18.58	51.82 ± 11.43	NS	NS	NS
	eNOS Glu298Asp	GG	48.52 ± 14.86	53.00 ± 13.23	0.07	NS	NS
		GT	48.10 ± 13.92	49.77 ± 10.42	NS	NS	NS
		TT	48.62 ± 15.00	57.00 ± 3.80	NS	NS	NS

Table 4 (continues). Anthropometric and biochemical parameters according to genotypes of the ACE I/D, AT1R A1166C, AGT M235T, and eNOS Glu298Asp polymorphisms in the whole population (hipertensive and normotensive groups)

Anthropometric/ biochemical parameters	Polymorphism	Genotype	Whole population (n=358)			Male (n=157)	Female (n=201)
			HT (n=208)	Control (n=150)	*p* value	*p* value	*p* value
LDL-C (mg/dl)	ACE I/D	II	118.72 ± 33.10	118.57 ± 44.55	NS	0.08	0.02
		ID	119.82 ± 35.12	115.58 ± 37.29	NS	NS	NS
		DD	122.58 ± 36.15	113.50 ± 37.30	NS	NS	NS
	AT1R A1166C	AA	119.70 ± 36.24	112.81 ± 38.30	NS	NS	0.08
		AC	119.62 ± 33.03	118.86 ± 42.79	NS	0.09	NS
		CC	121.94 ± 32.81	120.44 ± 21.47	NS	NS	NS
	AGT M235T	MM	119.48 ± 39.40	104.41 ± 33.26	NS	NS	NS
		MT	119.15 ± 32.26	115.94 ± 37.30	NS	NS	0.09
		TT	121.11 ± 35.77	121.21 ± 42.85	NS	NS	NS
	eNOS Glu298Asp	GG	119.73 ± 33.22	113.60 ± 34.08	NS	NS	NS
		GT	117.59 ± 35.53	114.89 ± 40.83	NS	NS	NS
		TT	132.54 ± 38.83	145.20 ± 58.45	NS	NS	NS
Triglycerides (mg/dl)	ACE I/D	II	182.77 ± 99.41	128.04 ± 58.50	0.02	0.06	NS
		ID	177.16 ± 94.66	128.82 ± 59.53	0.001	NS	0.002
		DD	182.08 ± 95.80	118.63 ± 66.17	0.009	NS	0.004
	AT1R A1166C	AA	167.03 ± 81.12	123.33 ± 52.81	0.001	NS	0.001
		AC	200.36 ± 99.23	124.65 ± 71.25	0.001	0.07	0.01
		CC	164.78 ± 99.81	148.56 ± 55.92	NS	NS	NS
	AGT M235T	MM	163.56 ± 68.34	150.35 ± 81.82	NS	NS	NS
		MT	172.60 ± 94.47	117.04 ± 54.30	0.001	NS	0.001
		TT	195.38 ± 98.61	126.62 ± 54.61	0.001	0.01	0.051
	eNOS Glu298Asp	GG	175.77 ± 89.56	129.68 ± 58.37	0.001	NS	0.001
		GT	185.09 ± 98.57	120.60 ± 65.35	0.001	0.056	0.01
		TT	177.62 ± 97.40	138.40 ± 38.76	NS	NS	NS

Values are presented as mean ± standard deviation (SD). BMI: body mass index.
NS: not significant ($p > 0.05$). HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol.

There is evidence suggesting an association between these genes and HT (Horani *et al.*, 2015; Lamelas *et al.*, 2019), however, these variants have yielded contradictory results across different populations (Agachan *et al.*, 2003; Moe *et al.*, 2006; Companioni Nápoles *et al.*, 2007; Bonfim-Silva *et al.*, 2016).

The potential role of the AT1R gene in the predisposition to hypertension is controversial, and conflicting results have been reported (Agachan *et al.*, 2003; Bautista *et al.*, 2008; Sharma *et al.*, 2024). The present study found no association between the AT1R A1166C polymorphism and hypertension. This finding is consistent with our previous results of this SNP in a population from San Luis (Lapierre *et al.*, 2006). Similarly, Bautista *et al.* (2008) and Isordia-Salas *et al.* (2023) found no association between AT1R A1166C polymorphism and hypertension.

The ACE I/D polymorphism is one of the most widely studied genetic variants of the RAAS genes. Several authors have reported that ACE DD genotype is associated with HT (Agachan *et al.*, 2003; Bautista *et al.*, 2008; Isordia-Salas *et al.*, 2023). However, we could not find a relationship between this variant and the HT in our population, which could be explained by the interactions of different factors. In fact, according to a recent genetic report for central Argentina, the genetic context cannot be analyzed without taking into account the different historical, migratory, socioeconomic and demographic processes that result in the particular genetic characteristics of each region (García *et al.*, 2015).

Regarding AGT M235 Tpolymorphism, our results revealed no differences in genotype and allele frequencies between both groups. This is consistent with some previous reports (Bautista *et al.*, 2008; Yuan *et al.*, 2009). In contrast, other studies have reported a strong association between the TT genotype and HT (Agachan *et al.*, 2003; Isordia-Salas *et al.*, 2023).

Table 5. Relationship between body mass index (BMI) and the genotypes of the ACE I/D, AT1R A1166C, AGT M235T, and eNOS Glu298Asp polymorphisms in the whole population (hipertensive and normotensive groups)

Parameter	Polymorphism	Genotype	Whole population (n=358)	*p* value
BMI (kg/m²)	ACE I/D	II	28.97 ± 5.36	
		ID	30.16 ± 5.45	0.05
		DD	28.42 ± 4.96	
	AT1R A1166C	AA	29.43 ± 5.21	
		AC	29.06 ± 5.28	0.03
		CC	31.85 ± 6.17	
	AGT M235T	MM	28.76 ± 5.25	
		MT	29.10 ± 4.89	0.05
		TT	30.55 ± 5.99	
	eNOS Glu298Asp	GG	30.16 ± 5.75	
		GT	28.78 ± 4.71	NS
		TT	28.96 ± 5.64	

Values are presented as mean ± standard deviation (SD). NS: non significant ($p > 0.05$).

The Glu298Asp polymorphism is one of the most widely studied variants of the eNOS gene. In our population we found no association between the Glu298Asp genotype and HT. Consistent with our results, Moe *et al.* (2006) reported that this eNOS polymorphism was not associated with hypertension.

Gene–environment interactions in HT are complex. While some studies report associations between RAAS and eNOS SNPs and HT, others do not, likely due to genetic and environmental heterogeneity (Horani *et al.*, 2015; Lamelas *et al.*, 2019).

The lack of association observed in our population may reflect underlying genetic heterogeneity. In addition, genetic, epigenetic, and environmental factors may interact to influence the hypertensive phenotype. Another possible explanation includes epistatic gene–gene interactions in which the effect of the studied gene is masked by the effect of other susceptible genes.

A limitation of this study is the relatively small sample size. Future research involving larger, more diverse cohorts is necessary to validate or refine these preliminary findings.

When we compared the demographic characteristics, the anthropometric and biochemical parameters of the hypertensive and control groups, we observed significant differences in fasting plasma glucose, total cholesterol, HDL-C, triglycerides, and dyslipidemia, with higher levels in the hypertensive group. These findings reinforce the importance of metabolic factors as key determinants of the risk of high blood pressure. It is noteworthy that the BMI was significantly higher in hypertensive patients than in controls; however, in both groups, the BMI was above the normal range, indicating a worrying fact about the existence of overweight throughout our study population. The pervasive overweight status within both groups underscores a broader health challenge that needs to be addressed.

We analyzed traditional cardiovascular risk factors in our population. The Odds Ratio (OR) analysis revealed that the age ($p<0.001$), the overweight ($p<0.001$), the elevated fasting glucose ($p<0.005$), and elevated triglycerides ($p<0.001$) as significant predictors of HT. The risk factors involved in the development of high blood pressure have been reportedin numerous prior studies, and our findings are consistent with most of them (Pereira *et al.*, 2006; Oliveira-Paula *et al.*, 2017; Lamelas *et al.*, 2019; Mills *et al.*, 2020; Zhou *et al.*, 2021; Giunta *et al.*, 2023).

Evidence highlights that hypertension is not an isolated problem, but is intrinsically linked to metabolic disorders (such as glucose and lipid abnormalities), forming a cardiometabolic risk complex that worsens the patient's prognosis, increasing vascular damage and the risk of serious cardiovascular events. Therefore, hypertension must be viewed in the context of other metabolic factors, as their combined management is

crucial for improving prognosis and reducing long-term cardiovascular risk (Mills *et al.*, 2020; Ordunez *et al.*, 2022).

A stratified analysis by sex was performed to study the association between the different genotypes with BMI, fasting glucose, and lipid profile parameters.

Overall, the results in Tables 4 and 5 indicate how different genotypes modulate the anthropometric and biochemical profile of our population, with more pronounced effects in women and specific variations according to each polymorphism. These findings suggest a possible interaction between genetic variants and adverse metabolic profiles associated with hypertension, with a pattern of greater susceptibility in women. This is consistent with Kauko *et al.* (2021), which suggests that the effect of genetics on hypertension risk, compared to that of modifiable factors, appears to be greater in women than in men.

Studies on the role of gene polymorphisms in the renin-angiotensin system and the eNOS gene in the development of hypertension are limited in the Argentine population.

To our knowledge, this is the first study of RAAS and eNOS polymorphisms conducted in a primary health care center attending population in San Luis; our prior work focused solely on the AT1R A1166C polymorphism and was performed in a private clinic setting (Lapierre *et al.*, 2006).

This research contributes to the cumulative growth of knowledge, leading to a more comprehensive understanding of hypertension and the genetic and cardiometabolic factors that characterize populations in our region.

CONCLUSION

These findings suggest that the ACE I/D, AT1R A1166C, AGT M235T, and eNOS Glu298Asp polymorphisms are not associated with the development of hypertension in the studied population.

Age, overweight, elevated fasting glucose, and elevated triglycerides are significant predictors of HT in this population.

Given HT's polygenic nature, larger studies in our region are needed to confirm these results.

Understanding the distribution of genetic polymorphisms and identifying their relationship to cardiometabolic risk factors is crucial for developing targeted public health strategies for hypertension.

REFERENCES

Al-Eitan L., Al-Khaldi S., Ibdah R.K.(2024) ACE gene polymorphism and susceptibility to hypertension in a Jordanian adult population. PLoS ONE 19(6): e0304271.

Agachan B., Isbir T., Yilmaz H., Akoglu E. (2003) Angiotensin converting enzyme I/D, angiotensinogen T174M–M235T and angiotensin II type 1 receptor A1166C gene polymorphisms in Turkish hypertensive patients. Exp. Mol. Med. 35: 545–549.

Agarwal A., Williams G.H., Fisher N.D.(2005) Genetics of human hypertension.TrendsEndocrinol. Metab.16: 127–133.

Aquieri A., Rodríguez P., Vissani S.*et al.*(2025) Consenso Argentino de hipertensión arterial. Rev. Argent.Cardiol. 93 (S10): 1-70.

Bautista L.E., Vargas C.I., Oróstegui M., Gamarra G. (2008) Population-based case–control study of renin–angiotensin system genes polymorphisms and hypertension among Hispanics. Hypertens. Res. 31: 401–408.

Bonfim-Silva R., Guimarães L.O., Santos J.S., Pereira J.F., Barbosa A.A.L., Souza Rios D.L.S. (2016) Case–control association study of polymorphisms in the angiotensinogen and angiotensin-converting enzyme genes and coronary artery disease and systemic artery hypertension in African-Brazilians and Caucasian-Brazilians. J. Genet. 95: 63–69.

Chobanian A.V., Bakris G.L., Black H.R., Cushman W.C., Green L.A., Izzo J.L. Jr, Jones D.W., Materson B.J., Oparil S., Wright J.T. Jr, Roccella E.J. (2003) Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension42: 1206–1252.

Companioni Nápoles O., Sautié Castellanos M., Leal L., Casalvilla R., Camacho H., Ferrer A., Cintado A., Villareal A., Benítez J.V., Nazabal M., Velasco J.G., Cabalé B., Novoa L.I., Dueñas M. (2007) ACE I/D polymorphism study in a Cuban hypertensive population. Clin. Chim. Acta378: 112–116.

Delucchi A.M., Majul C.R., Vicario A., Cerezo G.H., Fábregues G. (2017) Registro Nacional de Hipertensión Arterial. Características epidemiológicas de la hipertensión arterial en la Argentina. Estudio RENATA 2. Rev. Argent. Cardiol. 85: 354–360.

Franks P.W. (2009) Identifying genes for primary hypertension: methodological limitations and gene–environment interactions. J. Hum. Hypertens. 23: 227–237.

Frishberg Y., Becker-Cohen R., Halle D., Feigin E., Eisenstein B., Halevy R.,Lotan D., Juabeh I., Ish-Shalom N., Magen D., Shvil Y., Sinai-Treiman L., Drukker A. (1998) Genetic polymorphisms of the renin–angiotensin system and the outcome of focal segmental glomerulosclerosis in children. KidneyInt. 54: 1843–1849.

Gallo G., Volpe M., Savoia C. (2022) Endothelial dysfunction in hypertension: current concepts and clinical implications. Front. Med. (Lausanne) 8: 798958.

García A., Dermarchi D.A., Tovo-Rodrigues L., Pauro M., Callegari-Jacques S.M., Salzano F.M., Hutz M.H. (2015) High interpopulation homogeneity in Central Argentina as assessed by ancestry informative markers (AIMs). Genet. Mol. Biol. 38: 324–331.

Giunta G., Lavalle Cobo A., Brandani L., Lobo M., Forte E., Masson G., et al. (2023) Consenso de Prevención Cardiovascular. Rev. Argent. Cardiol. 91(3): 1–190.

Horani T., Best R.G., Edwards E., DiPette D.J. (2015) Genetics of hypertension: What is next? Curr. Cardiovasc. Risk Rep. 9: 1.

Isordia-Salas I., Santiago-Germán D., Flores-Arizmendi A., Leaños-Miranda A. (2023) Polymorphisms in the Renin–Angiotensin System and eNOS Glu298Asp genes are associated with increased risk for essential hypertension in a Mexican population. J. Renin Angiotensin Aldosterone Syst.17:4944238.

Kauko A., Aittokallio J., Vaura F., Ji H., Ebinger J.E., Niiranen T., Cheng S. (2021) Sex differences in genetic risk for hypertension. Hypertension78: 1153–1155.

Lamelas P., Diaz R., Orlandini A., Avezum A., Oliveira G., Mattos A., Lanas F., Seron P., Oliveros M.J., Lopez-Jaramillo P., Otero J., Camacho P., Miranda J., Bernabe-Ortiz A., Malaga G., Irazola V., Gutierrez L., Rubinstein A., Castellana N., Rangarajan S., Yusuf S. (2019) Prevalence, awareness, treatment and control of hypertension in rural and urban communities in Latin American countries. J. Hypertens. 37: 1813–1821.

Lapierre A.V., Arce M.E., López J.R., Ciuffo G.M. (2006) Angiotensin II type 1 receptor A1166C gene polymorphism and essential hypertension in San Luis. Biocell 30: 447–455.

Lind J.M., Chiu C.L. (2013) Genetic discoveries in hypertension: steps on the road to therapeutic translation. Heart99: 1645–1651.

Lindpaintner K., Pfeffer M.A., Kreutz R., Stampfer M.J., Grodstein F., LaMotte F., Buring J., Hennekens C.H. (1995) A prospective evaluation of an angiotensin converting–enzyme gene polymorphism and the risk of ischemic heart disease. N. Engl. J. Med. 332: 706–707.

Mills K.T., Stefanescu A., He J. (2020) The global epidemiology of hypertension. Nat. Rev.Nephrol. 16: 223–237.

Ministerio de Salud y Desarrollo Social de la Nación (2019). https://www.argentina.gob.ar/noticias/salud-publico-el-informe-completo-de-la-4deg-encuesta-nacional-de-factores-de-riesgo (accessed July 2025).

Moe K.T., Lim S.T., Wong P., Chua T., DeSilva D.A., Koh T.H., Wong M.C., Chin-Dusting J. (2006) Association analysis of endothelial nitric oxide synthase gene polymorphism with primary hypertension in a Singapore population. J. Hum. Hypertens. 20: 956–963.

NCD Risk Factor Collaboration (NCD-RisC). (2021) Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1 201 population-representative studies with 104 million participants. Lancet398: 957–980.

Oliveira-Paula G.H., Lacchini R., Tanus-Santos J.E. (2017) Clinical and pharmacogenetic impact of endothelial nitric oxide synthase polymorphisms on cardiovascular diseases. Nitric Oxide63: 39–51.

Ordunez P., Campbell N.R.C., Giraldo Arcila G.P., Angell S.Y., Lombardi C., Brettler J.W., Rodríguez Morales Y.A., Connell K.L., Gamarra A., DiPette D.J., Rosende A., Jaffe M.G., Rodríguez L., Piñeiro D.J., Martínez R., Sharman J.E.(2022) HEARTS en las Américas: innovaciones para mejorar el manejo de la hipertensión y del riesgo cardiovascular en la atención primaria. Rev. Panam. SaludPública 46: e197.

Padmanabhan S., Dominiczak A.F. (2021) Genomics of hypertension: the road to precision medicine. Nat. Rev. Cardiol. 18: 235–250.

Pereira A.C., Sposito A.C., Mota G.F., Cunha R.S., Herkenhoff F.L., Mill J.G., Krieger J.E. (2006) Endothelial nitric oxide synthase gene variant modulates the relationship between serum cholesterol levels and blood pressure in the general population. Atherosclerosis184: 193–200.

Rigat B., Hubert C., Corvol P., Soubrier F. (1992) PCR detection of the insertion/deletion polymorphism of the human angiotensin converting enzyme gene (DCP1) (dipeptidyl carboxypeptidase 1). Nucleic Acids Res. 20: 1433.

Sharma J.R., Fokkens H., Laubscher R., Apalata T.R., Nomatshila S.C., Alomatu S.Y., Strijdom H., Johnson R. (2024) No association between AGT gene polymorphisms and hypertension in a South African population. Diabetes Metab. Syndr. Obes. 17: 1853–1865.

Singh M., Mensah G.A., Bakris G. (2010) Pathogenesis and clinical physiology of hypertension. Cardiol. Clin. 28: 545–559.

Yuan J., Tang W., Chun Y., Ying H., Yang Y., Xiao C. (2009) Angiotensinogen T174M and M235T variants and hypertension in the Hani and Yi minority groups of China. Biochem.Genet. 47: 344–350.

Zhou B., Perel P., Mensah G.A., Ezzati M. (2021) Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. Nat. Rev. Cardiol. 18: 785–802.

AUTHOR CONTRIBUTION

LBF and MEA designed the study. MMC and LBF collected data. MMC performed genotyping and statistical analyses. MMC, MEA, and LBF drafted and revised the manuscript. All authors approved the final version.

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The authors declare no financial conflicts of interest.

DECLARATION OF GENERATIVE AI USE

During the preparation of this work, the authors used ChatGPT in order to assist in the writing process, improving readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.