Metabolic Syndrome components combinations: evidence of asymmetric clustering determined by central obesity and homeostasis model assessment

Combinaciones de los componentes de Síndrome Metabólico: evidencia de agrupación asimétrica determinado por obesidad central y HOMA

Valmore Bermúdez, MD, MPH, PhD1*, Joselyn Rojas, MD, MSc1, Roberto Añez, MD1, Juan Salazar, MD1, Luis Bello, MD1, Alexandra Toledo, MD1, Robys González, BSc1, Vanessa Apruzzese, BSc1, Edgar Miquelena, BSc1, Adriana David, BSc1, Carmen Chávez, BSc1, Maricarmen Chacín, MD1, Clímaco Cano, PharmD1, Manuel Velasco, MD, PhD2, José López-Miranda, MD, PhD3, Mayela Cabrera
1Endocrine and Metabolic Diseases Research Center, The University of Zulia, Maracaibo, Venezuela.
2Central University of Venezuela. Clinical Pharmacology. José María Vargas School of Medicine, Caracas – Venezuela.
3Lipid and Atherosclerosis Unit, Department of Medicine. IMIBIC/Reina Sofia University Hospital/University of Córdoba, and CIBER Fisiopatología Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Spain.
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ABSTRACT

Introduction: Metabolic syndrome (MS) is considered a cluster of metabolic risk factors which have been related with insulin resistance (IR), yet its role in the pathology of the syndrome remains unclear. The purpose of this study is to evaluate the prevalence of MS, the clustering of metabolic components, their relationship with IR and its degree of severity according to possible combinations.

Materials and Methods: this is a cross-sectional study, with 2,230 individual from both sexes randomly selected, which were given a complete medical evaluation, including anthropometric measurements, biochemical analysis and MS diagnosis was done using IDF/NHLBI/AHA-2009. The qualitative variables were expressed as absolute and relative frequencies, using c^2 test for significance and Z tests to assess proportion´ differences. Logistic regression models were calculated for Odds ratio for IR and MS.

Results: The overall prevalence of MS was 42.4%, with 40.4% in women and 44.6% in men, respectively. Several combinations do not present IR and lack abdominal obesity, including Hypertension-Low HDL-Hypertriacilglyceridemia (n=4), Hypertension-Hyperglycemia-Low HDL (n=3), and Hypertension-Hyperglycemia-Low HDL-Hypertriacilglyceridemia (n=3). Elevated waist circumference is observed accompanying metabolic combinations that present IR.

Conclusions: This study reports an alarming prevalence of MS in Maracaibo. When the possible combinations were studied IR is not observed as a common feature. There are several combinations which cluster less, suggesting that a variable such as WC could influence the variability and frequency of the phenotypes and associated IR, rendering central obesity as a mandatory feature in the diagnosis of MS.

Key Words: metabolic syndrome, metabolic risk components, HOMA, insulin resistance.

RESUMEN

Introducción: el Síndrome Metabólico (SM) se considera como una agrupación de factores de riesgo metabólicos los cuales han sido relacionados con insulinorresistencia (IR), sin embargo su rol en el síndrome aún no está claro. El propósito de este estudio fue evaluar la prevalencia de síndrome metabólico, agrupación de los componentes metabólicos, su relación con IR, y grado de severidad de acuerdo a las posibles combinaciones.

Materiales y Métodos: este fue un estudio transversal realizado en 2.230 individuos de ambos sexos seleccionados al azar, los cuales fueron evaluados clínicamente, incluyendo antropometría, y exámenes de laboratorio, para poder utilizar los criterios de la IDF/NHLBI/AHA-2009 para diagnóstico de SM. Las variables cualitativas fueron expresadas como absolutas y relativas, utilizando c2 para significancia y Z test de proporciones. Se aplicaron modelos de regresión logística para calcular Odds ratio para IR y SM.

Resultados: la prevalencia general de SM fue de 42.4%, siendo 40.4% en mujeres y 44.6% en hombres. Varias combinaciones no presentaron IR ni tuvieron obesidad abdominal, incluyendo: Hipertensión-HDL Baja-Hipertriacilgliceridemia (n=4), Hipertensión-Hiperglicemia-HDL Baja (n=3), Hipertensión-Hiperglicemia-HDL Baja-Hipertriacilgliceridemia (n=3). Circunferencia abdominal elevada se observó en combinaciones que tuviesen IR.

Conclusiones: este estudio reporta una alarmante prevalencia de SM en la ciudad de Maracaibo. Cuando se estudiaron las combinaciones posibles, la IR no es una característica común. Hay varias combinaciones las cuales se agrupan en menor frecuencia, sugiriendo que la CA puede influenciar la variabilidad y frecuencia de los fenotipos y asociación con IR, promoviendo entonces la obesidad como una característica mandatoria pata el diagnóstico de SM.

Palabras Clave: síndrome metabólico, componentes metabólicos de riesgo, HOMA, insulinorresistencia.

INTRODUCCIÓN

Metabolic Syndrome (MS) has been defined as a clustering of several cardiovascular risks factors, such as dysglycemia, central adiposity, hypertriacylglyceridemia, low HDL-C and hypertension[1], selected over the years as the definitions of the syndrome evolved. The search for a sole unifying mechanism of disease has been a struggling race for the past 20 years, being insulin resistance the usual established reason[2], yet not all concur with this statement[3].

Clinical presentation of MS depends on several features, including the presence or absence of obesity and its profound ability to modify several metabolic determinants such as low grade inflammation[4]. The recognition and characterization of metabolic phenotypes such as metabolically obese normal weight (MONW) and metabolically healthy obese (MHO) have challenged the canonical way MS, Type 2 Diabetes Mellitus (T2DM) and obesity are interlinked and explain the peculiar presentations of unusual phenotypes[5]. MS is not only heterogeneous in its clinical presentation, but also in the degree of components present in each subject. The latest harmonizing consensus, the IDF/NHLBI/AHA-2009[6] requires the presence of 3 of the 5 proposed components, rendering 16 possible combinations. Contrary to what was considered canon, insulin resistance is not present in all the combinations of the MS, as was published by Karnchanasorn et al.[7] based on their analysis of the NHANES 1999-2000 data using the ATP-III criteria[8] and application of HOMA-IR and HOMA-bcell, where they concluded that insulin resistance is a risk factor for developing MS but not required for its diagnosis; furthermore, this pattern is also observed in the pediatric population as reported by Kurtoglu et al.[9] where IDF/NHLBI/AHA-2009 failed to identify subjects with insulin resistance, and this breach was only bypassed when it specifically investigated.

The purposes of this investigation were to analyze the clustering of metabolic syndrome components and evaluate insulin resistance in each of the combinations with the intention of determining the epidemiological pattern of MS in the subjects enrolled in the Maracaibo City Metabolic Syndrome Prevalence Syndrome (MMSPS)[10].

MATERIALES Y MÉTODOS

Subject Selection

The study was approved by the Ethics Committee of the Endocrine and Metabolic Diseases Research Center, and all participants signed a written consent prior to any involvement. The MMSPS[10] is a cross-sectional study which took place in the city of Maracaibo-Venezuela, with the purpose of identifying and analyzing Metabolic Syndrome and Cardiovascular risk factors in the adult population of the Maracaibo municipality; currently with 2,230 individuals enrolled. Subjects were evaluated using routine medical examination chart provided by the Health and Social Development Ministry of Venezuela as data collecting tool. Socioeconomic status was evaluated with the Graffar Scale modified by Mendez-Castellano[11]. Educational status was obtained during anamnesis, using the question "Do you know how to read and write?", if the answer was No, they were classified as Illiterate. Those who answered yes were given the following question, "What is the last completed educational grade or course?" choosing between: a) primary school, b) secondary school, and c) university/technical education.

Blood Pressure

The assessment of blood pressure was done using a calibrated mercury sphygmomanometer, with the patient previously rested (15 minutes at least) in a sitting position with both feet touching the floor. The arm was posi-

tioned at heart level, and a proper sized cuff used for the procedure. Systolic blood pressure was determined when the first Korotkoff sound is heard, while diastolic blood pressure was determined at the fifth Korotkoff sound. The procedure was realized 3 times, 15 minutes apart, and at least in 2 different days. Blood Pressure classification was completed using the criteria proposed in the VII Joint National committee (JNC-7)[12].

Anthropometric Evaluation

Obesity was classified applying the WHO criteria[13] based on the BMI formula [Weight/Height^2, expressed in kg/m^2]. Weight was assessed using a digital scale (Tanita, TBF-310 GS Body Composition Analyzer, Tokyo – Japan), while Height was obtained with a calibrated rod in millimeters and centimeters; the patients were shoeless and wearing light clothing at all times. Waist Circumference (WC) was measured using calibrated measuring tape in accordance to the anatomical landmarks proposed by the USA National Institutes of Health protocol[14]: midpoint between the lower border of the rib cage and the iliac crest, taking the length at the end of expiration, with participants standing and wearing only undergarments.

Biochemical Analyses

After 8-12 hours of fasting, the following were determined using computer analyzer Human Gesellschaft für Biochemica und Diagnostica mbH, Germany: glucose, cholesterol, triglycerides, VLDL and HDL-C. LDL levels were calculated applying the Fridewald formula only if triglycerides were below 400 mg/dL[15]; if they were above the mentioned cut-off, LDL measure was done using lipoprotein electrophoresis. Insulin was determined using an ELISA double-sandwich method (DRG Instruments GmbH, Germany, Inc). Metabolic Syndrome was diagnosed with the IDF/NHLBI/AHA-2009 consensus criteria[6].

Insulin Sensitivity

This was assessed by Homeostasis Model Assessment (HOMA2-IR) calculator, which is available at http://www.dtu.ox.ac.uk/homacalculator/index.php from the Oxford Centre for Diabetes, Endocrinology and Metabolism (http://www.dtu.ox.ac.uk/); the results were distributed in percentiles and the 75th percentile was chosen as the cut-off for HOMA2-IR based on Reaven's statement in The First Annual World Congress on the Insulin Resistance Syndrome[16]; for our population the 75th percentile for HOMA2-IR equals 2.0.

Statistical Analysis

Normal distribution of continuous variables was evaluated by using Geary's test; variables without normal distribution were logarithmically transformed, achieving normal distribution. For normally distributed quantitative variables the results were expressed as arithmetic mean ± SD (standard deviation), complemented with the Coefficient of Variation (CV) or medians if groups size were very small or didn't have a normal distribution. The differences between them were established using Student's "t" test (when two groups were compared) or ANOVA (when three or more groups were compared) with Tukey's test post-hoc analysis. The qualitative variables were expressed as absolute and relative frequencies, considering the results statistically significant when $p < 0.05$ either in the Z test for Proportions or c^2 test when applied. HOMA2-IR medians according to phenotypes are presented in box plot. Two logistic regression models were calculated; one performed to calculate Odds Ratio (IC95%) for MS adjusted by sex, age and ethnic groups, presence of insulin resistance, personal history of diabetes mellitus, BMI and blood pressure categories, smoking and leisure time physical activity. The second one was for insulin resistance (HOMA2-IR) to obtain Odds Ratio (IC95%) adjusted by sex, age (continuous), and diagnostic criteria for MS; this last variable included subjects with possible diagnostic combinations. The database analysis was done using the Statistical Package for the Social Sciences (SPSS) v. 20 for Windows (IBM Inc. Chicago, IL).

RESULTADOS

General Characteristics of the Population

The overall arithmetic mean for age was 39.3±15.4 years (40.8±15.8 years for women and 37.7±14.8 years for men). Distribution of the population according to Age groups, Ethnic groups, overall BMI and diagnosis of MS according to the IDF/NHLBI/AHA-2009 criteria[9] are shown in Table 1. The most numerous age group was 20-29 years with 581 subjects (26.1%), while most predominant ethnic group was Mixed Race 1,692 individuals (75.9%). According to race, Hispanic Whites and Amerindians showed the higher percentages of MS with 45.5% each. Finally, Extreme Poverty was the socioeconomic group with most cases of MS with 48,6%, followed by Working Class (44.4%) and Middle-High Class (42.4%). In Table 2, the general biochemical and clinical characteristics of the subjects (n=946, 42.4%) with MS are shown. The overall prevalence of MS was 42.4%, with 40.4% in women and 44.6% in men.

Metabolic Syndrome and Cardiovascular Risk Factors

Cardiovascular factors as predictors for MS revealed the following significant odds ratios: Insulin Resistance 1.65 (1.25-2.18; p<0.01), Diabetes Mellitus 9.70 (5.00-18.81; p<0.01), Overweight 2.51 (1.71-3.69; p<0.01), Obesity 4.98 (3.34-7.42, p<0.01), Prehypertension 2.01 (1.46-2.77; p<0.01), Hypertension 5.37 (3.65-7.90; p<0.01), and the rest of the age groups after 30 years of age; see Table 3.

Metabolic Syndrome, Obesity and Insulin Resistance

To evaluate the possible combinations, we analyzed each phenotype combination labeled using the following acronym: C for elevated abdominal circumference; G for elevated fasting glycemia; H for low levels of HDL-C; P for hypertension; and T for elevated triglycerides.

The overall HOMA2-IR median was 1.90 (1.30-2.70), with 2.30 (1.60-3.30) in subjects with MS, and 1.60 (1.20-

2.20) in those without MS. Figure 1-Panel A show the distribution of the sample based on component clustering according to HOMA2-IR with a reference line in a cutpoint of 2.00. As can be observed, the phenotypes PHT, PGHT, PGH, Healthy and CPH have a median HOMA2-IR below the cutpoint, suggesting that an important level of insulin resistance is not observed in all the possible combinations of MS factors. In fact, combinations with normal HOMA2-IR do not have abdominal obesity as part of the phenotype; CPH is just on or barely above the baseline for 2.00, proposing that obesity is responsible for the development of insulin resistance in the combinations. It´s interesting to observe that the phenotype PGT (n=5) obtained the highest HOMA2-IR results, with median of 3.74±2.14; individual analysis of the subjects in this category showed that they were diabetic individuals probably in a catabolic phase which could explain the lack of central obesity.

Mean values for WC in subjects with or without MS were 100.3±16.2 cm vs. 89.9±12.7 cm ($p=8.23x10^{-54}$), which according to sex resulted in 94.8±14.1 cm vs. 87.9±12.6 ($p=1.27x10^{-16}$) respectively for women, and 106.4±16.2 cm vs. 92.2±12.3 cm ($p=2.17x10^{-46}$) respectively in men. Distributions of Women (Figure 1-Panel B) and Men (Figure 1-Panel C) according to combinations and HOMA2-IR per phenotype conclude that as insulin resistance worsens central obesity is increased, except in the PGT group.

Metabolic Syndrome Phenotypes and Insulin Resistance interactions

With HOMA2-IR <2.00 the most prevalent combination in Men was CPG (1.3%), while in Women it was CPH (5.1%). In the Insulin Resistance group, CPHT was prevalent in Men (4.3%), while CH was in Women (3.3%). Table 4 depicts the odds ratios obtained after analyzing the risk offered by the component´s combinations in the development of Insulin Resistance. Figure 2 shows the prevalence of metabolic combinations, observing an interesting pattern where those phenotypes without abdominal obesity are the least common with prevalences below 1%, whereas, those with this variables show intermediate or high prevalence, ranging from 2.01% to 16.91%. In regards to sex, women tended to present more high prevalence phenotypes than men (71,5% vs. 62,5%, p<0.05), while in the intermediate prevalence phenotypes this behavior switched being more common in men (32.6% vs. 25.1%, p<0.05).

Table 1 . General characteristics of the population, according to the presence or absence of Metabolic Syndrome. The Maracaibo City Metabolic Syndrome Prevalence Study, 2013

	Without SM (n=1284; 57,6%)	With SM (n=946; 42,4%)	χ2(*p*)*	Z test *p* value**
Age Groups (%)			450.973 (<0.0001)	
< 20	89.4	10.6		<0.05
20-29	82.6	17.4		<0.05
30-39	63.9	36.1		<0.05
40-49	43.3	56.7		<0.05
50-59	35.2	64.8		<0.05
60-69	24.5	75.5		<0.05
≥ 70	25.3	74.7		<0.05
Educational Status (%)			86.465 (<0.0001)	
Iliterate	42.3	57.7		<0.05
Primary School	39.1	60.9		<0.05
High School	66.1	33.9		<0.05
College/Univesity	55.6	44.4		NS
Marital Status (%)			136.491 (<0.0001)	
Single	70.9	29.1		<0.05
Married	47.5	52.5		<0.05
Other	47.0	53.0		<0.05
Smoking (%)			40.914 (<0.0001)	
Non-smokers	50.8	49.2		<0.05
Current smokers	61.8	38.2		<0.05
Ex-smokers	44.8	55.2		<0.05
Diabetes (%)	9.9	90.1	129.399 (<0.0001)	<0.05
Hypertension (%)	18.2	81.8	340.351 (<0.0001)	<0.05
Obesity (%)	33.7	66.3	261.444 (<0.0001)	<0.05
Insulin resistance (%)	42.3	57.7	160.973 (<0.0001)	<0.05

* C^2 test.
** Z test for proportions

Table 2. Clinical and biochemical characteristics in the subjects with Metabolic Syndrome. The Maracaibo City Metabolic Syndrome Prevalence Study, 2013

	Without SM (n=1284)				With SM (n=946)				*p**
	Mean±SD	p25	p50	p75	Mean±SD	p25	p50	p75	
Age (years)	33.4±13.6	22.0	30.0	43.0	47.4±13.9	38.0	47.0	56.0	$9.63x10^{-123}$
BMI (Kg/m^2)	26.2±5.4	22.5	25.4	28.9	31.3±6.1	26.9	30.4	34.4	$1.12x10^{-97}$
Waist Circumference (cm)	88.4±13.1	79.0	87.0	96.0	102.9±14.2	93.0	101.0	110.0	$7.05x10^{-131}$
HOMA2-IR	1.84±1.10	1.20	1.60	2.20	2.70±1.63	1.60	2.30	3.30	$1.86x10^{-45}$
Insulin (µU/ml)	12.6±7.9	7.8	10.8	14.9	17.5±10.9	10.7	14.9	21.4	$7.52x10^{-34}$
Glycemia (mg/dL)	89.7±16.0	82.0	89.0	95.0	110.7±42.3	91.0	100.0	111.0	$3.74x10^{-64}$
Triacilglycerids (mg/dL)	88.2±46.9	56.0	80.5	109.6	186.9±126.6	112.0	163.0	221.0	$1.28x10^{-184}$
Total Cholesterol (mg/dL)	179.9±40.3	151.0	176.0	203.0	205.5±48.9	173.1	201.0	231.0	$2.34x10^{-40}$
HDL-C (mg/dL)	48.2±12.4	40.0	46.0	54.0	38.5±8.9	32.0	38.0	44.0	$2.52x10^{-93}$
LDL-C (mg/dL)	113.9±36.1	88.4	110.4	134.4	130.6±39.4	105.0	127.8	154.4	$5.00x10^{-20}$
SBP (mmHg)	113.6±13.8	106.5	110.0	120.0	127.9±17.1	117.0	130.0	140.0	$5.06x10^{-96}$
DBP (mmHg)	73.4±9.6	70.0	70.0	80.0	82.5±11.2	75.0	80.0	90.0	$7.84x10^{-88}$

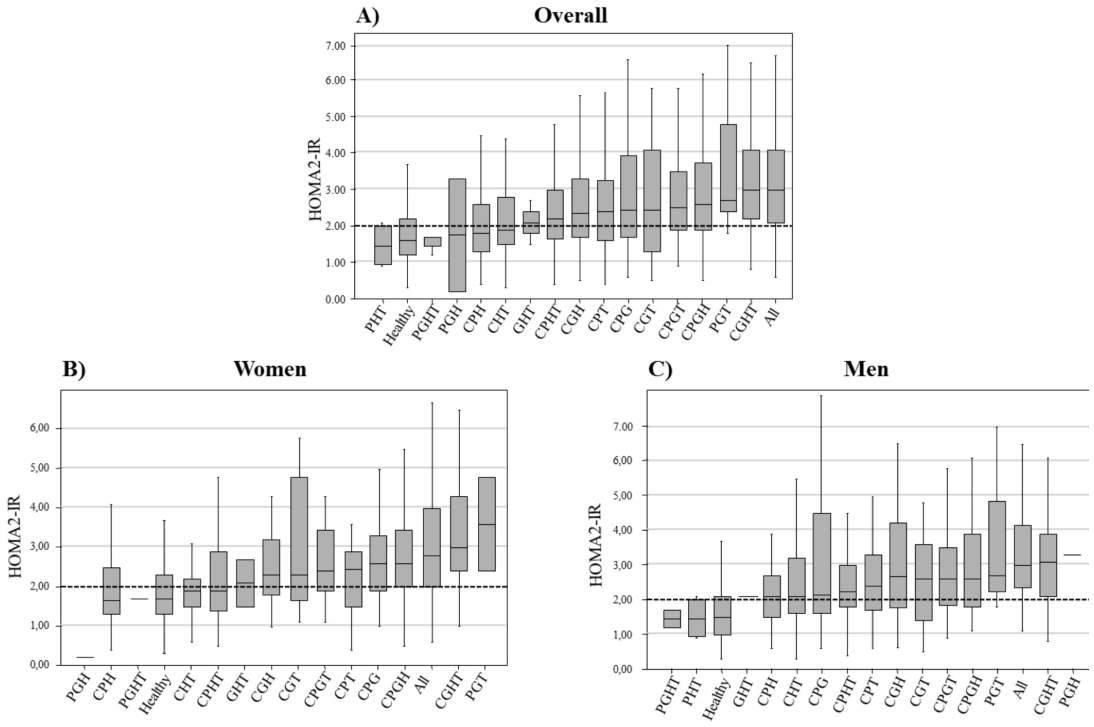
* t Student Test between gender (after log transformation).
BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

Table 3. Logistic regression models of risk factors for Metabolic Syndrome. The Maracaibo City Metabolic Syndrome Prevalence Study, 2013

	Odds Ratio (IC 95%[a])	*p*[b]	Adjusted Odds Ratio[c] (IC 95%)	*p*
Age Groups (years)				
< 20	1.00	-	1.00	-
20-29	1.77 (1.05 - 2.98)	0.03	1.07 (0.49 - 2.33)	0.86
30-39	4.79 (2.85 - 8.04)	< 0.01	2.23 (1.02 - 4.87)	0.04
40-49	11.16 (6.70 -18.56)	< 0.01	3.39 (1.55 - 7.42)	< 0.01
50-59	15.58 (9.25 - 26.24)	< 0.01	5.16 (2.31 - 11.53)	< 0.01
60-69	26.06 (14.38 - 47.21)	< 0.01	5.40 (2.26 - 12.92)	< 0.01
≥ 70	24.99 (12.47 - 50.10)	< 0.01	3.77 (1.32 - 10.80)	0.01
Insulin resistance[d]				
Absent	1.00	-	1.00	-
Present	3.21 (2.67 - 3.86)	< 0.01	1.65 (1.25 - 2.18)	< 0.01
Diabetes mellitus				
Absent	1.00	-	1.00	-
Present	23.08 (12.88 - 41.36)	< 0.01	9.70 (5.00 -18.81)	< 0.01
BMI (kg/m^2)				
< 24.9	1.00	-	1.00	-
25-29.9	3.97 (3.10 - 5.09)	< 0.01	2.51 (1.71 - 3.69)	< 0.01
≥ 30	10.30 (7.99 - 13.26)	< 0.01	4.98 (3.34 - 7.42)	< 0.01
BloodPressure				
Normal	1.00	-	1.00	-
Pre-hypertensive	2.92 (2.36 - 3.61)	< 0.01	2.01 (1.46 - 2.77)	< 0.01
Hypertensive	13.22 (10.15 - 17.23)	< 0.01	5.37 (3.65 - 7.90)	< 0.01

a Confidence Interval (95%); **b** Level of Significance.
c Adjusted by: Gender, ethnic groups, presence of insulin resistance, personal history of diabetes mellitus , BMI categories, blood pressure, smoking habit, physical activity during leisure time.
d Calculated using HOMA2-IR formula, cut-off: ≥2.

Figure 1. HOMA2-IR median for any possible combination of Metabolic Syndrome criteria. Panel A depicts the overall population. Panel B represents the Women`s group while Panel C the Men`s. The HOMA2-IR cutpoint is 2.00.



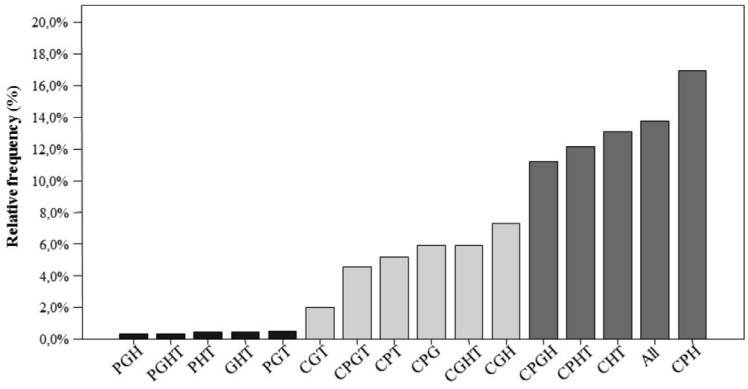
C = Elevated Waist Circumference; G = Elevated Fasting Glycemia; H = Low HDL-C; P = Elevated Arterial Blood Pressure; T = Elevate Triacilglyceride levels; Healthy = subjects without MS diagnosis; All = Individuals with all 5 components of MS. HOMA2-IR cutpoint ≥ 2.00.

Table 4. Logistic regression models of risk factors for Insulin resistance. The Maracaibo City Metabolic Syndrome Prevalence Study, 2013

MS criteria	Odds Ratio crudo (IC 95%[a])	p[b]	Adjusted Odds Ratio[c] (IC 95%)	p
Healthy	1.00	-	1.00	-
Abdominal circumference (C)†	2.23 (1.44 - 3.46)	< 0.01	2.59 (1.66 - 4.05)	< 0.01
Blood pressure (P)†	0.94 (0.33 - 2.63)	N/S	1.20 (0.42 - 3.42)	N/S
Glycemia (G)†	3.37 (1.45 - 7.83)	< 0.01	3.32 (1.43 - 7.75)	< 0.01
HDL-C (H)†	1.23 (0.73 - 2.08)	N/S	1.22 (0.72 - 2.06)	N/S
Triglycerides (T)†	1.96 (0.64 - 6.06)	N/S	2.21 (0.71 - 6.85)	N/S
C-P	2.35 (1.41 - 3.91)	< 0.01	3.51 (2.05 - 6.02)	< 0.01
C-G	4.87 (2.60 - 9.13)	< 0.01	6.61 (3.46 - 12.61)	< 0.01
C-H	2.97 (1.95 - 4.52)	< 0.01	3.31 (2.16 - 5.09)	< 0.01
C-T	2.72 (1.09 - 6.80)	0.03	3.50 (1.38 - 8.84)	< 0.01
P-G	0.65 (0.14 - 3.04)	N/S	0.93 (0.20 - 4.41)	N/S
P-H	1.31 (0.45 – 3.81)	N/S	1.47 (0.50 - 4.32)	N/S
G-H	4.80 (1.87 - 12.35)	< 0.01	5.48 (2.10 - 14.27)	< 0.01
G-T	0.98 (0.11 - 9.02)	N/S	1.39 (0.15 - 13.10)	N/S
H-T	2.75 (0.99 - 7.66)	0.05	2.91 (1.04 - 8.16)	0.04
C-P-G	6.82 (3.52 - 13.20)	< 0.01	11.72 (5.80 - 23.67)	< 0.01
C-P-H	3.09 (1.92 - 4.98)	< 0.01	4.55 (2.74 - 7.54)	< 0.01
C-P-T	6.63 (3.27 - 13.44)	< 0.01	10.06 (4.83 - 20.92)	< 0.01
C-G-H	7.67 (4.09 - 14.36)	< 0.01	10.06 (5.29 - 19.14)	< 0.01
C-G-T	6.17 (2.25 - 16.90)	< 0.01	9.09 (3.26 - 25.33)	< 0.01
C-H-T	3.79 (2.28 - 6.29)	< 0.01	4.94 (2.93 - 8.32)	< 0.01
P-G-H	3.93 (0.24 - 64.12)	N/S	5.27 (0.31 - 88.78)	N/S
P-G-T	15.71 (1.71 - 144.33)	0.02	27.14 (2.88 - 255.62)	< 0.01
G-H-T	7.85 (0.70 - 88.75)	N/S	8.68 (0.76 - 99.45)	N/S
P-H-T	1.31 (0.13 - 12.91)	N/S	1.81 (0.18 - 18.25)	N/S
C-P-G-H	10.47 (5.98 - 18.33)	< 0.01	17.51 (9.58 - 31.98)	< 0.01
C-P-G-T	8.13 (3.94 - 16.78)	< 0.01	13.90 (6.49 - 29.79)	< 0.01
C-P-H-T	6.03 (3.58 - 10.16)	< 0.01	9.08 (5.23 - 15.76)	< 0.01
P-G-H-T	1.00 (0.80 - 1.25)	N/S	1.00 (0.90 - 1.10)	N/S
C-G-H-T	24.68 (10.36 - 58.81)	< 0.01	36.17 (14.90 - 87.77)	< 0.01
All the criterions	15.55 (8.91 - 27.14)	< 0.01	26.86 (14.67 - 49.21)	< 0.01

a Confidence Interval (95%); **b** Level of significance.
c Adjusted by: Gender, age (continuos), and MS criteria.
† According to the IDF/NHLBI/AHA-2009
N/S=Not significant

Figure 2. Overall prevalence of metabolic phenotypes



	Low frequency combinations		Intermediate frequency combinations		High frequency combinations	
	n	%	n	%	n	%
Women	15	3,2%	119	25,1%	340	71,7%
Men	23	4,9%	154	32,6%	295	62,5%

Significative statistical diferences (p<0,05 between groups fot both males and females in z test proportions)

DISCUSIÓN

Insulin resistance is considered to be the metabolic background for several entities such as T2DM[4]. Even though this disorder has been suggested as the foundation for MS, current definition criteria doesn´t support this proof-of-concept. Karnchanasorn et al.[7], reported that insulin resistance is a risk factor for MS in all ethnic groups (OR 4.17; IC95: 4.17-12.01), yet it is neither necessary nor required to make a diagnosis of this syndrome. In this light, MS cannot be regarded as a predictor of insulin resistance and vice versa, such as stated by Kurtoglu et al.[9] whose study concluded that MS fails to detect subjects with insulin resistance. Such failure to detect insulin resistant overweight and obese subjects applies even when using different criteria models for MS diagnosis[17].

In this study, the results are in agreement with the changing points of view concerning insulin resistance and metabolic risk factors[7,9]. Even though, insulin resistance was observed in 57.7% of the subjects with MS, it is not an absolute variable within this population, especially when 42.3% of subjects without MS have insulin resistance. In the combinations of 3 or more components for MS[6], HOMA2-IR rises as elevated abdominal circumference becomes positive, confirming that central obesity is a predictor of insulin resistance in MS. In fact, 80% of the combinations for MS that bear increased WC have insulin resistance, compared to those that have elevated fasting glucose (55.0%), low HDL-C (50.0%), hypertriglyceridemia (50.0%) and hypertension (45.0%). On the contrary, the combinations that lack abdominal obesity have HOMA2-IR median below de cutoff point: PG, PH, GT, PGH, GHT, PGHT, and individual risk factors like P, H and T.

As can be observed in the results of this study, there seem to be several "types" of MS according to which components are clustered, offering different degrees of cardiovascular and metabolic risk[18]. Every MS variant appears to have diverse HOMA2-IR, combinations and very distinctive prevalences, implying that simple clustering by chance is not at work in the developing of such phenotypes. In fact, the results demonstrate that central obesity is the most important clustering factor, which would explain the metabolic unbalance concerning insulin network and visceral adiposity[19]. Therefore we propose that there seem to be –at least – 2 types of MS, one which conveys the metabolically sick obese individual (obese MS) and another in which the other components aggregate but in a very low frequency (non-obese MS).

Each component offers a degree of risk, which would explain the differences observed in different populations, such as reported by Kim et al.[20] where elevated fasting glucose is a better predictor of coronary artery disease severity. In our case, obesity was the most prevalent component as an individual factor (10,8%, n=240) or as part of the phenotypes. In fact, other studies have suggested that WC is a good indicator for metabolic risk and insulin resistance[21], including the results by Jennings et al.[22] which concluded that WC is a better predictor of HOMA-IR in women compared to ATP-III[9] or IDF/NHLBI/AHA-2009 criteria[6], suggesting that WC should be vastly applied in public health screening strategies after establishing a proper population specific cut-off point.

If WC is able to predict the presence of insulin resistance, then its occurrence should be mandatory during the diagnosis of MS, as was proposed by the International Diabetes Federation back in 2005[23], when central obesity was an invariant component. WC is considered a surrogate measure for central obesity and has been associated directly with insulin resistance[24]. The problem regarding WC is what cut-point to use, especially in groups like Hispanics which do not have a properly assigned cut-off point, and in populations like ours that have an overall obesity prevalence of 33.3% and overweight of 34.8%[25]. Indeed, the need for proper WC cutoff point values is of importance when the role of central obesity in the developing of insulin resistance and prediction of MS components come into play.

Finally, it`s important to highlight the interesting frequencies observed regarding the metabolic combinations, as shown in Figure 2. Elevated WC seems to be a pivoting variable when it comes to increasing insulin resistance and prevalence, since phenotypes without abdominal obesity showed frequencies below 1%. Such behavior allows for an impromptu classification of metabolic phenotypes in Low Prevalence (<2%), Intermediate Prevalence (2-10%) and High Prevalence (>10%). As was expresses previously, our population has a high rate of obesity[25], increasing the chance of these intermediate-high prevalence phenotypes to prevail. Whether insulin resistance and MS are associated within these metabolic phenotypes is an ongoing discussion, yet as observed in this study the answer lies in the combination: there are in fact phenotypes that do not present insulin resistance (Figure 1) and they are still currently diagnosed as MS. Future research is needed to properly assess the cardiovascular risk offered by each metabolic component, its interdependency on other issues such as physical activity, and their role in developing insulin resistance.

In conclusion, the present study reports an alarming prevalence of MS of 42.4% in Maracaibo, the second largest city of Venezuela, which is expressed in various combinations of 3 or more positive components, being CPH the most common phenotype. Insulin resistance is not observed in all possible combinations of MS risk factors and is not mandatory for its diagnosis. Nevertheless, WC and abdominal obesity are associated with increasing HOMA2-IR values, which begs the possibility of new definition for MS that would guarantee the presence of central obesity in any MS diagnostic combination.

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Disclosure

The authors have are no conflicts of interest to disclose.

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