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Analysis of Relationship of Hypertension with Metabolic Syndrome and Rs1137101 LepR Gene Polymorphism in Mexican Treated Hypertensive Subjects

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Abstract

Insulin resistance and hypertension are closely related with metabolic syndrome (MS). To explore the relationship between hypertension with metabolic syndrome and rs1137101 LepR polymorphism in Mexican hypertensive patients treated. We recruited two groups of both genders aged 30 to 50 years: 1) Normotensive subjects without antecedents of metabolic or chronic diseases; and 2) treated hypertensive patients. The anthropometric measurements were measured, adiposity distribution indices were calculated and blood pressure was taken. The fasting serum glucose, lipid, insulin and leptin levels were quantified, and rs1137101 was genotyped. We selected 248 normotensive subjects and 173 treat hypertensive patients, 227 women and 194 men. In subjects with metabolic syndrome (MS) 67.9% were hypertensive, and 51.1% of hypertensive patients had MS. The waist-height index was significantly higher in MS subjects than in hypertensive patients. The analysis by genotype in the entire group showed that carriers of the AA and AG rs1137101 genotypes had higher systolic and diastolic pressure, and higher leptin levels in hypertensive patients with the GG genotype. The waist-height index could help distinguish only treated hypertensive patients from those with metabolic syndrome. The rs1137101 polymorphism is related with blood pressure and leptin levels.

Keywords: Hypertension, Metabolic syndrome, rs1137101 polymorphism, leptin levels.

1. Introduction

Hypertension is one of the most important problems of public health and is the leading preventable for cardiovascular disease and all-cause mortality worldwide [Mills et al., 2020). In México, the prevalence of hypertension is of 49.2% (46.8% in women and 52.2% in men). Several factors that are associated with metabolic syndrome and contribute to the development of hypertension include: obesity, insulin resistance, sympathetic overactivity, activated Renin-

Vol.9, No. 02; 2025

ISSN: 2581-3366

angiotensin system, stress oxidative, increased inflammatory mediators, and obstructive sleep apnea (Soleimani et al.,2023).

1.1 Hypertension and Insulin Resistance

Hypertension can result of the sustained anti-natriuretric effect of hyperinsulinemia that directly stimulate renal tubular sodium reabsorption could translate into increased Blood Pressure (da Silva et al., 2020). Hyperinsulinemia is associated with elevated concentrations plasmatic catecholamines irrespective of plasmatic glucose levels (Rowe et al., 1981), an effect that is not only preserved in insulin resistance but can even be increased, therefore can lead to hypertension within metabolic syndrome (Yanai H et al., 2008) The plasma levels of leptin are increased by insulin resistance, and leptin positively influences the activity of the nervous system, which can lead to hypertension associated with obesity (Egan et al., 2010; Shankar et al., 2010)]. Several studies have demonstrated that adipose tissue is a secretory endocrine organ of adipokines such leptin, tumor factor alfa (TNF-α), IL-6, angiotensinogen, and non-esterified fatty acids, that have multiples effects, one of them is the production of hypertension (Katagiri et al., 2007)].

Several pathophysiological mechanisms have been proposed to explain hypertension in the metabolic syndrome. The presence of obesity, the activation of the sympathetic nervous system and sodium retention are the prevailing mechanisms (Katsimardou et al., 2020). The insulin resistance activates the sympathetic nervous system, upregulating angiotensin II receptors and reduce the synthesis of nitric oxide leading to increases heart rate and blood pressure (Mancia et al., 2007).

1.2 Leptin receptor (rs1137101 LepR) polymorphism and hypertension

The leptin is secreted in proportion to adipose tissue mass. Leptin acts through the leptin receptors, which are encoded by the LepR gene located in ch1p31. Several SNPs (single nucleotide polymorphism) in the coding region of the LepR have been described. One of them is the rs1137101 polymorphism which consists of a substitution of A to G at codon 223 resulting in a glutamine to arginine change (Quinton et al., 2001). The rs1137101 polymorphism is within the region encoding the extracellular domain of leptin receptor, and therefore, the amino acid change affects all forms of the receptor and may consequently change functional characteristics of the receptor (Houseknecht et al., 1996). In menopausal women and patients with obesity, the A allele of the rs1137101 LepR polymorphism was associated with significantly higher BMI, greater fat mass, and higher circulating leptin compared with another allele (Quinton et al., 2001; Ben et al., 2009). In subjects with overweight and obesity the GG genotype was associated with BMI (0.04) and WC (waist circumference) (p=0.02) (Illangasekera et al., 2020). On the other hand, in Malaysian population the subjects with A allele of rs1137101 had significantly higher systolic blood pressure and adiposity indices (Fan et al., 2014). In Chinese populations the carries of AA/AG genotypes showed higher risk of hypertension. In addition, BMI, fasting serum insulin, glucose, leptin, and LDL cholesterol were also independent risk factors of hypertension (Gu et al 2012). Instead, the carries of rs1137101 GG or AG genotypes showed higher risk of

Vol.9, No. 02; 2025

ISSN: 2581-3366

hypertension than homozygotes AA (p=0.007, OR = 3.69, 95% CI 1.44-9.48) in population of Han Chinese (Liu et al 2014). However, not evidence of association of rs1137101 polymorphism with mild hypertension was found in a study in Brazil (Pena et al, 2014). The results of a meta-analysis showed that the rs1137101 polymorphism is associated with hypertension (OR=1.36, 95% CI=1.23-1.51, p<0.00001) (Lian et al., 2015). The rs1137101 polymorphism (AA vs GG) also have been association with heart rate (p=0.03), fat mass (p=0.03), and triglycerides levels (p=0.03) (de Faria et al., 2017). In Type 2 Diabetes Mellitus patients from East of Indonesia the rs1137101 AA genotype was associated with hypertension but not with BMI and diabetes (p=0.027, OR12.3 95% CI=1.33-114.6) (Hastuti et al., 2020). In Mongolian and Han populations the rs1137101 polymorphism (A/G and A/A) was associated with development of hypertension only in Mongolian population (1.49 (1.13-1.95), p=0.004), but Han and Mongolian populations the rs1137101 was associated with a significantly decrease risk of hypertension with T2DM (Zhao et al., 2022). The objective of study was to analyze the relationship of hypertension between with metabolic syndrome and rs1137101 LepR gene polymorphism in treated hypertensive Mexican subjects.

2.0 Methods

2.1 Subjects

Through a cross section design, we recruited two subject groups of both gender aged 30 to 50 years: 1) Normotensive subjects without antecedents of metabolic or chronic diseases; and 2) patients with diagnosis of hypertension with a blood pressure ≥130 and/or ≥80 mmHg [23], without secondary hypertension to other pathology. The hypertensive subjects were under treatment with anti-hypertension agents as telmisartan, metoprolol, lozartan, captopril, verapamilo, and ibersartan, and without hypolipidemic agents.

2.2 Anthropometric measurements and blood pressure (BP)

The participants were quoted at 8 AM after an overnight fast. Personal and clinical data were registered and systolic and diastolic blood pressures were measured in a sitting position after ten minutes of rest according ACC/AHA hypertension guidelines (Flack et al., 2019). Weight and % fat were measured with a roman type Tanita BC533 scale, height was measured using a SECA 406 Stadiometer. Waist circumference (WC) was measured at the midpoint between the lower border of the ribs and the anterior iliac crest, Hip circumference was measured at the level of maximum gluteal extension in a horizontal plane using a Lufkin brand flexometer. We calculated the indices: body mass index (BMI), waist-to-hip ratio (WHR), and waist-to height ratio (WHtR). Neck circumference was measured with the body upright and the head placed in the Frankfurt horizontal plane using a metal flexometer. All measurements were conducted in duplicate by qualified personnel. The diagnosis of metabolic syndrome was made using the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP-III): blood pressure ≥130/85, glucose > 100 mg/dL, triglycerides >150 mg/dL, HDL-C men< 45 mg/dL and women <50 mg/dL, waist circumference in men > 102 cm and in women > 88 cm (Carr et al., 2004).

Vol.9, No. 02; 2025

ISSN: 2581-3366

2.3 Metabolic measures

Venous blood samples were taken after an overnight fasting for the measurement of serum glucose, lipid profile, insulin, and leptin concentrations and for genomic DNA extraction. Serum glucose, creatinine and lipid profile were measured using enzymatic methods with a chemical analyzer semiautomatic (SPINLAB, SPINREACT, MÉXICO). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedwald's formula. Serum insulin and leptin were measured by ELISA Kit (both purchased by ALPCO Immunodiagnostic AG, Stubenwald-Allee, Bensheim, USA) with a sensitivity of 0.399 µIU/mL (normal range 3.0-200 µIU/mL) for insulin, and for leptin a sensitivity of 0.42 ng/mL (normal range 1-100 ng/mL). Insulin Resistance (IR) was calculated using the Homeostatic Model Assessment (HOMA) (Matthews et al., 1985).

2.4 Genotyping of rs1137101 LepR (leptin receptor)

Genomic DNA from all participants was extracted from peripheral blood leucocytes according to the TSNT protocol and quantified using the NanoDrop system (Roche). The genetic variant of the Leptin Receptor rs1137101 was genotyped using a validated Taqman® allelic discrimination assay (Thermo Fisher Scientific® Waltham, MA, USA). All samples were carried out and analyzed with a CFX96 Touch Thermalcycler (Bio-Rad) using the recommended cycling conditions: 1) denaturation phase (95°C for 10 minutes) followed by annealing (95°C for 15 seconds) and extension for 40 cycles (60°C for 1 minute). To check the reliability of genotyping, 10% of samples were reanalyzed, and 99% matching was obtained.

2.5 Statistical analysis

The Kolmogorov-Smirnov test was uses for prove normality of data. The anthropometric and metabolic data are expressed as mean ± SD or median (25-75 quartiles). Differences between groups were examined using the *t* independent test, Mann-Whitney *U* test or ANOVA one way and Kruskal Wallis Test. Both groups were tested for the Hardy-Weinberg equilibrium for rs1137101 polymorphism. We compared allelic frequency between groups using Yates-corrected χ^2. Analyses were performed using a statistical package (Statistica, Statsoft Inc., Tulsa, OK). The level of statistical significance was defined as $P < 0.05$.

3. Results

3.1 Metabolic and hormonal

We selected a total of 421 subjects, 227 women and 194 men of which 248 were normotensive subjects and 173 were treated-hypertensive patients. Among treated hypertensive patients, 51.1% had MS, while 67.9% of MS subjects were hypertensive. The table 1 shows the comparison of anthropometric and metabolic variables among normotensive subjects and hypertensive patients. There were significant differences in most of variables compared, with exception of height, neck circumference, total cholesterol, and leptin levels.

In the total group, we found significant differences in most of the anthropometric and metabolic variables between subjects with and without MS, except in height and LDL- cholesterol levels (table 2). It is important to observe that neck circumference was only significantly greater in subjects with metabolic syndrome, and the increase in the WHtR index that ranges from normotensive, hypertensive and MS subjects (table 1 and 2).

Table 1. Comparison of somatometric and biochemical characteristics between healthy subjects and patients with hypertension

Characteristics	**Normotensive subjects Mean ± S.D. (n=248)**	**Hypertensive subjects Mean ± S.D. (n=173)**	**t**	***p-value***
Age (yr)	37.9 ± 7	43.1 ± 5.8	7.984	<0.00001
Weight (kg)	74.5 ± 12.7	79.9 ± 13.4	4.153	0.000040
Height (m)	1.62 ± 0.08	1.60 ± 0.9	-1.652	NS
BMI (kg/m^2)	28.2 ± 4.1	30.8 ± 4	6.355	<0.00001
Waist (cm)	92.7 ± 11	98.7 ± 9.6	5.803	<0.00001
Hip (cm)	103 ± 7.7	106.7 ± 9.2	4.073	0.000055
Neck (cm)	37.7 ± 3.5	38.2 ± 3.6	0.963	NS
Waist hip index	0.89 ± 0.07	0.92 ± 0.07	4.0229	0.000068
Waist height index	0.57 ± 0.07	0.61 ± 0.06	6.554	<0.00001
% Fat	33.3 ± 8.4	35.5 ± 7.8	2.169	0.030
SBP (mmHg)	111 ± 9	133 ± 14	18.689	<0.00001
DBP (mmHg)	73 ± 7	88 ± 10	16.762	<0.00001
Glucose (mg/dl)	88.7 ± 12	93.3 ± 12	3.842	0.00014
Triglycerides (mg/dl)*	121 (83.5-177)	131 (100-178)	2.055	0.039
Total cholesterol (mg/dl)	188 ± 39	194.8 ± 36.8	1.814	0.070
HDL-cholesterol (mg/dl)	47 ± 12.1	43.5 ± 11	-3.274	0.0011
LDL cholesterol (mg/dl)	112 ± 40.7	119.3 ± 36.7	1.872	0.061
Insulin (µIU/ml)*	13 (7.9 - 19.9)	17.4 (12 - 24.5)	3.780	0.00015
HOMA-IR*	2.8 (1.7 - 4.4)	4.1 (2.4 - 5.8)	3.912	0.00009
Leptin (ng/dl)*	22.2 (12.1-38.6)	23.2 (13.8-33.1)	-0.123	NS

BMI = body mass index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HDL-cholesterol = high-density lipoprotein cholesterol; LDL-cholesterol = low-density lipoprotein

cholesterol; HOMA-IR = Homeostatic model assessment of insulin resistance. t Student test; * The non-parametric were examined using the U Mann-Whitney test.

Table 2. Comparison of somatometric and biochemical characteristics between metabolic syndrome and healthy subjects

Characteristics	**Healthy subjects Mean ± S.D. (n=290)**	**Metabolic syndrome Mean ± S.D. (n=131)**	**t**	***p-value***
Age (yr)	39.1 ± 7	42.1 ± 5.9	-4.14	0.00004
Weight (kg)	74 ± 13	83 ± 12	-6.64	<0.00001
Height (m)	1.62 ± 0.08	1.60 ± 0.09	1.58	NS
BMI (kg/m^2)	28 ± 4.1	32 ± 3.2	- 9.67	<0.00001
Waist (cm)	92 ± 10.5	102 ± 8.1	- 9.15	<0.00001
Hip (cm)	102.7 ± 7.9	109 ± 8.1	-7.46	<0.00001
Neck (cm)	37.5 ± 3.4	38.7 ± 3.5	- 2.63	0.009
Waist hip index	0.89 ± 0.07	0.93 ± 0.06	- 4.78	0.000002
Waist height index	0.56 ± 0.06	0.63 ± 0.06	- 9.98	<0.00001
% Fat	32.3 ± 8.2	37.9 ± 7	- 5.41	<0.00001
SBP (mmHg)	115 ± 13	131 ± 16	- 10.74	<0.00001
DBP (mmHg)	76 ± 9	88 ± 12	- 11.8	<0.00001
Glucose (mg/dl)	87 ± 10	99 ± 13	- 10.34	<0.00001
Triglycerides (mg/dl)*	112 (82 – 148)	167 (122 - 226)	-7.81	<0.00001
Total cholesterol (mg/dl)	188 ± 38	197 ± 37	- 2.20	0.028
HDL-cholesterol (mg/dl)	48 ± 11.7	40.8 ± 10.4	5.99	<0.00001
LDL cholesterol (mg/dl)	114 ± 40	117 ± 36	- 0.56	NS
Insulin (µIU/ml)*	12 (7.9 - 18.6)	19.8 (14.8 – 28.7)	- 6.46	<0.00001
HOMA-IR*	2.6 (1.7 - 4.2)	4.6 (3.4 - 7)	- 7.15	<0.00001
Leptin (ng/dl)*	20.4 (11.3 - 32)	27.7 (16.8 – 38.7)	-3.12	0.0017

BMI = body mass index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HDL-cholesterol = high-density lipoprotein cholesterol; LDL-cholesterol = low-density lipoprotein cholesterol; HOMA-IR = Homeostatic model assessment of insulin resistance. t Student test. * The non-parametric were examined using the U Mann-Whitney test.

Vol.9, No. 02; 2025

ISSN: 2581-3366

The BMI, waist, hip, WHtR, fat mass, serum glucose, triglycerides, insulin, HOMA-IR, and leptin levels, were significantly higher in MS subjects than hypertensive patients. In contrast, the HDL-cholesterol levels were lower in MS subjects (table 3).

Table 3. Comparison of somatometric and biochemical characteristics between hypertensive patients and metabolic syndrome

Characteristics	**Hypertensive patients Mean ± SD (n=173)**	**Metabolic syndrome subjects Mean ± SD (n=131)**	**t**	**p-value**
Age (yr)	43.1 ± 6	42.1 ± 5.9	1.45	NS
Weight (kg)	79.9 ± 13	83 ± 12	-1.95	0.05
Height (m)	1.60 ± 0.08	1.60 ± 0.09	0.14	NS
BMI (kg/m^2)	30.8 ± 4	32 ± 3.2	-2.77	0.005
Waist (cm)	99 ± 9.5	102 ± 8.1	- 2.91	0.02
Hip (cm)	106.6 ± 9.1	109 ± 8.1	-2.30	0.02
Neck (cm)	38.2± 3.6	38.7 ± 3.5	- 1.03	NS
Waist hip index	0.92 ± 0.07	0.93 ± 0.06	- 0.96	NS
Waist height index	0.615 ± 0.06	0.63 ± 0.06	- 2.98	0.003
% Fat	35.5 ± 8	37.9 ± 7	- 2.24	0.02
SBP (mmHg)	133 ± 14	131 ± 16	1.07	NS
DBP (mmHg)	88 ± 10	88 ± 12	0.16	NS
Glucose (mg/dl)	93 ± 12	99 ± 13	- 3.82	0.0001
Triglycerides (mg/dl)*	131 (100 – 178)	167 (122 - 226)	- 4.12	0.00003
Total cholesterol (mg/dl)	195 ± 37	197 ± 37	- 0.47	NS
HDL-cholesterol (mg/dl)	43.5 ± 11	40.8 ± 10.4	2.17	0.03
LDL cholesterol (mg/dl)	119 ± 37	117 ± 36	0.62	NS
Insulin (µIU/ml)*	17.4 (11.9 – 24.5)	19.8 (14.8 – 28.7)	- 2.14	0.032
HOMA-IR*	4.07(2.4 – 5.8)	4.6 (3.4 - 7)	-2.53	0.011
Leptin (ng/dl)*	23.3 (13.8 – 33.1)	27.7 (16.8 – 38.7)	-2.07	0.037

BMI = body mass index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HDL-cholesterol = high-density lipoprotein cholesterol; LDL-cholesterol = low-density lipoprotein cholesterol; HOMA-IR = Homeostatic model assessment of insulin resistance. t Student test. * The non-parametric were examined using the U Mann-Whitney test.

3.2 Relationship of rs1137101 LepR polymorphism with metabolic variables

Table 4 shows the genotypic and allelic frequencies of the of LepR gene. The genotype frequencies of the rs1137101 polymorphism were in agreement with the Hardy-Weinberg proportions. No significant differences in allelic and genotypic frequencies among normotensive subjects and hypertensive patients were found (table 5). In the comparison of the anthropometric and metabolic variables by rs1137101 genotypes in total group under dominant model, we found lower systolic and diastolic blood pressure in carriers of the GG genotype than in carriers of the AA and AG genotypes.

Table 4. Distribution of leptin polymorphism frequencies

n= 367	**Genotypic Frequency (%)**	**Allele**	**Allelic Frequency**	χ^2	**p**
A>G*					
AA	118 (32)	A	0.56	0.1698	0.9186
AG	175 (47.7)	G	0.44		
GG	74 (20.2)				

Table 5 Comparison of genotypic frequencies among normotensive subjects and hypertensive subjects

n=367			χ^2	**p**
rs1137101 A>G	**Normotensive subjects**	**Hypertension subjects**		
AA	64(31.5)	54(33.1)	2.138	0.3433
AG	94(46)	82(50.3)		
GG	46(22.5	27(16.5)		

Also, a significant increase leptin levels and a marginally significant increase in WHtR index in GG genotype were observed (table 6). In the analysis by genotype only in the group of normotensive subjects, pressure blood systolic was significant higher in carries of AA genotype than AG and GG genotypes (F=3.30, p=0.038), and when we analyzed only hypertensive patients group, the leptin levels were significantly higher in GG genotype (F=5.80, p=0.004) than other genotypes. No association of rs1137101 polymorphism with MS was found.

Table 6. Comparison of somatometric and metabolic variables by genotype of rs1137101 LepR polymorphism

	Genotype AA Mean ± SD n=118	Genotype AG Mean ± SD n=175	Genotype GG Mean ± SD n=74	F	p-value	Post-Hoc
Age (yr)	40.6 ± 7.2	40.1 ± 7	39.7 ± 7	0.24	NS	
Weight (kg)	77.7 ± 13.8	77.7 ± 12.9	77.2 ± 14	0.03	NS	
Height (m)	1.62 ± 0.08	1.6 ± 0.09	1.6 ± 0.09	0.65	NS	
BMI (kg/m^2)	29.4 ± 4.3	29.5 ± 3.9	29.8 ± 4.5	0.18	NS	
Waist (cm)	95.7 ± 11.2	95.9 ± 10.2	96.8 ± 10.3	0.19	NS	
Hip (cm)	104.5 ± 8.8	105.2 ± 8.4	104.5 ± 9.2	0.31	NS	
Neck (cm)	38.1 ± 3.5	37.7 ± 3.4	39 ± 3.6	0.31	NS	
Waist hip index	0.91 ± 0.07	0.91 ± 0.07	0.92 ± 0.06	0.67	NS	
Waist height index	0.59 ± 0.07	0.59 ± 0.06	0.60 ± 0.06	2.93	0.054	
% Fat	33.4 ± 8.3	35.1 ± 8	35.3 ± 7.4	1.00	NS	
SBP (mmHg)	**123 ± 15**	**122 ± 16**	**116 ± 14**	**3.75**	**0.024**	**3 vs 1,2**
DBP (mmHg)	**81 ± 11**	**81 ± 11**	**77 ± 10**	**3.09**	**0.046**	**3 vs 1,2**
Glucose (mg/dl)	90.6 ± 10.8	90.7 ± 12.2	90.8 ± 12.5	2.88	0.057	
Triglycerides (mg/dl)*	122 (95-180)	127 (88-171)	137 (101-201)	0.67	NS	
Total cholesterol (mg/dl)	190 ± 36	188.9 ± 36	193.8 ± 49	0.31	NS	
HDL-cholesterol (mg/dl)	47.6 ± 12.1	45.2 ± 11.3	48 ± 12	1.92	NS	
LDL cholesterol (mg/dl)	112.1 ± 36.9	113.5 ± 37	114.6 ± 48	0.07	NS	
Insulin (µIU/ml)*	15.5 (8.6-20.7)	15.1 (10.1-22.2)	18.3 (12.4-27.9)	1.80	NS	
HOMA-IR*	3.4 (1.95-4.9)	3.3 (2.2-5.1)	4.3 (2.6-7.2)	1.77	NS	
Leptin (ng/dl)*	**16.2 (9.7-34.6)**	**23.3 (15.3-35.3)**	**26.8 (17.3-38.9)**	**4.08**	**0.018**	**1 vs 3**

BMI = body mass index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HDL-cholesterol = high-density lipoprotein cholesterol; LDL-cholesterol = low-density lipoprotein cholesterol; HOMA-IR = Homeostatic model assessment of insulin resistance. * ANOVA test one way or non-parametric were examined using the Kruskal Wallis test and Fisher- LSD Post-hoc.

Vol.9, No. 02; 2025

ISSN: 2581-3366

4. Discussion

In our work analyzed the relationship of hypertension with metabolic syndrome and with rs1137101 LepR gene polymorphism. We found that the prevalence of MS in overall sample was 31.1%, appearing with a frequency of 60% in women and 40% in men. The prevalence of MS in Latin American countries was 24.9% (range: 18.8-43.3), being more frequent in women (25.3%) than in men (23.2%) (Márquez-Sandoval et al., 2011), and a tendency to increase in México 26.6%; 40.2, 57.3, 59.99 and 56.3% in 2004, 2006, 2012, 2016 and 2018 respectively) (Aguilar-Salinas et al., 2004; Rojas-Martínez et al 2021). In our study the prevalence of MS in treated hypertensive subjects was 51.1%, has previously been reported prevalence of MS of 60.7% and 68% in hypertensive subjects (Marchi-Alves et al., 2012; Senarathne et al 2021). We found that 67.9% of patients with MS are hypertensive, previous reports had shown frequencies of 80% and 95.4% of hypertension in MS subject (Katsimardou et al 2020; Mancia et al 202007). This disparity is probably due in part to the fact that our hypertensive patients are under treatment. The height, neck circumference, circulating total cholesterol and leptin levels were similar between normotensive subjects and hypertensive patients. Adiposity indices and some metabolic variables in treated-hypertensive patients were lower than in MS subjects, these differences could reflect the effect of the treatment in hypertensive subjects. In subjects with metabolic syndrome, measurements neck circumference and circulating levels of leptin emerge as other parameters that can be added to the list of criteria since these parameters were not significantly different among normotensive subjects and treat-hypertensive patient groups. However, these data require additional confirmation. It is important to emphasize that in comparison among treated-hypertensive patient with MS subjects, only the waist-height index was significantly higher in the MS group, which suggests greater cardiovascular risk in this group than in treated hypertensive patients. In 2018, a study showed that the waist-height ratio can be considered a predictive index for the incidence of hypertension in adults aged 39-72 years (Choi et al., 2018). Another study showed that the waist-height ratio can be considered a screening tool for hypertension in outpatients, which is as effective as BMI (Shrestha et al., 20121). Increasing the waist-height ratio above 0.53 augmented the risk of developing metabolic syndrome and the same study suggests that controlling the waist-height ratio could prevent the appearance of metabolic syndrome (Kammar-Garcia et al., 2019).

Also, a significant increase leptin levels and a marginally significant increase in WHtR index in GG genotype were observed (table 6). In the analysis by genotype only in the group of normotensive subjects, pressure blood systolic was significant higher in carries of AA genotype than AG and GG genotypes ($F=3.30$, $p=0.038$), and when we analyzed only hypertensive patients group, the leptin levels were significantly higher in GG genotype ($F=5.80$, $p=0.004$) than other genotypes. No association of rs1137101 polymorphism with MS was found.

Several studies have reported different results in regarding to association of rs1137101 LepR polymorphism with BMI and leptin level. While, in non-obese postmenopausal and obese women the carries of A allele (A homozygotes and heterozygotes) were associated with a higher BMI and with higher circulating levels of leptin than the other genotypes (Quinton et al., 2001;

Vol.9, No. 02; 2025

ISSN: 2581-3366

Ben et al., 2009), in Sri Lankans population the G variant was associated with higher BMI and waist circumference than A variant, conferring greater risk of adiposity (Illangasekera et al., 2020), and in morbidly obese Mexicans the rs1137101 was not a risk factor to development disease (Rojano-Rodríguez et al., 2016). By contrast, the Gln/Gln and Gln/Arg genotypes had higher heart sympathetic activity, body fat percentage, and leptin levels in Mexican adolescents with obesity (Guizar-Mendoza et al., 2005). In our work, the carriers of the AA and AG genotypes of rs1137101 polymorphism showed higher systolic and diastolic pressure as previously reports (Fan et al., 2014; Gu et al ., 2012; Lian et al 2015). In Northern Han population have documented the association of rs1137101 G allele with hypertension (Liu et añ., 2014), however, in Brazilian population the rs1137101 polymorphism was not associated with hypertension (Pena et al., 2014). We do not find differences in leptin concentrations among normotensive and hypertensive subjects. However, when compare the serum leptin concentrations among the rs1137101 genotypes, the carriers of GG genotype showed higher circulating levels of leptin than the other genotypes. Confirmed this finding in only the hypertensive group with the GG genotype had circulating levels of leptin significantly higher than other genotypes. Instead, in the carries of AA and AG genotypes higher circulating levels of leptin were found in postmenopausal Caucasian women, Tunisian obese women, and Chinese population with hypertension (Quinton et al., 2001; Ben et al., 2009; Gu et al., 2012). In treatment-resistant hypertension and controlled hypertensive patients there was no difference in circulating leptin level (de Faria et al., 2017).

The circulating leptin levels were higher in metabolic syndrome subjects than treated-hypertensive subjects and normotensive. However, circulating leptin levels were significantly elevated in treated-hypertensive subjects group with GG genotype, which suggests a relationship among hypertension with leptin levels and with rs1137101 polymorphism. Besides, in the normotensive subjects group we observed that the carries of AA y AG rs1127101 genotypes had high systolic blood pressure than GG genotype. This relationship is not observed in hypertensive patients, since they are hypertensive patients under treatment.

5. Conclusion

Prevalence of MS in treated hypertensive subjects was 51.1% and 67.9% of patients with MS were hypertensive. Our findings show that neck circumference and leptin levels were significantly higher in subjects with MS than in subjects without MS, and that waist height index emerges as other parameters that could be added to the list of criteria since only were significantly higher in MS subjects than treated-hypertensive patients. AA and AG genotypes of rs1137101 polymorphism showed higher systolic and diastolic pressure, and we found higher levels of circulating leptin in treated hypertensive patients carrying the GG genotype.

Limitations

In hypertensive patients, no association was observed with rs1137101 of LepR, probably due to being under treatment.

Vol.9, No. 02; 2025

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Authorship contribution statement: Elva Perez-Luque conceptualized the study design and funding acquisition wrote the manuscript. Monica I. Cardona-Alvarado and Nicté Figueroa-Vega selected of the patients and data collection. Nicté Figueroa-Vega carried out the experiments. Elva Perez-Luque and Mónica I. Cardona-Alvarado carried out data interpretation and statistical analysis, and wrote the manuscript.

All authors reviewed and approved the manuscript and approved the submission of the article.
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Vol.9, No. 02; 2025

ISSN: 2581-3366

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