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Lipid Accumulation Product (LAP) and Visceral Adiposity Index (VAI) a Simple and Clinically Useful Surrogate Marker for Metabolic Syndrome and Cardiovascular Disease Predictor in Non-diabetic Venezuelan Adults

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Abstract

Objective: To evaluate and compare the relationship between Lipid Accumulation Product (LAP) and Visceral Adiposity index (VAI) with the components of the metabolic syndrome (MetS) in Venezuelan adults.

Methods: Cross-sectional, observational analytical study, comprising 332 individuals selected at the Endocrine Service of the Hospital Militar "Dr Carlos Arvelo". Anthropometry (BMI, WC) and fasting biochemical parameters (TG, HDL-cholesterol) were measured and the LAP and VAI (fats indexes) were estimated. Patients were classified into 3 groups with and without Metabolic Syndrome following the ATPIII criteria and a group with Cardiovascular Disease (CVD).

Results: 73.17% of the individuals were female and 26.82% were male, with 123 (37.04%) individuals without Metabolic Syndrome (non-MetS), 137 (41.27%) with Metabolic Syndrome and 72 (21.68%) with CVD. In the group without Metabolic Syndrome, we found: LAP (6.72 - 26.28) and VAI (0.71 - 1.85), for the group with Metabolic Syndrome: LAP (42.09 - 108.57) and VAI (1.11 - 4.15), with significant differences between groups ($p < 0.005$) and in the CVD group LAP (45.72 - 86.42) and VAI (1.46 – 4.78).

Discussion: the results obtained agreed with studies carried out in different populations and ethnic groups (Asia, Middle East and Latin America), indicating that the LAP index obtained better precision for MetS screening, regardless of gender and BMI, the VAI index was best predictor of Cardiovascular Disease.

Keywords: Fat indexes, Metabolic Syndrome, Cardiovascular Disease, Screening.

Introduction

There has been several definitions of Metabolic syndrome (MetS), but the most commonly used criteria are from the World Health Organization (WHO) [1], the European Group for the study of Insulin Resistance (EGIR) [2], the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) [3], American Association of Clinical Endocrinologists (AACE) [4], the International Diabetes Federation (IDF) [5], and the Asociacion Latinoamericana de Diabetes (ALAD) [6]. In spite of several emerging studies reporting the prevalence of MetS in Venezuela, its estimation remains underestimated due to a variety of definitions used and selection biases in the sample population. In Venezuela, at least 1.7 million people suffer from T2DM, and prediabetes prevalence in the country has been reported in four different regions with the number varying between 1.0% and 18.6% [7-10]. The prevalence of MetS in the Bolivarian Republic of Venezuela has been reported by different studies carried out in different states of the country, however there is no population study in the last 10 years. Flores et al [7], 2005 reported a prevalence of MetS of 31.2% in 3108 subjects of Zulia state; the CARMELA study in 2008 that evaluated the prevalence of cardiovascular risk factors, carotid plaques and carotid intima-media thickness in 11,150 individuals from 7 Latin American cities (Barquisimeto, Venezuela; Bogotá, Colombia; Buenos Aires, Argentina; Lima, Peru; Mexico, Mexico; Quito, Ecuador

and Santiago, Chile) found in Venezuela a prevalence of MetS of 25.8% [10].

Metabolic syndrome is a multifactorial disorder, which are linked to the development of type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular diseases (CVD), involving 5 conditions - high fasting glucose, elevated triglyceride (TG) and arterial pressure levels, increased waist circumference (WC) and low HDL cholesterolemia, if three out of five parameters are altered a MetS can be diagnosed [11].

Out of all the risk factors, obesity and body fat seems to be the predominant underlying risk factor not only in the development of MetS but also other cardiovascular risk factors. Traditionally anthropometric evaluation parameters such as WC and BMI have been used in clinical practice as estimators of obesity; however, BMI does not reflect the distribution of total body fat (TAG), which is an important limitation, since the metabolic complications of obesity have been found to be associated with visceral fat deposits [12,13].

Epidemiological studies have shown that adipose tissue has complex functions, according to its anatomical location, and that the hyperplasia of the same occurs by different mechanisms [14-15]. Imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are considered the gold standard, in the measurement of visceral adiposity, as well as body composition techniques: X-ray absorptiometry (DXA) or plestimography allows for an easier characterization of visceral fat deposits, however, in clinical practice its use is limited because it requires a great technical and economic investment exposing patients to ionizing radiation [16,18].

Recently, indexes of abdominal obesity have also been reported to be better discriminators of cardiovascular and metabolic risk factors than BMI. However, studies from different countries and ethnicities have different conclusions regarding the superiority of the obesity indexes and optimal cutoff points for the diagnose of obesity and hence MetS. Researchers believe that ethnic and racial variation among population from different regions might need different cutoff points and/or use of different anthropometric measurement to diagnose obesity and MetS. In obese individuals, reductions in waist circumference (WC) and total abdominal and visceral adiposity were observed, along with improvements in insulin sensitivity [19,20].In the last decade, new parameters have been developed capable of estimating the presence of obesity and the distribution pattern of adipose tissue, predominantly visceral; such as the lipid accumulation products index (LAP) proposed by Khan [21] in 2005, which is a mathematical model that relates the anthropometric variable WC, with the lipid metabolism (fasting triglycerides). Subsequently, the visceral adiposity index (VAI), described by Amato [22] in 2010, allows discriminating the degree of adipose tissue dysfunction, in this case, in addition to the WC and triglycerides, The BMI and the value of HDL-cholesterol are taken into account.

Measurement of the LAP and VAI (fats indexes) is an alternative approach that is increasingly important, especially in the early detection of MetS [23,24]. Other groups such as Depres [25] reported that WC in combination with fasting triglycerides can be used to identify people with "hypertriglyceridemia-waist phenotype", the results of which are in agreement with other researchers who have demonstrated a strong association between the aforementioned phenotype and the risk of coronary artery disease [26,27].

The published population studies that have used the fats indexes in the early detection of MetS and other cardiovascular risks in individuals distributed according to gender and race (African American, Caucasian, Asian, Hindu) have encouraging results, showing that they are superior to BMI and WC [24,28,29]. In the Venezuelan population, no published studies were available to validate the use of fats indexes; however, it was found that Barrios and Rivero used the Body Adiposity Index (BAI) in 90 patients from the Lara state, concluding that BAI did not represent a reliable index to determine new cases of MetS [30].

Considering the previously described, there is a need to carry out this study, which aims to evaluate and compare the relationship of fats indexes (LAP and VAI) with the components of MetS in patients with or without metabolic syndrome in a population of Venezuelan adult.

Materials and Methods

A cross-sectional observational study was carried out, and the sample was selected from an intentional probabilistic type of the population of patients who come from all states of Venezuela to the Endocrine and Metabolic Diseases Service of the Hospital Militar "Carlos Arvelo" in Caracas, during the years 2013-2015. The inclusion criteria were: female and male patients, aged between 30 and 70 years, who previously authorized informed consent to be part of the study. The study was carried out in accordance with the Helsiski (2010) statement and the guidelines of good medical practice. Exclusion criteria for the three groups were: (1) endocrinopathies including cushing's syndrome, acromegaly and thyroid diseases; (2) chronic renal disease in advanced stages; (3) patients with prolonged steroid use; (4) patients pregnant or in puerperium mediate and (5) patients with chronic liver diseases.

Inclusion criteria of the group without metabolic syndrome (control): patients between 30 and 70 years old and who did not present more than two criteria for Metabolic Syndrome established in the ATPIII (19). Group with Metabolic Syndrome (MetS): patients between 30 and 70 years old and who presented three or more criteria for Metabolic Syndrome established in the ATPIII except the WC, which was taken as reference to the Latin American population by GLESMO [31] 90 cm for Female sex and 94 cm male sex. Group with cardiovascular event (CVD): Patients between 30 and 70 years old and who presented the TIMI score criteria [20] for acute coronary syndrome during the

first three months of the event, nor did they present the diagnosis of T2DM.

Each patient was interviewed about identification data and pathological personal history. Vital signs and anthropometric measurements were determined: weight (kg), height (m), waist circumference (WC). Measurements of fasting biochemical parameters were performed: glycaemia, triglycerides, HDL-cholesterol and uric acid by enzymatic colorimetric method (Randox); The insulin by electrochemiluminescence (DiaSorin) and LDL-cholesterol (Friedewald's formula) and HOMA according to the formula: fasting glucose (mmol/L) for fasting insulin (mU/mL) between 22.5. Patients were classified according to BMI in normal weight, overweight and obesity; they were also distributed according to sex.

The LAP, BAI and VAI indices were estimated according to the following formulas:

$$\text{LAP Male} = (WC - 65)\, x\, TRG$$

$$\text{LAP Female} = (WC - 58)\, x\, TRG$$

$$\text{VAI Male} = \frac{WC}{39{,}68 + (1{,}88\, x\, BMI)}\, x\, \frac{TRG}{1{,}03}\, x\, \frac{1{,}31}{HDL}$$

$$\text{VAI Female} = \frac{WC}{36{,}58 + (1{,}89\, x\, BMI)}\, x\, \frac{TRG}{0{,}81}\, x\, \frac{1{,}52}{HDL}$$

Where WC is in cm, TRG and HDL in mmol/L, BMI in kg/m^2.

Statistical analysis

Data were analyzed using the software SPSS ver 22.0. The mean (arithmetic mean) and the standard deviation of the quantitative variables were calculated. Pearson's correlation, scatter plots and linear regression were used to evaluate the possible association between the independent variable and the dependent variables, ROC curve was made of value of LAP or BAI with the absence or presence of MetS. To establish the statistical significance of the Kruskal-Wallis H test for independent groups, with a Significant value of contrast if $p < 0.05$.

Results

The samples of Controls were made up of 123 individuals between the ages of 32 and 63 years with an average of 47 years, where 73.17% were female and 26.82% were male. The group of individuals with MetS was comprised of 137 individuals aged between 30 and 60 years with an average of 44.8 years, where 53.28% were female and 46.71% were male. The CVD group consisted of 72 individuals aged 49.8 to 70 years with an average of 59.6 years, where 55.55% were male and 44.44% were female.

The values of registered BMI ranged from 19.6 to 24.2 kg / m^2 in Control subjects, from 23.2 to 35.6 kg / m^2 in the MetS group and from 23.4 to 30.8 kg / m^2 in the group, obtaining a significant difference between them ($p = 0.000$).

Waist circumference was found between 68.44 and 83.40 cm. in the Control group, between 84.29 and 116.31 cm. For the MetS group, and between 85.12 and 111.74 cm, making a significant difference ($p = 0.027$).

The values of the lipid accumulation (LAP) products for male individuals in Control group were found between 13.9 and 21.7 and for individuals of female sex between 10.6 and 21.27; In the MetS group, the male individuals were between 59.79 and 112.19 and between 41.29 and 87.69 for the female sex, in the CDV group the male individuals were between 59.4 and 101.13 and between 45.47 and 68.47 for the female sex.

The values of the visceral adiposity index (VAI) for Control males were found to be between 1.04 and 1.44 and for females between 0.89 and 1.69; In the MetS group, the male individuals were between 1.07 and 4.17 and between 0.88 and 4.48 for the female sex, in the ECV group the male individuals were between 2.55 and 3.95 and between 2.54 and 3.54 for the female sex.

The values of the body adiposity index (VAI) for Control individuals were found between 14.44 and 22.25; In the group with MetS between 21.0 and 35.67; In the ECV group between 23.35 and 35.14.

Discussion

The progressive accumulation of lipids, particularly in the abdominal region, is characterized by increased insulin resistance (IR). It is reasonable to argue that the LAP and VAI indices might be able to reflect not only visceral fat deposits, but also increases of the lipolytic activity within this compartment of adipose tissue, and this is the genesis of the lipid, glucose, anthropometric and hemodynamic alterations that characterize MetS [32,33].

It is now widely recognized that increased adiposity is the most important criterion out of the five that characterizes MetS, because this measure is the nucleus of the rest of the alterations [34]. However, visceral adipose tissue has a higher rate of lipolysis and therefore produces more adipocytokines, such as interleukin-6 (IL-6) and plasminogen activator inhibitor-120 (PAI-1). Several studies have suggested that visceral adiposity is validated for the prediction of MetS [12,13,15,16,24,31].

The LAP index in different scientific studies has shown great precision to identify alterations in glucose metabolism [24,35]; similarly, in the third National Health and Nutrition Survey Program (NHANES III), LAP showed a greater association with T2DM, when compared to BMI [36]. This indicates the importance of including in practice for the screening of cardiometabolic risk, indicators that estimate visceral adiposity in an easy and economical way.

In the present study, it was possible to determine a relationship between LAP and VAI with cardiometabolic risk in patients without and with MS, with statistically significant ($p < 0.005$) between the groups, regardless of gender and BMI (Table 2). Those results are consistent with the study published by Hoshi et al [24] in 2016, who found that the application of three indices (LAP, VAI and TG / HDL) are tools that have an accuracy comparable to the criteria of ATPIII [8], screening Of MetS in a rural population of India, where the LAP index was the

Table 1: Clinical data and clinical laboratory results expressed as the mean ± standard deviation for the different (Control, MetS and CVD) groups

		Control	MetS	CVD	P
N		123	137	72	0.000
Sex	**M**	33	64	40	0.000
F	90	73	32		
Age (years)		47.4 ± 15.3	44.8 ± 14.5	59.6 ± 10.9	0.000
Weight (kg)		59.0 ± 8.1	80.9 ± 22.4	77.8 ± 15.9	0.000
Height (m)		1.64 ± 0.08	1.66 ± 0.10	1.65 ± 0.09	0.329
BMI		21.9 ± 2.3	29.2 ± 6.4	28.6 ± 5.2	0.000
WC (cm)	**M**	81.52 ± 14.7	105.01 ± 25.5	104.38 ± 20.8	0.000
F	74.17 ± 21.4	96.16 ± 25.7	93.80 ± 16.8		
PAS (mmHg)		112,55 ± 16,36	125,73 ± 13,64	131,23 ± 14,78	0.000
PAD (mmHg)		73.44 ± 12.02	82.10 ± 11.12	79.85 ± 10.86	0.000
Glucose (mg/dL)		82.01 ± 9.94	94.71 ± 22.69	100.04 ± 17.90	0.000
Cholesterol (mg/dL)		167.71 ± 35.85	197.04 ± 40.24	164.68 ± 42.26	0.000
HDL (mg/dL)	**M**	45.15 ± 8.2	42.06 ± 10.7	35.02 ± 5.6	0.000
	F	55.07 ± 16.3	48.64 ± 13.2	39.875 ± 5.3	
LDL (mg/dL)		94.45 ± 34.21	117.72 ± 43.09	96.97 ± 26.53	0.000
No-HDL (mg/dL)		115.30 ± 40.09	151.47 ± 55.15	127.50 ± 39.73	0.000
Triglycerides (mg/dL)		89.24 ± 33.4	168.8 ± 97.69	156.94 ± 77.10	0.000
Uric Ac. (mg/dL)		4.34 ± 2.89	8.81 ± 15.7	6.02 ± 2.3	0.000
Insuline (µUI/mL)		7.85 ± 4.27	15.55 ± 10.52	14.87 ± 7.71	0.000
HOMA		1.61 ± 0.51	3.67 ± 2.89	3.56 ± 0.80	0.000

Significant differences were obtained between the groups using the Kruskal-Wallis H test

Table 2: Values for BMI, LAP and VAI discriminated by sex, expressed as the mean ± standard deviation, for the different experimental groups Control, MetS and CVD

	Control		MetS		CVD	
	M	F	M	F	M	F
N	33	90	64	73	40	32
BMI	22.21 ± 14.0	21.92 ± 6.3	30.41 ± 15.8	28.19 ± 14.7	28.20 ± 5.6	29.30 ± 5.3
LAP (cm.mmol.L)	17.80 ± 3.9	15.97 ± 5.3	85.99 ± 26.2	65,99 ± 21.7	80.23 ± 20.9	56.97 ± 11.5
VAI	1.24 ± 0.2	1.29 ± 0.4	2.62 ± 1.55	2.68 ± 1.8	3.25 ± 0.7	3.04 ± 0.5

Significant differences were obtained between the groups using the Kruskal-Wallis H test

most accurate, followed by the VAI and TG / HDL indices, in discriminating the MetS, for this population.

In this sense, several studies have used the LAP index as a subrogate marker to discriminate insulin resistance, and this index was validated in women with polycystic ovary syndrome (PCOS) and menopause, observing a perfect positive correlation between the LAP and HOMA-IR [37,38] corresponding to the results obtained in this study, a statistically significant correlation between the LAP and VAI with HOMA was also observed (Figure 1 and Figure 2). An assay published by Taverna et al [39] in healthy Argentine males, LAP showed an area under the highest curve even than other IR variables, such as HOMA-IR and QUICKI, whereby LAP has been associated with lipolysis of visceral compartment, which is considered by De Fronzo to be the beginning of the cascade of changes that characterize the pathophysiology of IR [40].

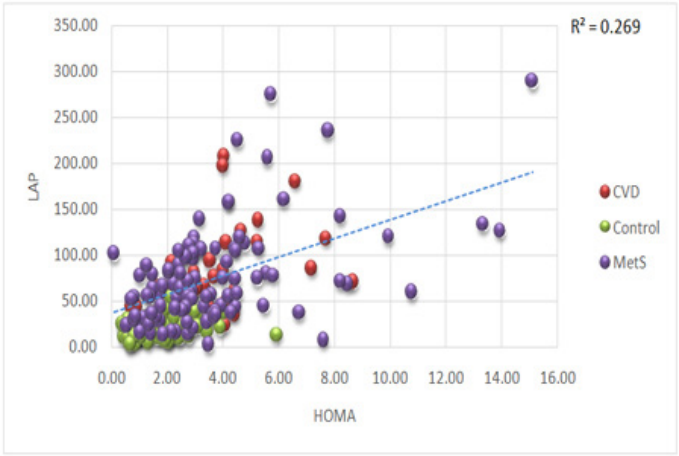

Figure 1: Relation between insulin resistance (HOMA-IR) and the Lipid Acumulation Products (LAP)

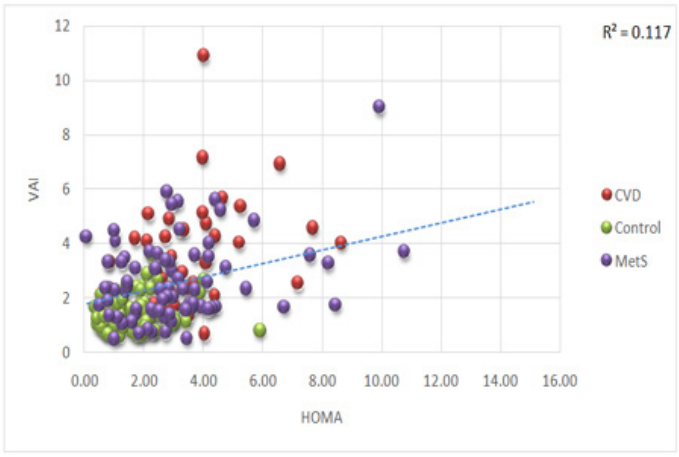

Figure 2: Relation between the insulin resistance (HOMA-IR) and the visceral adiposity index (VAI)

By evaluating individually, the components of the MetS, the VAI and LAP indexes were correlated with better precision with the value of WC and triglycerides; To measure the risk of MetS (Figure 3, Figure 4, Figure 5 and Figure 6). This is explained by the fact that the variables that make up the VAI and LAP are included in the criteria for MetS. Interestingly, in our study, when distributing VAI and LAP indices according to sex (Table 2) was found in the groups (Control, MetS) the LAP index was found to be more increased in males, whereas VAI was observed higher in the female of the MetS group. Although explanations for this observation have not yet been elucidated, it is likely to be related to differences in the regional distribution of adipose tissue by sex as well as patterns of visceral fat deposition. In addition, in fact, men have, on average, more visceral fat and less subcutaneous fat [39].

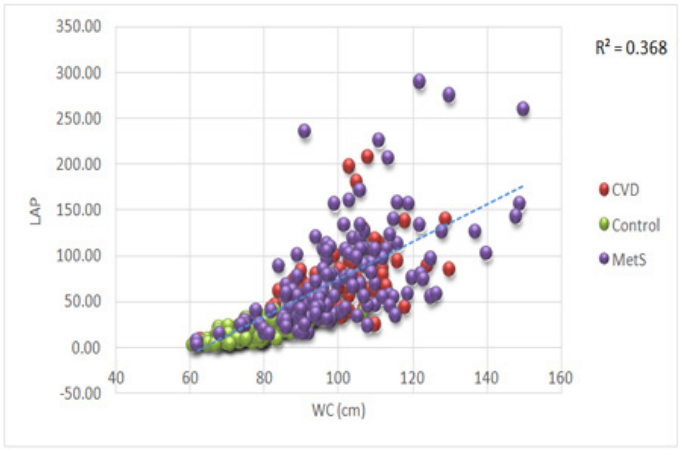

Figure 3: Relation between the waist circumference (WC) and the lipid accumulation products (LAP)

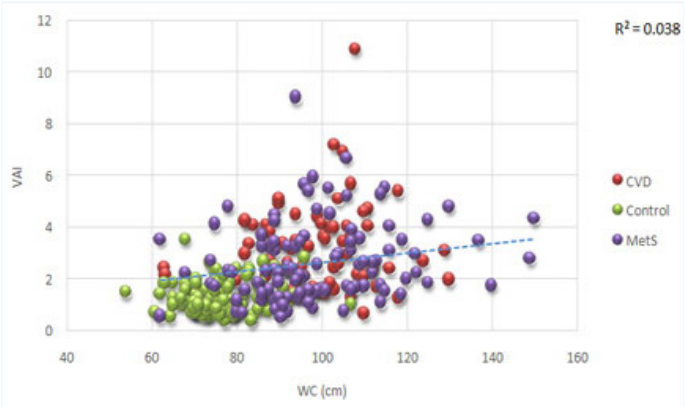

Figure 4: Relation between the waist circumference (WC) and visceral adiposity index (VAI)

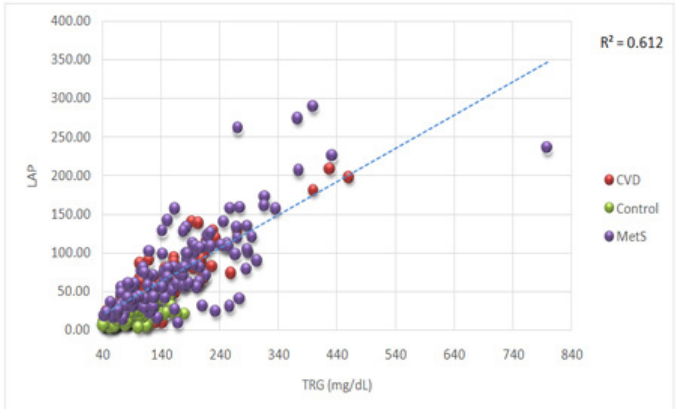

Figure 5: Relation between triglyceride (TRG) and lipid accumulation products (LAP)

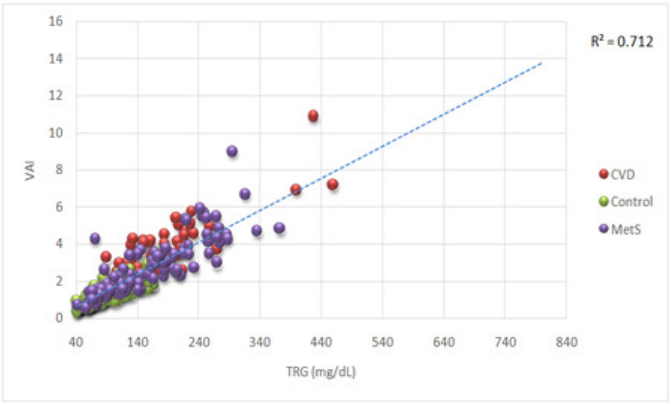

Figure 6: Relation between triglyceride (TRG) and visceral adiposity index (VAI)

In our results, the LAP index was the parameter with the highest sensitivity discriminating individuals with and without MetS in the ROC curve, with AUC 0.9489 (Figure 7 and Figure 8), which is consistent with several population studies conducted in individuals from China [41,42] and Iran, which showed the same conclusions [29], similarly to Abruzzese et al. [43] in a population of Latin America, found similar results, with similar cutoff points for different populations and ethnic groups.

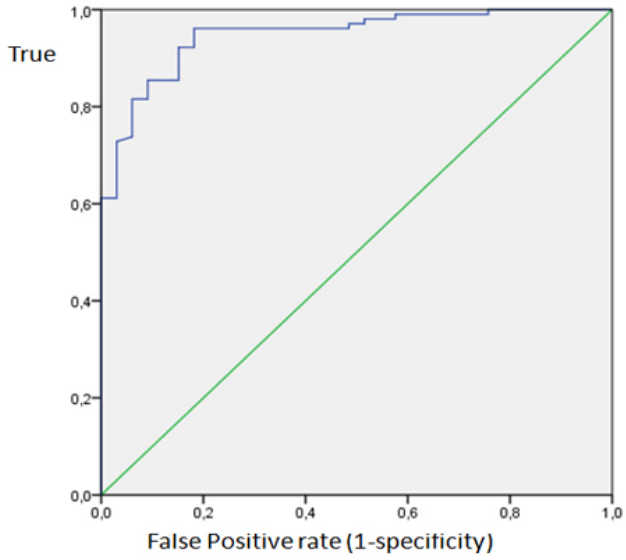

Figure 7: ROC plot for LAP for prediction of MetS

In this study, LAP and VAI were acceptable indicators for MetS screening, however LAP presented a better correlation between WC and triglyceride values, whereas VAI was the index that was worse correlated with the rest of the variables that make up (Table 2). The results of this study suggest that VAI behaves as a good predictor of CVD, as it is found to be significantly higher in the group of patients with CVD (Table 2). And the LAP, in this study behaved as the best predictor for MetS (Table 2). In a study published by Vogel et al [34], performed in patients with CVD, it was evidenced that VAI was associated with all the components of MetS, however, for the MetS screening it was lower than that of LAP in men and women, and found a statistically significant increase in the group of patients with acute myocardial infarction (AMI), findings similar to this study. Considering the fats indexes, they would tend to be indicators of early cardiometabolic risk in all border conditions in which MetS has not been manifested, with special application in subjects and metabolically obese with-normal weight (MONW phenotype) (Table 3), in concordance with the other authors [36].

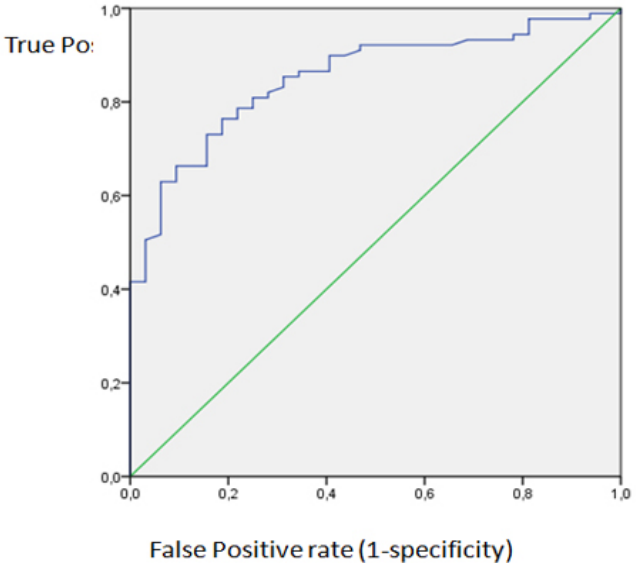

Figure 8: ROC plot for VAI for prediction of MetS

In conclusion, the results obtained from this study suggest that the LAP index obtained better precision for MetS screening in patients without a diagnosis of MetS in both sexes, regardless of BMI; The VAI index, behaves as the best predictor of cardiovascular events in patients with MetS. We recommend the utility of these indices for the screening of insulin resistance and cardiovascular diseases in the Venezuelan population.

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Table 3: Body mass index (BMI), expressed as the mean ± standard deviation, for the different groups, Control, MetS and CVD

	Normal Weight			Over Weight			Obese	
	Control	MetS	CVD	**Control**	**MetS**	**CVD**	**MetS**	**CVD**
LAP	15.74 ± 9.41	34.6 ± 15.0	45.4 ± 24.6	24.14 ± 6.9	55.7 ± 37.0	67.5 ± 49.9	97.5 ± 57.4	78.8 ± 43.7
VAI	1.25 ± 0,66	2.2 ± 0.9	3.2 ± 1	1.35 ± 0.38	2.6 ± 1.7	3.2 ± 1.9	2.8 ± 1.6	3.0 ± 1.8

Significant differences were obtained between the groups using the Kruskal-Wallis H test

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