

UNIVERSIDAD DE CÓRDOBA

Departamento de Medicina

COMPORTAMIENTO CLÍNICO – EPIDEMIOLÓGICO DE LA OBESIDAD EN EL ESTUDIO DE PREVALENCIA DEL SINDROME METABÓLICO DE LA CIUDAD DE MARACAIBO:

INFLUENCIA DE LOS FENOTIPOS METABÓLICOS SOBRE EL PUNTO DE CORTE DE LA CIRCUNFERENCIA ABDOMINAL

Trabajo presentado por Valmore José Bermúdez Pirela, licenciado en Medicina, para optar al grado de Doctor.

Córdoba, 24 de Julio de 2015

TESIS DOCTORAL

TITULO: *Comportamiento clínico- epidemiológico de la obesidad en el estudio de prevalencia del síndrome metabólico de la ciudad de Maracaibo: influencia de los fenotipos metabólicos sobre el punto de corte de la circunferencia abdominal*

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Dirigido por:

Dr. José López Miranda
Catedrático de Medicina
Universidad de Córdoba

Córdoba, 24 de Julio de 2015



TÍTULO DE LA TESIS:

COMPORTAMIENTO CLÍNICO – EPIDEMIOLOGICO DE LA OBESIDAD EN EL ESTUDIO DE PREVALENCIA DEL SINDROME METABÓLICO DE LA CIUDAD DE MARACAIBO: INFLUENCIA DE LOS FENOTIPOS METABÓLICOS SOBRE EL PUNTO DE CORTE DE LA CIRCUNFERENCIA ABDOMINAL

DOCTORANDO: VALMORE JOSÉ BERMÚDEZ PIRELA

INFORME RAZONADO DEL DIRECTOR DE LA TESIS D. JOSÉ LÓPEZ MIRANDA, CATEDRÁTICO DE MEDICINA DE LA UNIVERSIDAD DE CÓRDOBA

HACE CONSTAR:

Que el trabajo titulado “COMPORTAMIENTO CLÍNICO – EPIDEMIOLOGICO DE LA OBESIDAD EN EL ESTUDIO DE PREVALENCIA DEL SINDROME METABÓLICO DE LA CIUDAD DE MARACAIBO: INFLUENCIA DE LOS FENOTIPOS METABÓLICOS SOBRE EL PUNTO DE CORTE DE LA CIRCUNFERENCIA ABDOMINAL” ha sido realizado por D. Valmore José Bermúdez Pirela bajo nuestra dirección, dentro de la línea de investigación de Síndrome Metabólico en el Centro de Investigaciones Endocrino - Metabólicas (CIEM), de la Facultad de Medicina de la Universidad del Zulia, Venezuela. Este trabajo ha conseguido un nivel científico de suficiente relevancia como para derivar en la publicación de tres artículos en revistas internacionales: 1) *American Journal of Therapeutics*, 2010 17(3):288-94, con índice de impacto de 1.1; 2) *PLoS ONE* 7(4): (2012) e35392. doi: 10.1371/journal.pone.0035392, con índice de impacto 3.73 y 3) *Journal of Diabetes Research*, vol. 2015, Article ID 750265, 14 pages, 2015. doi:10.1155/2015/750265, con índice de impacto 2.164 para el momento de su publicación.

A mi juicio reúne los méritos suficientes para ser defendido ante el tribunal correspondiente y poder optar al grado de Doctor.

Por todo ello, se autoriza la presentación de la tesis doctoral.

Córdoba, 30 de Octubre de 2015

Firma del director

Fdo.: Prof. Dr. José López Miranda

“Llegará una época en la que una investigación diligente y prolongada sacará a la luz cosas que hoy están ocultas. La vida de una sola persona, aunque estuviera toda ella dedicada al cielo, sería insuficiente para investigar una materia tan vasta... Por lo tanto, este conocimiento sólo se podrá desarrollar a lo largo de sucesivas edades. Llegará una época en la que nuestros descendientes se asombrarán de que ignoráramos cosas que para ellos son tan claras... Muchos son los descubrimientos reservados para las épocas futuras, cuando se haya borrado el recuerdo de nosotros. Nuestro universo sería una cosa muy limitada si no ofreciera a cada época algo que investigar... La naturaleza no revela sus misterios de una vez para siempre”

LUCIO ANNEO SÉNECA, Cuestiones naturales,

Libro 7, siglo primero

“En algún sitio algo increíble espera ser descubierto.”

“En la Ciencia, la única verdad sagrada, es que no hay verdades sagradas.”

CARL SAGAN

“...comencé investigando esta materia a petición de Náucrato, el geómetra, en la época en la que vino a Alejandría y permaneció conmigo, y, cuando terminé los ocho libros se los entregué en el momento, muy deprisa, porque estaba marchándose por mar; no habían sido revisados, de hecho los escribí de un tirón posponiendo su revisión hasta el final...”

APOLONIO DE PÉRGAMO

Apodado el gran Geómetra

Desafortunadamente no nos ha llegado ningún texto intacto de Eratóstenes. Conocemos su obra por la multitud de fragmentos diseminados en las obras de autores posteriores. Sus contemporáneos, por envidia le llamaron “el beta”, haciendo referencia a que era el segundo mejor en todo. Sin embargo, está claro que Eratóstenes fue Alfa en muchos campos. En sus últimos años, cuando era ya octogenario, se dice que se volvió ciego y que murió por suicidio dejando de comer.....

Sin embargo, Carl Sagan acota que “Eratóstenes no tuvo más herramientas que palos, ojos, pies y cabeza y un gran deseo de experimentar, y que con estas pocas herramientas (y sin salir de Alejandría) dedujo correctamente la circunferencia de la Tierra con una enorme precisión y un porcentaje de error mínimo”.

AGRADECIMIENTOS

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A papá y mamá, grandes brújulas que me han guiado siempre

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A TODOS, mis más profundo y sincero agradecimiento.

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NOTA: Los capítulos que conforman el siguiente documento son artículos que han sido publicados en diferentes revistas de investigación y se presentan en formato JPG. El apartado de referencias bibliográficas contiene aquellas incluidas en la introducción, resultados y discusión

RESUMEN

Introducción y Objetivos: La obesidad es un grave problema de salud pública en la mayoría de las sociedades con estilos de vida occidentalizados. En Venezuela, son pocos los estudios que han abordado la epidemiología de la obesidad y ninguno que haya determinado los puntos de corte de circunferencia abdominal para nuestra localidad. Por esto, el objetivo del presente estudio fue diseñar un estudio clínico-epidemiológico que permitió establecer el comportamiento epidemiológico del SM y sus componentes individuales, incluyendo la obesidad, así como la determinación de los puntos de corte para la circunferencia abdominal.

Resultados: La prevalencia de obesidad según el IMC para ambos sexos y todos los grupos etarios fue del 33,3% (n=701) mientras que la prevalencia de sobrepeso fue del 34,8% (n=733). La prevalencia de obesidad abdominal usando los puntos de corte sugeridos IDF/AHA/NHLBI/IASO/ADA y los sugeridos por el ATPIII fueron del 74,2% y del 51,7% respectivamente.

En relación con el cálculo de los puntos de corte para nuestra población, las mejores variables metabólicas predictivas para la obtención de clústers de individuos sanos metabólicamente ó enfermos fueron en conjunto: HOMA2-IR, HOMA2- β cell y Triacilglicéridos los puntos de corte para circunferencia abdominal tanto para hombres como para mujeres fue de 98,15 cm y 91,5 cm, respectivamente.

Conclusiones: La prevalencia de obesidad en la Ciudad de Maracaibo es elevada, equiparable a la de países como los EUA. Este problema se acentúa si se toma en cuenta el número de individuos con obesidad abdominal según los puntos de corte considerados como clásicos. Sin embargo, dicha prevalencia se reduce drásticamente a un 35% al utilizar los puntos de corte propuestos por este estudio.

ABSTRACT

Introduction and objectives: Obesity is a serious public health problem in most westernized societies. In Venezuela, few studies have addressed the epidemiology of obesity even less those who have undertaken waist circumference cut-off points for our city. In this sense, the objective of this study was to design a clinical-epidemiological trial with multistage random sampling design in order to establish the epidemiological behavior of the MS and its individual components, including obesity, as well as determining the cut-off points for abdominal circumference.

Results: obesity prevalence according to BMI for both sexes and all age groups was 33.3% (n=701) and the overweight prevalence was 34.8% (n=733). The prevalence of abdominal obesity using the cut-offs suggested by IDF/AHA/NHLBI/IASO/ADA-2009 and those suggested by the ATP III were 74.2% and 51.7% respectively.

In relation to WC cutoffs calculation, the best metabolic overall predictors' variables for clusters formation were: HOMA2-IR, HOMA2- β cell and triglycerides (TAG). The cut-off for WC was 98.15 cm and 91.5 cm, for men and women respectively.

Conclusions: The prevalence of obesity according to BMI in the city of Maracaibo is high, comparable to that of countries like the US. This problem is accentuated taking into account the number of individuals with abdominal obesity, since the prevalence individuals with a high-risk waist circumference doubles the number of obese people by diagnosed by BMI. The cut-off points for our population in this study (Male: 98.15 cm and Women: 91.5 cm) is shown to be in an intermediate point between those suggested by the recent harmonization of criteria for SM and those suggested by the ATP III.

INTRODUCCIÓN

1. Epidemiología de la Obesidad: La obesidad como problema de salud pública

La obesidad es un grave problema de salud en el ámbito mundial y su prevalencia sigue incrementándose, incluso en países en vías en desarrollo¹. En Venezuela, la obesidad emerge como un punto de importancia en la agenda de salud particularmente en áreas urbanas donde coexiste con sus comorbilidades clásicas (hipertensión arterial, síndrome metabólico, diabetes mellitus tipo 2 y enfermedad cardiovascular) y paradójicamente, con la desnutrición².

El creciente aumento en la prevalencia de la obesidad y el sobrepeso y su influencia sobre la salud global se ha venido aceptando como un fenómeno pandémico, ya que para el año 2010 ambas condiciones estuvieron involucradas en 3,4 millones de muertes en el ámbito mundial. Datos derivados de estudios realizados en los Estados Unidos de América (EUA) han sugerido que si la prevalencia de obesidad sigue en ascenso podría llevar a una caída importante en la expectativa de vida. De hecho, hay una preocupación casi universal sobre los riesgos asociados a la obesidad, de forma que la Organización Mundial de la Salud (OMS) introdujo una iniciativa para detener el crecimiento de esta condición para el año 2025, recomendando un monitoreo global de los posibles cambios en su prevalencia en todos los países del orbe³.

Lamentablemente -hasta la fecha- la vigilancia de los cambios en la prevalencia de la obesidad y el sobrepeso han dependido en gran parte de la realización de estudios “domésticos” y no de iniciativas a nivel mundial. Peor aún, muchos de los estudios de salud nacionales que se han diseñado para estudiar la prevalencia de obesidad se han llevado a cabo mediante cuestionarios auto-administrados, por lo que el auto-reporte en relación al peso y la talla suele estar sometido a un sesgo importante. En el caso contrario, en aquellos estudios donde se evalúa a los participantes

con personal entrenado se obtiene información directa y veraz del peso y la talla, pero resulta evidente que pocos países tienen la capacidad económica y logística de implantar estudios de este tipo tanto en un diseño transversal como en valoraciones repetidas en función del tiempo⁴.

A pesar de la relativa escasez de información completa sobre la prevalencia de sobrepeso y obesidad en la mayoría de los países del mundo (fuera del ámbito Europeo y Norteamericano), diversos análisis sistemáticos han tratado de evaluar sus niveles y tendencias. Por ejemplo, *Finucane y cols.* utilizaron datos de 369 encuestas nacionales y 591 encuestas sub-nacionales (provenientes de encuestas de salud publicadas y no publicadas) de 199 países con 9 millones de participantes para estimar las tendencias del IMC promedio entre 1980 y 2008 en adultos mayores de 20 años⁵. Estos autores encontraron que entre 1980 y 2008 el IMC promedio estandarizado por edad se incrementó $0,4 \text{ kg/m}^2$ por década para el sexo masculino y $0,5 \text{ kg/m}^2$ por década para el sexo femenino, observándose diferencias sustanciales según el género y la región estudiada. Notablemente las tendencias sub-regionales abarcaron cambios en un rango de $1,4 \text{ Kg/m}^2/\text{década}$ en hombres y $1,9 \text{ kg/m}^2/\text{década}$ en mujeres, observándose que el mayor incremento del IMC para ambos sexos ocurrió en Oceanía. Las regiones con la tendencia más aplanada o incluso con potencial de reducción en la prevalencia de obesidad fueron Europa Central y del Este para las mujeres y África Central y el Sur de Asia para los hombres⁵.

De forma global, el IMC promedio para el año 2008 fue de $23,8 \text{ kg/m}^2$ ($23,6\text{--}24,0 \text{ kg/m}^2$) para hombres y del $24,11 \text{ kg/m}^2$ ($23,9\text{--}24,4 \text{ kg/m}^2$) para las mujeres, observándose que los hombres presentaron un IMC mayor que las mujeres en las subregiones de alto ingreso económico y un IMC menor en la mayoría de las regiones de ingresos medianos a bajos. En conjunto, la prevalencia de la obesidad fue del 9,8% ($9,2\text{--}10,4\%$) en hombres y del 13,8% ($13,1\text{--}14,7\%$) en mujeres para el año 2008, lo cual casi duplica las prevalencias de 1980 $4,8\%$ ($4,0\text{--}5,7\%$) para los hombres y $7,9\%$ ($6,8\text{--}$

9,3%) para las mujeres, de forma que en el 2008 un estimado de 205 millones de hombres (193–217 millones) y 297 millones de mujeres (280–315 millones) mayores de 20 años alrededor del mundo eran obesos y 1,46 billardos de personas (1,41–1,51 billardos) adultas presentaban un IMC igual o mayor a 25 kg/m² representando una prevalencia estandarizada por edad del 34,3% (33,2–35,5%)⁵.

En una revisión sistemática reciente conducida por *Ng M y cols.* realizada sobre encuestas, reportes y estudios publicados (n=1769 estudios) entre 1980 y 2013 que reportaron datos de peso y talla (tanto de recolección directa como auto-reportados) calcularon la prevalencia de obesidad y sobrepeso por sexo, edad, país y año sobre una muestra de 19.244 individuos utilizando regresión lineal de efectos mixtos para corregir los posibles sesgos por el auto-reporte. Estos investigadores encontraron que la proporción de adultos con un IMC mayor de 25 kg/m² se incrementó entre 1980 y 2013 del 28,8% (95% UI 28,4-29,3%) al 36, 9% (36,3-37,4%) en el sexo masculino y del 29,8% (29,3-30,2%) al 38,0% (37,5-38,5%) en mujeres. Igualmente, la prevalencia de estas condiciones aumentó de forma sustancial en niños y adolescentes tanto en los países desarrollados como en aquellos en vías de desarrollo, ya que el 23,8% (22,9-24,7%) de los niños y el 22,6% (21,7-23,6%) de las niñas padecían de obesidad o sobrepeso en los países desarrollados, mientras que del 8 al 12,9% de los niños y del 8,4 al 13,4% de las niñas de los países sub-desarrollados presentan trastornos ponderales por exceso. En adultos, el panorama epidemiológico no resultó ser alentador ya que la proporción de hombres y mujeres con sobrepeso se incrementó del 28,8% (28,4-29,3%) en 1980 a 36,9% (36,3-37,4%) en el 2013 para los hombres, y del 29,8% (29,3-30,2%) al 38,0% (37,5-38,5%) para las mujeres. Estos cambios se han observado tanto en países desarrollados como en vías de desarrollo, aunque con diferencias en relación al sexo: En los países desarrollados los hombres tienden a presentar más obesidad que las mujeres mientras que en los países en vías de desarrollo la obesidad es más prevalente en mujeres que en hombres, recalándose que dicho patrón se ha mantenido en el tiempo⁶.

En relación a la distribución de la obesidad según los grupos etarios se detectaron comportamientos diferentes según el sexo y el grado de desarrollo económico. En los países desarrollados, en individuos del sexo masculino mayores de 10 años pudo observarse un mayor porcentaje de obesidad y sobrepeso que en mujeres. Por el contrario, en los países sub-desarrollados las mujeres presentaron una prevalencia mayor de obesidad en relación a los hombres en edades mayores a los 25 años. En los países desarrollados la prevalencia de obesidad en hombres exhibió un pico alrededor de los 55 años, de forma que de cada tres hombres, dos presentaron sobrepeso y uno de cada 4 fue obeso. En el caso de las mujeres este pico se observó alrededor de los 60 años, con un 31,3% (95% UI 28,9-33,8%) de obesidad y un 33,5% de sobrepeso. En los países en vías de desarrollo la distribución por sexo fue bastante similar (14,4% para las mujeres y 14,4% para los hombres)³. Las tendencias en la prevalencia de obesidad en cohortes sucesivas en países desarrollados y en vías de desarrollo demostraron que ha habido un incremento en el peso para todas las edades, incluyendo niños y adolescentes, con una mayor ganancia de peso en el grupo de los 20 a 40 años. En los países desarrollados el pico de prevalencia de obesidad se está desplazando a edades más jóvenes⁶.

En cuanto a la distribución espacial se observó que la prevalencia de obesidad difiere ampliamente entre los diferentes continentes e incluso entre países del mismo continente. En adultos, la prevalencia excede el 50% en Tonga, Nauru y Papúa-Nueva Guinea para ambos sexos y en Kuwait, Kiribati, Micronesia, Libia, Qatar, Tonga y Samoa en mujeres. Para el año 2013, en los Estados Unidos de Norteamérica (USA) un tercio de los hombres (31,6% [30,0-33,4%]) y las mujeres (33,9% [31,8-35,7%]) eran obesos, mientras que en Centroamérica y Sudamérica 14 países tienen prevalencias de obesidad por encima del 20%. A pesar que se expresó anteriormente que la prevalencia de obesidad se ha incrementado con el tiempo, China y la India se presentan como excepciones importantes, ya que para el año 2013 presentaron prevalencias menores al 5% (China:

3,8% (3,5-4,3%) en hombres y 5,0% (4,5-5,5%) en mujeres; India: 3,7% (3,3-4,1%) para hombres y 4,2% (3,8-4,8%) para mujeres⁶. Este estudio enfatiza que el 50% de los 671 millones de obesos en el mundo viven en 10 países: USA, China, India, Rusia, Brasil, México, Egipto, Alemania, Pakistán e Indonesia. Los USA da cuenta del 13% del total de los individuos obesos, con un 15% para China y la India considerado en conjunto. Por otro lado, a pesar que las prevalencias de obesidad son menores en los países en vías de desarrollo, su elevada densidad poblacional hace que el 62% de los obesos se encuentren en el tercer mundo⁶.

Venezuela no ha escapado de esta realidad ya que han sido pocos los estudios que han puesto en evidencia la magnitud del problema tanto en adultos como niños y adolescentes, la mayoría de ellos de tipo transversal y locales⁷⁻⁹. Más aún, no contamos con datos de prevalencia de obesidad abdominal, ni con estudios que hayan revelado los puntos de corte apropiados para definirla en nuestra población, tal como han sugerido diversas instituciones avocadas al estudio de la obesidad, diabetes y SM como la International Diabetes Federation (IDF)^{10,11}.

Hasta la fecha no se han diseñado estudios prospectivos que investiguen el impacto de los factores de riesgo para obesidad sobre individuos sanos en el contexto de nuestra cultura, trasfondo genético y demográfico, ni tampoco estudios que hayan explorado el comportamiento de la obesidad en un marco secular para todos los grupos etarios. Sin embargo, recientemente el Instituto Nacional de Nutrición ha publicado los primeros datos nacionales sobre el comportamiento epidemiológico de esta condición derivados de un estudio transversal realizado sobre 24.000 individuos de ambos sexos con edad comprendida entre los 7 y 40 años seleccionados con muestreo aleatorio dentro instituciones educativas de nivel primario, secundario y universitario. Este estudio arrojó que en el grupo de 7 a 17 años se registró una prevalencia de sobrepeso de un 14,52% y un 9,56% de obesidad, mientras que en los adultos el 54,95% presentó malnutrición por exceso,

observándose que la prevalencia de sobrepeso fue de 29,52% y 25,43% de obesidad. Es importante destacar que en los estados Barinas, Delta Amacuro y Zulia se observaron cifras de obesidad mórbida que casi duplican las cifras encontradas a nivel nacional¹².

2. Adiposidad total vs obesidad abdominal: La grasa visceral y su vínculo con las enfermedades cardiometabólicas

La composición del cuerpo humano puede ser estudiada desde varios “niveles estructurales”. En el nivel más básico puede realizarse sobre la base de la cuantificación de sus átomos constituyentes: es decir, Carbono, Calcio, Potasio, Hidrógeno, entre otros. En el siguiente nivel – el molecular- se pueden cuantificar la cantidad de agua, proteínas y grasa. A nivel celular, puede medirse el fluido extracelular y la masa celular corporal, y finalmente, ya al nivel tisular puede estudiarse la cantidad y distribución del tejido adiposo, músculo y hueso. Los niveles de composición atómico, molecular y celular pueden estudiarse mediante métodos de análisis directos como la activación de neutrones, la dilución isotópica y el conteo corporal total¹³.

Los métodos de referencia (*Criterion methods*) miden una propiedad del cuerpo fundamentalmente a nivel tisular, como por ejemplo su densidad, o describen la cantidad y distribución del tejido óseo, muscular y adiposo mediante el uso de rayos-X o técnicas de resonancia magnética: densitometría, Tomografía computada (CT), Resonancia magnética nuclear (MRI) y la absorciometría con rayos X de doble energía (DXA). En general, los métodos directos son costosos y requieren equipos especializados que no están al alcance para el uso clínico de rutina. Por esta razón los denominados métodos indirectos como la antropometría y la impedancia bioeléctrica (BIA) proveen un estimado (o índices) de la composición corporal real obtenida a partir de los métodos directos o de los métodos de referencia¹³. Es por esto que los métodos indirectos dependen de las interacciones biológicas entre los componentes corporales, los tejidos y su

distribución en individuos normales y como resultado tienden a tener errores predictivos mayores y a ser modificados de forma importante en procesos patológicos¹⁴. Sin embargo, en función de su simplicidad, rapidez en la medición y costo, no es de extrañar que los métodos indirectos basados en la antropometría sean la base de la valoración clínico-epidemiológica de los trastornos ponderales.

Las mediciones antropométricas representan los métodos más básicos para evaluar la composición corporal¹⁵, de forma que puede describirse la masa corporal, su tamaño, forma y grado de adiposidad. En vista que las medidas corporales cambian en función de la ganancia o pérdida peso corporal (asumiendo que la mayor pérdida sea de masa grasa), este método le proporciona por lo tanto al clínico o al investigador un surrogado de la adiposidad total en el contexto de una estandarización adecuada¹⁶.

El IMC es tal vez el índice antropométrico más utilizado y las ventajas más evidentes de su uso se encuentran la facilidad de su cálculo pues no se requiere de equipos sofisticados para su determinación, la gran disponibilidad de datos estandarizados a nivel mundial y a su bien establecida relación con los niveles de adiposidad corporal, morbilidad y mortalidad en adultos¹⁷. Debido a todas estas bondades, no resulta extraño que la OMS haya recomendado la clasificación ponderal basada en el IMC incluyendo grados para el bajo peso, el sobrepeso y la obesidad bajo la premisa que el riesgo de padecer DM-2 y de morir por enfermedades cardiovasculares se incrementa a partir de un IMC mayor o igual a 25 kg/m²^{17,18}. De hecho, en 1993 un grupo de expertos de la OMS propuso puntos de corte para el IMC de 25-29,9 kg/m² para sobrepeso grado 1, de 30,0-39,9 kg/m² para sobrepeso grado 2, y de 40,0 kg/m² en adelante para sobrepeso grado 3¹⁷, enfatizando que la ganancia de peso en la vida adulta se asocia a un incremento en la morbilidad por desórdenes músculo esqueléticos, alteraciones en la función respiratoria y de la mortalidad por DM-

2 y enfermedades cardiovasculares¹⁹. En 1997, una segunda reunión de consulta de expertos de la OMS¹⁸ propuso una subdivisión adicional del IMC entre 35,0–39,9 kg/m², reconociendo que el manejo de la obesidad difería si esta sobrepasaba los 35 kg/m². Para el año 2000 la OMS publica el reporte técnico N° 894 “*Obesity: Preventing and managing the global epidemic*” en el cual se reporta la forma final de la clasificación ponderal según el IMC que se conserva hasta la fecha^{19,20}.

En un meta-análisis muy reciente elaborado por el grupo de *Flegal y cols.* se investigaron las razones de riesgo (Hazard ratios, HR) para todas las causas de muerte en individuos con sobrepeso y obesidad en relación a los individuos normopeso en la población general, haciendo una revisión sistemática de la literatura hasta el 2012 seleccionando 97 estudios prospectivos con 2,88 millones de individuos y más de 270.000 muertes, encontrando que los HR promedio fueron de 0,94 (95% CI, 0,91-0,96) para los individuos con sobrepeso, 1,18 (95% CI, 1,12-1,25) para todos los grados de obesidad, 0,95 (95% CI, 0,88-1,01) para la obesidad grado 1, y 1,29 (95% CI, 1,18-1,41) para los grados 2 y 3 de obesidad. Este estudio revela que la obesidad en general (y particularmente grado 2 y 3) se asocia con un incremento modesto, aunque estadísticamente significativo, de muerte por todas las causas, reflejando que el IMC no se comportó como una variable de alto poder predictivo en este grupo de pacientes²¹. Este fenómeno puede explicarse desde múltiples hipótesis que van desde un mal ajuste de ciertas variables confundidoras como el consumo de cigarrillos hasta otras más plausibles como la asociación no uniforme entre el riesgo a enfermar y el IMC, ya que una proporción importante de la población puede tener exceso de peso y ser metabólicamente sana o tener un peso normal y tener disturbios metabólicos importantes²²⁻²⁴. De hecho, *Wildman y cols.* en un estudio realizado sobre los datos del NHANES entre 1999 y 2004 encontró que una considerable proporción de los individuos obesos de los EUA eran metabólicamente sanos, mientras que un número importante de personas delgadas presentaban la agregación de varias anormalidades metabólicas. Traducido esto a números el 29,2% de los

hombres obesos y 35, 4% de las mujeres obesas (un total de 19,5 millones de individuos) tenían un perfil metabólico normal. En contraste, el 30,1 % de los hombres y el 21,1% de las mujeres delgadas presentaron anomalías metabólicas (2 ó más), es decir, 16,3 millones de adultos²⁵.

Estas debilidades han llevado a que diversos autores hayan analizado las fuentes de posibles errores asociados al empleo del IMC como índice antropométrico. Por ejemplo, parece claro que parte de los errores de clasificación entre individuos de bajo riesgo cardiometabólico se deben a que los puntos de corte utilizados en la actualidad por la OMS se derivan de estudios de morbilidad y mortalidad realizados sobre población caucásica de ambos sexos y todas las edades^{17,19}. Más aún, muchos estudios han sugerido la necesidad de explorar la posibilidad de puntos de corte por género²⁶, grupos étnicos²⁷ e incluso por grupos etarios^{28,29}, de forma de compensar la imposibilidad del IMC de cuantificar el porcentaje total de grasa y distinguir entre la grasa total corporal y la masa magra total^{30,31}, a pesar que muchos estudios han encontrado su asociación con un perfil lipídico desfavorable caracterizado por triacilglicéridos y colesterol de LDL elevados con HDL colesterol bajas^{32,33}.

En la búsqueda de un mayor indicador antropométrico, la evidencia clínica sugiere que la asociación entre la DM-2 y la obesidad central es mucho mayor que la observada con el porcentaje total de grasa. Estudios realizados con RMN y TAC han suministrado evidencia que soporta el hecho que la obesidad central y el tejido adiposo visceral son los mayores contribuyentes a las complicaciones metabólicas observadas en la obesidad³⁴⁻³⁷. De esta manera, la obesidad central se asocia a una disminución en la tolerancia a la glucosa, alteraciones en la homeostasis de la insulina, y una disminución en la deposición tisular de glucosa estimulada por insulina. Además de esto, varios estudios que han analizado la asociación de las diversas mediciones antropométricas y de

grasa visceral han encontrado que la circunferencia abdominal es una mejor forma de medir la obesidad central debido a que es un mejor predictor de la cantidad de tejido graso visceral³⁸⁻⁴².

Es importante señalar que existe fuerte evidencia sobre la existencia de diferencias étnicas relacionadas con la CA y la cantidad de tejido adiposo visceral (TAV) cuantificado por tomografía computarizada (Gold Standard para la determinación de esta variable)⁴³⁻⁴⁶. De esta manera, una medida antropométrica puede representar diferentes cantidades de TAV y/o tejido adiposo subcutáneo (TAS) en diferentes grupos étnicos. Además, si la TAV es el indicador con mayor asociación al riesgo metabólico, los puntos de corte actuales de CA para identificar a individuos con riesgo elevado podrían sobrestimar o en su defecto subestimar la alteración en diferentes grupos étnicos^{47,48}.

La composición de los tejidos presentes en abdomen muestra gran heterogeneidad, especialmente en cuanto a la proporción entre tejido adiposo y muscular así como de su localización específica, grado de irrigación e infiltración de macrófagos, por lo que es posible observar una relación cambiante en su interacción con los factores de riesgo metabólicos y cardiovasculares en las diferentes razas, grupos etarios y géneros, lo cual no permite el desarrollo de una definición universal de obesidad abdominal que pueda aplicarse uniformemente. Un caso particular es el de los asiáticos, quienes presentan mayor morbilidad con puntos de corte de CA más bajos que los individuos caucásicos^{27,46,49-52}. De hecho, las definiciones propuestas para el SM tanto por la IDF como la de la armonización de criterios (IDF/AHA/NHLBI/IASO/ADA-2009)⁵³ consideran que la circunferencia abdominal debe ser específica para cada etnia y recomienda que deberían desarrollarse investigaciones exhaustivas antes de emplear puntos de corte para su uso en la práctica clínica⁵³.

La determinación de puntos de corte adecuados para la CA es de primordial importancia en el campo de la prevención, diagnóstico y pronóstico de la obesidad, SM, DM-2 y enfermedad

coronaria. El punto de corte más utilizado durante años para el diagnóstico de obesidad abdominal fue propuesto por ATPIII (National Cholesterol Education Program's Adult Treatment Panel III) en su definición de SM (CA >102 cm para hombres; y >88 cm para mujeres)⁵⁴. Eventualmente se demostró que estos puntos de corte son inapropiados para las poblaciones asiáticas pero aplicables a poblaciones caucásicas no europeas⁴⁹⁻⁵². Es por esto que en estas poblaciones los puntos de corte son relativamente más bajos; por ejemplo, para los habitantes del sur de Asia y de China los puntos de corte para CA son de <90 cm para hombres y <80 cm para mujeres, y para los japoneses <85 cm para hombres y <90 cm para mujeres. En aquellas localidades en las que no se han determinado puntos de cortes específicos se recomienda el uso de aquellos de otras regiones hasta que se dispongan de los datos apropiados⁴⁹⁻⁵².

En la actualidad es claro que la mayoría de los individuos con obesidad desarrollan insulinoresistencia, DM-2, dislipidemia, gota, HTA y ECV, pero tal como ya se ha expuesto, un porcentaje variable de los individuos obesos son sanos desde el punto de vista metabólico lo que incluye una sensibilidad a la insulina conservada. Estudios recientes sugieren que la inflamación, hipoxia y disfunción del tejido adiposo visceral y el depósito ectópico de TAG son los mediadores de la insulinoresistencia en humanos independientemente de la masa grasa corporal total^{55,56}, hecho que se encuentra en consonancia con la idea de la existencia de los cuatro fenotipos metabólicos sugeridos por autores como *Karelis*⁵⁷, que surgen de la combinación de la clasificación ponderal del IMC y la presencia o no de alteraciones metabólicas asociadas a la resistencia a la insulina y que dependiendo del trasfondo genético se expresarían a volúmenes y funcionabilidades diferentes de TAV.

3. De la muerte adipocitaria al miocito disfuncional: ¿Nexo común entre los individuos delgados y obesos metabólicamente enfermos?

Clásicamente, los adipocitos del tejido adiposo blanco han sido reconocidos como células profesionales almacenadoras de lípidos, remarcando el término profesional para diferenciarlas de otras células capaces de acumular lípidos en condiciones patológicas como los miocitos, células beta, neuronas y hepatocitos. La característica principal del adipocito maduro es su capacidad de almacenar grandes cantidades de grasa sin comprometer su integridad estructural. Aunque la ontogenia del adipocito aún se comprende este proceso es motivo de gran investigación en la actualidad^{58,59,60}. Hasta la fecha, se conoce que las células mesenquimatosas se diferencian a adipoblastos, los cuales subsecuentemente expresan marcadores tempranos de transcripción propios de entrada a diferenciación a Pre-adipocito I, es decir las proteínas $\alpha 2\text{Col}6$, Lipoprotein-lipasa, IGF-1 y Krox20. Una vez que el destino biológico de esta célula se ha determinado se inicia la mitosis y el proceso de expansión clonal lo que dicta la entrada a la fase de Pre-adipocito II, caracterizada por la expresión de las proteínas C/EBP β/γ , SREBP-1, PPAR $\gamma 2$ y KLF5. La madurez de esta célula no se alcanza hasta que ocurre la regulación en alta de marcadores que producen el arresto celular y el comienzo de la acumulación de lípidos intracitoplasmáticos: C/EBP α , GLUT4, Perilipina, TNF- α , TGF- β , enzimas lipogénicas y lipolíticas. Finalmente, la aparición del adipocito maduro se completa cuando se expresan hormonas, citoquinas y enzimas relacionadas con el almacén y liberación de lípidos al torrente circulatorio^{61,62,63}

Tal vez, el aspecto más interesante de la diferenciación es como el Pre-adipocito es conducido hacia la obtención del perfil adipocitario maduro gracias a la interacción de miembros de la familia de los receptores PPAR- γ y las CCAAT-enhancer-binding protein (C/EBP). En primer término es la expresión a corto plazo de C/EBP β y C/EBP $\gamma 2$, seguido cercanamente de la expresión de C/EBP α que activan la expresión de receptores PPAR $\gamma 2$, que en última instancia regulan la expresión de todos los genes responsables de la adipogénesis.

El adipocito maduro es una célula altamente especializada cuya función principal es el almacén de energía en forma de triacilglicéridos, cuyo metabolismo se encuentra bajo un sistema de control central y periférico muy preciso^{58,64,65}. Junto con este papel primordial, el adipocito también es una célula endocrina capaz de secretar una cantidad importante de hormonas como la leptina, adiposina, angiotensinógeno, adiponectina, TNF- α , la proteína estimulante de la acilación (SPARC) y la PGAR/FIAF (PPAR γ Angiopoietin related/fasting-induced adipose tissue). Este secretoma incorpora a este tejido a procesos de índole inmunológica como la inflamación de bajo grado, fenómenos de auto-inmunidad, angiogénesis, deposición de matriz extracelular y remodelamiento por metaloproteinasas^{64,56}, por lo que no es inusual que el tejido adiposo sea parte de varios sistemas como el eje adipo-insular^{66,67}, el eje adipocito-vásculo-cerebral^{68,69,70} y el eje adipocito-miocito^{71,72}.

La plasticidad, es decir, la capacidad de una célula de adaptarse a cambios en el ambiente externo puede observarse en las células adiposas maduras en forma de hipertrofia e hiperplasia adipocitaria⁷³. En el estado de sobre-ingesta de alimentos la capacidad del tejido adiposo de guardar el exceso de energía en forma de grasa puede alcanzar un límite causando el llamado “*spill-over*” (Rebosamiento) que puede afectar varios sistemas orgánicos en forma de síndrome de acumulación ectópica de grasa^{74,75,76}. Esta sobrecarga nutricional y subsecuente daño ha sido observado en modelos de detención de crecimiento, en el que la realimentación se asocia a hiperinsulinemia, lipogénesis exagerada, cambios en la estructura de la membrana (con aumento en la proporción de ácidos grasos saturados) e incremento en la producción de triacilglicéridos que en última instancia conduce a hipertrofia adipocitaria y resistencia a la insulina muscular/hepática por acumulación anómala de triacilglicéridos en hígado y músculo, con activación de enzimas como las proteínasas C atípicas y disrupción de la señalización insulínica en tejido muscular^{74,75}. Sin embargo, es importante señalar que junto a estas alteraciones asociadas a la interferencia en la señalización mediada por TAG, también la senescencia adipocitaria conlleva a cambios en el patrón

de secreción cuantitativo y cualitativo de proteínas expresadas en el mismo. Por ejemplo, es bien conocido que la producción de Adiponectina disminuye en individuos con obesidad mientras que la secreción de resistina y TNF-alfa aumenta en consecuencia de la expansión de los depósitos grasos^{77,78,79}.

El estímulo continuo por sobre-alimentación y en consecuencia, la acumulación continua de lípidos produce hipertrofia adipocitaria (140 – 180 μm de diámetro) progresiva que es limitada en última instancia por el suministro de oxígeno⁸⁰. Numerosos estudios han demostrado que el flujo sanguíneo al tejido adiposo se encuentra disminuido en la obesidad⁸¹, sugiriendo que la hipoxia puede ser la principal causa del estrés del retículo endoplasmático adipocitario a través de la vía de respuestas de proteínas mal plegadas (UPR)⁸¹. De hecho, en el año 2004 *Trayhurn y Woods* sugirieron por primera vez que la hipoxia en el tejido adiposo más periférico produce un incremento en la secreción de citoquinas, factores de crecimiento y proteínas de fase aguda a nivel local en un intento por incrementar una angiogénesis que no ocurrirá, incluso a pesar de la sobre-expresión de PDGF, TGF- β y Angiopoyetina⁸²⁻⁸⁵. Es probable que la detención del proceso de angiogenesis ocurra vía bloqueo de la expresión del VEGF, ya que se ha observado que en tejido adiposo de ratas *ob/ob* la expresión de este factor de crecimiento no se incrementa con la hipoxia⁸⁶ defecto que se asocia con una reducción del flujo sanguíneo al tejido adiposo en el ratón obeso y que podría explicar la reducción del flujo sanguíneo en la obesidad en seres humanos⁸⁷. De esta forma, es muy probable que la hipoxia en el tejido adiposo se deba a hipoperfusión, especialmente luego que el adipocito ha ganado más de 100 μm de diámetro en plena fase hipertrófica. Este hecho trae como consecuencia una alteración en la expresión de varios genes -en particular, el de la adiponectina- (el cual es activado por C/EBP e inhibido por UPR-induced CHOP (C/EBP homologous protein), lo cual modifica de forma crítica el secretoma adipocitario, resultando en un incremento de la

expresión del factor inducido por hipoxia 1α (HIFactor- 1α) que a la vez induce la transcripción del gen del GLUT1, IL-6, leptina, Inhibidor del activador del Plasminógeno - 1 (PAI-1)^{88,89}. Este proceso había sido descrito en músculo hace más de 10 años, ya que se conocía que la hipoxia es un modulador del metabolismo de la glucosa, la cual, en una primera instancia (de forma aguda) induce la incorporación de glucosa vía incremento de la síntesis del GLUT-1, pero ya en una instancia crónica puede observarse una caída en el transporte de glucosa debido a serin-treonin-fosforilación del IRS-1 y el receptor de insulina. Si este proceso ocurre en el adipocito traería como consecuencia la estimulación en la lipólisis, liberación de ácidos grasos al torrente circulatorio y finalmente más resistencia a la insulina^{90,91}.

De forma de completar el panorama del adipocito en este ambiente hipóxico, debe recalcarse el papel de los macrófagos en este contexto pro-inflamatorio^{92,93}. Como se ha descrito anteriormente, la resistencia a la insulina depende en buena parte de la distribución regional del tejido adiposo y de la capacidad de plasticidad del mismo⁹⁴. En este sentido, los macrófagos que infiltran el tejido adiposo en esta fase son responsables de impedir que nuevos adipocitos se originen a partir de pre-adipocitos mediante la secreción de TNF- α e IL-1, muy reconocidos supresores del programa adipogénico que acúan por intermedio de la proteína NF- κ B inhibiendo la expresión del gen del receptor PPAR γ . El secretoma macrofágico incluye proteínas como el VEGF, TNF-a, IL-1b, IL-6, especies reactivas de oxígeno (ROS) y prostaglandinas. El reclutamiento de monocitos dentro del tejido adiposo es regulado por muchas moléculas pero el C-C motif chemokine ligand 2 (CCL2) y su receptor (CCR2) son quizá los más importantes, hecho que abre un marco terapéutico al bloquear la infiltración de macrófagos alrededor de los adipocitos agonizantes o muertos⁹⁵.

El crecimiento progresivo y la posterior muerte de adipocitos producen daño colateral importante: la generación de miocitos esqueléticos resistentes a la insulina y con una expresión disminuida de miogenina (factor de transcripción específico involucrado en la miogénesis), IL-6, IL-8 y MCP-1 (proteína quimiotáctica de monocitos), con más altos niveles de ceramidas y menor capacidad mitocondrial⁹⁶. La forma de cómo el músculo se vuelve resistente a la insulina implica la alteración de vías de señalización relacionadas con el receptor de esta hormona. De hecho, *Sir Phillip Randle* fue el primero en formular una hipótesis que proponía que los FFA competían con glucosa como sustrato para la oxidación mitocondrial de combustible, de forma que el exceso de Acetil-CoA inhibía al complejo multienzimático de la piruvato deshidrogenasa y posteriormente a la Fosfofructokinasa-1, lo cual bloqueaba la oxidación de la glucosa en la vía glucolítica⁹⁷. Más de 30 años después, *Shulman*, replanteó la hipótesis de *Randle* al encontrar que la acumulación de FFA y TAG intramiocelulares conduce a la acumulación citosólica de metabolitos como diacilglicerol, ceramidas y acil-CoA, que fosforilan e inhiben tanto al receptor de insulina como al IRS-1, con bloqueo de las vías post-receptor de insulina IP-3K dependientes, disminuyendo la captación de glucosa a través del GLUT4⁹⁸.

Al igual que el adipocito, el músculo esquelético también muestra rasgos de plasticidad anatómica y funcional. Se puede utilizar la glucosa o lípidos para la producción de combustible; sin embargo, en la obesidad la oxidación de lípidos se reduce debido a la disminución de la actividad de la carnitina palmitoil acil transferasa -1 (CPT1)⁹⁹. En este sentido, la acumulación de TAG en tejido muscular puede atribuirse a dos razones básicas: Una reducción de la oxidación de los ácidos grasos y a un incremento en la síntesis de TAG^{100,101}. De esta manera, se ha evidenciado que los lípidos intramiocelulares son mejores predictores de resistencia a la insulina en músculo que el IMC y la relación cintura cadera^{102,103}, y que se correlaciona de forma inversa con los niveles de Visfatina en tejido adiposo¹⁰⁴. Es probable que el recambio de IMCL determine la cantidad de lípidos

acumulados dentro del miocito, modulando el nivel de metabolitos lipídicos que inhiben la vía de la PI3K vía activación PKC atípicas.

Pareciera difícil intentar explicar cómo un individuo delgado, con relativamente “poco” TAV podría exhibir la mayoría de las alteraciones metabólicas observadas en un individuo obeso metabólicamente enfermo. Desde una perspectiva histórica, *Ruderman y cols.*¹⁰⁵ en 1981 plantearon la existencia de individuos que a pesar de no ser obesos presentaban alteraciones metabólicas que se asociaban comúnmente con la obesidad –especialmente- la hiperinsulinemia y la hipertrofia adipocitaria^{105,106}. Estos autores acuñaron el término MONW (**M**etabolic **O**bese with **N**ormal **W**eight) para identificar a las personas con este fenotipo/genotipo metabólico distintivo. Es importante recalcar que la resistencia a la insulina, hiperinsulinemia y la dislipidemia puede evolucionar enmascarada por años debido al peso normal y la edad de estos individuos, ya que no se cree necesaria la pesquisa de este tipo de condiciones en individuos con estas características^{57,107}. En general, las personas MONW son más jóvenes y responden mejor a la intervención nutricional y el ejercicio que las personas obesas con comorbilidades bien establecidas. Es por esto importante la identificación temprana de personas con MONW ya que pueda ayudar a prevenir su evolución a individuos obesos metabólicamente enfermos y en consecuencia, a diabetes mellitus tipo 2.^{108,109,110} En un estudio conducido por *DeLorenzo y cols.*, las mujeres con MONW tienen niveles elevados de marcadores pro-inflamatorios como la proteína C-reactiva, el TNF- α , IL-6, IFN- γ y la IL-1 β , los cuales se correlacionaron con la adiposidad en comparación con individuos no obesos¹¹¹, de forma que el tercil superior de porcentaje de grasa corporal se caracterizó por tener mayor edad, mayor IMC, mayor circunferencia de cintura, mayor LDL, TAG, HOMA, menor porcentaje de masa magra, menores HDL y menor sensibilidad a la insulina en comparación con el primer tercil de % de grasa corporal. En otro estudio conducido por *Romero y cols.* se encontró que el diagnóstico de SM en individuos delgados fue más prevalente en el tercil superior de grasa corporal total que en el tercil inferior¹⁰⁸. Finalmente, otros estudios han encontrado que los MONW presentan una mayor

cantidad de grasa central¹⁰⁹, mayor adiposidad subcutánea y visceral que los individuos normales^{109,112,113} así como una menor práctica de actividad física, menor gasto energético¹¹² y un menor metabolismo basal que aquellos con peso y metabolismo normal^{112,113}.

Sin embargo, *Conus y cols.* ha resaltado la consistencia de varias observaciones en relación con los individuos con MONW: 1) Su prevalencia puede ser tan alta como el 45% dependiendo de los criterios utilizados, en especial, la edad, IMC y la etnicidad; 2) Las principales características que distinguen a los individuos con MONW de los controles son la sensibilidad a la insulina alterada, un perfil lipídico aterogénico, una mayor presión arterial, una menor actividad física y una mayor adiposidad abdominal/visceral, así como una menor actividad física; 3) Los individuos MONW tienen un riesgo mayor de padecer DM tipo 2 y enfermedad cardiovascular aterosclerótica¹¹⁴. En este sentido, *Ruderman y cols.* ha propuesto un método de puntuación basado en estas características en el que un score mayor o igual a 7 identifica a individuos portadores de MOWN¹⁰⁶.

A pesar que los individuos MOWN pueden presentar una mayor masa grasa que los individuos metabólicamente sanos con peso normal resulta evidente que dicha proporción no es mayor que la de un individuo obeso metabólicamente enfermo, sobre todo a niveles de IMC extremos con suficiente acumulación de grasa que pudiese producir una hipoxia adipocitaria suficientemente importante como para expresar las mismas alteraciones descritas en los obesos metabólicamente enfermos, de hecho, hasta la fecha no se han conducido estudios que demuestren si la infiltración de macrófagos es un fenómeno de importancia dentro del tejido adiposo visceral en individuos con el fenotipo MONW.

A manera de conclusión, varias dudas surgen acerca de estos dos fenotipos en particular en relación con la capacidad de la circunferencia abdominal como variables predictiva de salud metabólica. Por ejemplo, en el caso de un individuo portador de MONW una circunferencia de cintura normal puede arrojar un diagnóstico falso de buen estado de salud (falso negativo) porque

no es de esperar un metabolismo alterado en un individuo con peso normal (o circunferencia abdominal por debajo del punto de corte). Por otro lado, la primera impresión en un individuo obeso sugiere una elevada probabilidad de que se trata de una persona enferma desde un punto de vista metabólico. En este sentido, al cuantificar la circunferencia abdominal en este individuo sería clasificado como enfermo sin estarlo (Falso positivo). Desde el punto de vista de la teoría de detección de señales, el falso positivo representa la detección de una señal anómala siendo en verdad normal y el falso negativo representan la no detección de una señal por lo demás anormal. Llevando esto a la práctica clínica, usando solo la circunferencia abdominal se podría detectar a una persona delgada como sana o como metabólicamente enferma? o por lo contrario, ¿se podría clasificar a un individuo obeso como sano o enfermo? En estos casos, claramente la presencia de los fenotipos MONW y MHO pueden ser los responsables de la relativamente baja especificidad y sensibilidad que la CA ha mostrado en la mayoría de los estudios para separar a los individuos sanos de los enfermos metabólicamente hablando.

HIPÓTESIS

La obesidad se ha convertido en un grave problema de salud pública en el ámbito mundial. Sin embargo, en Latinoamérica la prevalencia de esta enfermedad no se ha estudiado en profundidad en la mayoría de los países de nuestro continente. Venezuela -y en particular- la ciudad de Maracaibo no escapa a esta situación de falta de información en relación con el comportamiento epidemiológico de los trastornos ponderales por exceso. En vista de la elevada prevalencia de la obesidad en países como los EUA, México y Chile nos ha impulsado a diseñar el Estudio de Prevalencia del Síndrome Metabólico de la Ciudad de Maracaibo, en el cual nos hemos planteado como primera hipótesis de trabajo que la prevalencia de obesidad es elevada y se comporta en espacio, tiempo y persona de forma similar a aquellos países americanos donde su frecuencia es elevada.

Por otro lado, en vista de que carecemos de puntos de corte regionales para la circunferencia abdominal se propone el uso de un novedoso método de selección de individuos sanos/enfermos desde un punto de vista metabólico mediante la técnica de análisis de conglomerados, planteándonos como hipótesis: 1) que este método conducirá a una mejor selección de individuos y en consecuencia mejores AUC, sensibilidades y especificidades durante la construcción de curvas COR y 2) Que este método permitirá reconocer de forma adecuada los fenotipos MONW y MHO de forma que al extraerlos del proceso de construcción de curvas COR mejorará de forma estadísticamente significativa las áreas bajo la curva COR, la sensibilidad y la especificidad diagnóstica.

OBJETIVOS

El objetivo general de este trabajo fue el estudio del comportamiento epidemiológico de la obesidad en la Ciudad del Maracaibo, Venezuela.

El primer objetivo específico fue el diseño de un estudio transversal cuyo propósito fue la estimación de la prevalencia de SM y la de sus componentes individuales, en ellos la obesidad. El segundo objetivo específico se relacionó con la estimación de la prevalencia de obesidad según la clasificación ponderal de la OMS, así como la de obesidad abdominal tomando según los puntos de corte CA propuestos por la armonización de criterios de SM del año 2009¹⁰ y por el ATPIII⁵⁴. El tercer objetivo específico fue la estimación de los puntos de corte apropiados para la circunferencia abdominal en individuos de Maracaibo mediante el uso de técnicas de análisis multivariante. Por último, el cuarto objetivo específico fue evidenciar el efecto que tiene la presencia de los fenotipos metabólicos MHO y MONW sobre la especificidad, sensibilidad y área bajo las curvas COR.

En el primer trabajo de esta tesis, publicado como "The Maracaibo city metabolic syndrome prevalence study: design and scope"¹¹⁵, se planteó el diseño de un estudio de tipo transversal, con muestreo aleatorio multietápico por conglomerados sobre la población de la Ciudad de Maracaibo (1.428.043 habitantes) con la finalidad de obtener estimaciones de la prevalencia de SM y de factores de riesgo cardiometabólicos en individuos adultos de nuestra localidad, obteniéndose un tamaño muestral de 1986 participantes en base a una prevalencia de SM del 27% obtenida de un estudio previo, un margen de error no mayor del 5% y un intervalo de confianza del 95%. En este estudio se delinear las estrategias de muestreo, entrenamiento del personal de salud que participó en el proceso de evaluación de los individuos enrolados y los procedimientos estadísticos generales involucrados en la auditoría y validación de la base de datos, así como del análisis general de los mismos.

Por su parte, en el segundo trabajo publicado como “Epidemiologic Behavior of Obesity in the Maracaibo City Metabolic Syndrome Prevalence Study”¹¹⁸, se estimó la prevalencia de obesidad usando la data generada en el estudio de prevalencia de Síndrome Metabólico de la Ciudad de Maracaibo. La muestra consistió en 2108 individuos de ambos sexos seleccionados al azar a los cuales se les evaluó clínicamente de forma completa incluyendo la recolección de medidas antropométricas como la talla, el peso y la circunferencia abdominal. El diagnóstico de obesidad se realizó mediante el cálculo del IMC y posterior clasificación de los individuos según los criterios de diagnóstico ponderal según el IMC de la OMS y los puntos de corte de CA de la IDF-2009¹⁰ y el ATPIII⁵⁴.

Finalmente, en el tercer trabajo titulado “Sensitivity and Specificity Improvement in Abdominal Obesity Diagnosis Using Cluster Analysis during Waist Circumference Cut-Off Point Selection”¹²¹ se utilizó la base de datos del estudio de prevalencia de SM de la ciudad de Maracaibo y se clasificó ponderalmente dicha muestra según su IMC para luego estratificarlos en metabólicamente sanos o enfermos mediante técnicas de minería de datos, específicamente por análisis de conglomerados. Se utilizaron como variables predictivas para la obtención de dichos conglomerados el HOMA2IR, HOMA2bcell, TAG, PAD, PAS, PAM, TAG, glucosa en ayuno, Colesterol no HDL, índice TAG/HDL-C y hs-CRP. El proceso de la obtención de los puntos de corte se realizó con los 6 fenotipos metabólicos y luego excluyendo en un primer término los individuos MONW y MHO y luego a los individuos con sobrepeso, analizando las áreas bajo las curvas con la prueba de DeLong.

CAPÍTULO I

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The Maracaibo City Metabolic Syndrome Prevalence Study: Design and Scope

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The metabolic syndrome (MS) is a conglomerate of interrelated risk factors—including obesity, atherogenic dyslipidemia, arterial hypertension, and insulin resistance—which exponentially increase the risk of developing cardiovascular disease and type 2 diabetes mellitus. The purpose of this study was to determine the prevalence of MS according to the criteria published by the International Diabetes Federation, in individuals of both sexes over 18 years of age. This is a cross-sectional study based on MS prevalence in a representative sample from the Maracaibo district, Zulia State. The population of Maracaibo, according to the last census in 2001, was 1,219,927 habitants, with a 2007 population estimation of 1,428,043 habitants according to the National Institute of Statistics (NIS). Likewise, NIS projects that for the year 2009, 59.7% of the population of Venezuela will have individuals over 18 years of age. Using these data, the sample for Maracaibo District corresponds to 1986 individuals with or above 18 years of age. The data recollection was conducted by health professionals and medicine students, previously trained. The participants were subject to inquiry previous written consent and a medical examination, and qualitative variables such as smoking habit, socioeconomic status, physical activity, race, alcoholism, and nutritional habits, and quantitative ones like blood pressure, anthropometry, and blood works were determined. There is clear evidence that there is a lack of research and validated values to use as reference in our country and maybe in Latin America. Taking into account all that has been exposed here, this study will serve as a pilot for the numerous statistical determinations that will soon come afterward, providing first-hand accurate evidence on the behavior of the MS in the Latin American populace.

Keywords: metabolic syndrome, cardiovascular risk factors, blood pressure, dyslipidemia, cross-sectional studies

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INTRODUCTION

The metabolic syndrome (MS) is a conglomerate of interrelated risk factors—including obesity, atherogenic dyslipidemia, arterial hypertension, and insulin resistance—which exponentially increase the risk of developing cardiovascular disease (CVD) and type 2 diabetes mellitus (DM2).^{1,2} The main goal for preventive strategies has been to discover the prevalence

of these factors, such as the Framingham study,³ where cardiovascular risk factors were first identified. Nonetheless, its simple diagnosis and association with other clinical entities, MS prevalence, and its repercussion toward health in the general population (like CVD and diabetes) have not been described clearly.

The results from the Third National Health and Nutrition Examination Survey⁴ showed an alarming prevalence of MS in 24% of the population; other American⁵ and European studies have verified these data.⁶ These alarming numbers have precipitated a number of classifications^{7,8} where worldwide experts and diverse panels, actually try to define this "elusive" syndrome. Knowing the possible consequences of MS, it is perceived as a potential threat, that beyond its inevitable consequences,⁹⁻¹¹ it can be used in our favor, with the development of prevention programs in the near future.

Important background reference values from the Latin American population cannot be easily found, which is extremely necessary when comparing the different ethnic groups that can be found here—blended—which alters the applicability of any MS definition in our region, and of course, any preventive measure.

The purpose of this study is to determine the prevalence of MS according to the criteria published by the International Diabetes Federation and The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III), in individuals of both sexes over 18 years of age. The specific objectives of the study were the following: quantify waist circumference, blood pressure, fasting glycemia values, serum triacylglycerides, serum high density protein (cHDL) value, and psychobiologic habits in the adult sample in Maracaibo district, Venezuela. Besides, it is also the object of this investigation to estimate the prevalence of MS according to sex, ethnic group, and race in our population sample. The association (or lack thereof) of family history of CVD and metabolic disorders with the occurrence of MS will be also analyzed. This work is meant to add a more profound knowledge to this noxa in our geographic location, with the future goal of developing better tools to a proper combat.

MATERIALS AND METHODS

Design and size of the sample

This research proposal is a cross-sectional study based on MS prevalence in a representative sample from the Maracaibo district, Zulia State. This prevalence study

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was designed to provide realistic estimations about the prevalence of this entity and cardiovascular risk factors in our population, including members of the same sex and over 18 years of age. The population of Maracaibo, according to the last Venezuelan census made in 2001, was 1,219,927 habitants,¹² with a 2007 population estimation of 1,428,043 habitants according to the National Institute of Statistics (NIS). Likewise, NIS projects that for the year 2009, 59.7% of the population of Venezuela will have individuals over 18 years of age. Using these data, the sample size estimate for Maracaibo District corresponds to 1986 individuals with or above 18 years of age. We based this calculation on an expected prevalence of MS in an adult population of 27%, an absolute precision between 1% and 5%, a confidence level of 95%, and a design effect of 2. Maracaibo municipality is geopolitically divided in parishes and the sample size of each parish (parishes: Antonio Borjas Romero, Bolívar, Cacique Mara, Caracciolo Parra Pérez, Cecilio Acosta, Cristo de Aranza, Coquivacoa, Chiquinquirá, Francisco Eugenio Bustamante, Idelfonso Vásquez, Juana de Ávila, Luis Hurtado Higuera, Manuel Dagnino, Olegario Villalobos, Raúl Leoni, Santa Lucía, San Isidro, and Venancio Pulgar) was done proportionally, taking the total population of each parish and the one from Zulia State (for year 2008) as base number for individuals, that were chosen using a 2-phase sampling process: During the first phase, the sorting was random and stratified—where each stratus was represented by sectors from each of the 18 parishes—choosing 4 from each parish. The second sampling was stratified to represent a city block, in which they were selected using a random number generation tool.

Finally, all the adult individuals from each family unit (from the selected city blocks) who fulfilled the inclusion criteria in each of the selected houses were invited to participate in the study and were interviewed on prior written consent, and subjected to a routine medical examination using the clinical chart provided by the Health and Social Development Ministry of Venezuela as a data collecting tool.

It is worth mentioning that the basic criterion for MS is high risk abdominal circumference. Within the International Diabetes Federation (IDF) consensus, it is recognized that this parameter does not hold a fixed point in all populations, giving various cut-off points, such as in Afro-Americans, South Asians, Japanese, Chinese, and others. It also points out the lack of information on Arabs, Sub-Saharan Africans, Eastern Mediterranean's, Central Americans, and South Americans, and given that situation the data from the Southeastern Asians should be used until further data can be compiled.²

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Statistical analysis

Study forms were reviewed to ensure that they were complete before data entry. Data were entered by duplicate into SPSS 15.0 (SPSS Inc., Chicago, IL) for Windows spreadsheets and compared using Epi-Info 2000 (CDC, Atlanta, GA). Any discrepancy was corrected using the original study forms. The phase of data analysis is now in progress. Bivariable analyses for dichotomous and continuous variables will be performed by chi-square test, *t* tests, or Mann-Whitney tests, respectively. The association between components of MS and the higher quintile of the Homeostasis Model Assessment index will be analyzed through a logistic regression model considering adjustments by clustering effect. All *P* values will be 2 tailed, and a *P* < 0.05 value will be considered statistically significant. All data are being actually analyzed using SPSS ver. 15.0.

DATA COLLECTION

Study participants

The following measures were taken to facilitate and encourage the participation of the selected individuals in the study: (1) paperwork for the blood test was performed and given to the participants; (2) involvement of local health professionals was guaranteed; (3) invitations were sent directly through the local community leaders, or through a professional social worker in primary health centers whom are part of the

communities; (4) the invitations were confirmed by telephone; (5) the evaluation site and blood samples were taken according to the location of the participants (either in a school, local community center, or primary care center).

The data recollection was conducted by health professionals and medicine students (previously trained), all from the "Endocrine and Metabolic Diseases Research Centre Dr Félix Gómez" (CIEM) staff in the 18 parishes of the Maracaibo District from January 2007 through April 2009.

The participants were subject to inquiry previous written consent and a medical examination using the medical history chart provided by the Health and Social Development Ministry as data collecting tool (Table 1).

Definition of qualitative variables

1. Smoking habit: To define smoking habit, the Brinkman index was used, which is obtained multiplying the number of cigarettes consumed daily per number of years with this habit. A smoker was considered when the habit was active and a Brinkman index equal or above 801.¹³ Recent former smokers (less than a year) at the moment of the study were also categorized as smoker. An individual was considered a non-smoker if he referred to have never smoked or not achieving a positive index value.
2. Socioeconomic status: It was studied using the Graffar scale modified by Mendez Castellano,¹⁴

Table 1. Data recollecting components in the Maracaibo city MS prevalence study.

Type of data	Components
Anamnesis	General information: age, education, marital status, demographics, race, socioeconomic status. Family and personal history of various disorders: cardiovascular, endocrine, metabolic, immunological, pulmonary, pancreatic, parasite/bacterial/viral infections, hepatic, ocular, gastrointestinal, hematological, gynecological, obstetrics, neoplastic, urologic, cutaneous, and relating to the male apparatus, neurologic, psychiatric, sexually transmitted diseases. And also, automobile accidents, trauma, previous surgeries, and current medication. Life style risk factors: smoking habit, alcohol consumption and physical activity. Nutritional habits.
Physical examination	Vital signs: blood pressure in 2 positions (standing and sited), temperature, pulse, respiratory frequency, and heart rate. Physical exam of systems and apparatus: skin, head, eyes, nose, mouth and pharynx, neck, lymph nodes, thorax, breasts, heart, lungs, blood vessels, abdomen, genitalia, rectum, bones and articulations, muscles, extremities, neurological, and psychic. Basic anthropometry: weight, height, body mass index, abdominal circumference, waist circumference.
Laboratory	Total cholesterol, cHDL cLDL, triacylglycerides, fasting glycemia, and insulin.

whose criteria are as follows: (1) profession of the head of the family, (2) instruction level of the mother, (3) source of income, and (4) housing conditions. The stratuses were defined according to the score obtained from the arithmetic sum of each criterion; having then: Stratus I (high class), Stratus II (medium high class), Stratus III (medium class), Stratus IV (working class), and Stratus V (extreme poverty). Such a scale was developed for the Venezuelan population, where the unequal economic, cultural, and social levels are evident, and influence social behavior, growth, alimentary habits, and biologic development.

3. **Physical activity:** As a tool for evaluating physical activity, the International Physical Activity Questionnaire¹⁵ was used. It is a tool that has been used in countless clinical and epidemiologic surveys to estimate physical activity in countries with different cultures and sociocultural classes. It is based on the physical activity preformed in the last 7 days, and it takes into account 4 elements of evaluation: (1) physical activity in leisure time, (2) domestic and gardening activities, (3) physical activity related to work, and (4) physical activity related to transport. There are 3 levels of physical activities that are proposed by the International Physical Activity Questionnaire: low, moderate, and high, using as measuring unit the metabolic equivalent, defined by the energy consumption of an individual in a resting state, which is approximately 1 kcal/kg and hour, for example, 4.184 kJ kg⁻¹ h⁻¹.
4. **Race:** Many concepts for race and ethnicity have been developed, and all have been motives for controversy. The current tendency is to classify human populations according to socioanthropologic customs and cultural aspects of each group, without taking into account its genetic background. In biomedicine, there is a clear relationship between racial groups and cluster of diseases. In this matter, several studies have been conducted using this racial classification¹⁶: (1) Amerindians or American Indigenous, (2) Venezuelan mixed race, (3) Black race, (4) Orientals, and (5) Arabs.
5. **Alcohol Consumption:** The American Heart Association¹⁷ criteria are taken into account to consider a person a drinker or not. An alcohol drinker was considered when that individual drank over 30 g of alcohol (2 glasses of wine or its equivalent) per day, or, 210 g of ethanol per week. The CAGE¹⁸ test was applied to early detection of alcohol related problems, which consists of 4 items, 3 that explore the subjective aspects of the

person related to alcohol consumption, and the last one explores aspects of alcohol withdrawal. The sum of all gives a score that relates to an alcoholic dependency or not.

6. **Nutritional Habit:** They were defined by a validated questionnaire;¹⁹ and for this purpose, the test was divided into 2 parts: (1) 24 hours reminder and (2) listing of alimentary preferences and quantity of such during the past month. From these data, the daily caloric consumption will be calculated, along with alimentary preferences, daily calories obtained from carbohydrates, lipids, and proteins, approximate ingestion of hydrophilic and lipidic vitamins, daily ingestion of cholesterol, saturated fats, mono, and polyunsaturated fats.

Defining quantitative variables

1. **Blood Pressure Measuring:** It will be done using the auscultatory method for which a calibrated sphygmomanometer will be used. The patients will be sitting still—with their feet on the ground—for less than 15 minutes before the determination. During the procedure, the arm will be at the same level of the heart, being the systolic pressure the first sound that is heard (phase 1) and diastolic pressure the point where the sound fades (phase 5). The procedure will be done 3 times, 15 minutes apart from each other, and at least, in 2 different days (the day of blood sampling and the day for results delivery).
2. **Basic Anthropometry:** (1) Abdominal circumference is taken using a plastic measuring tape, graded in centimeters, in a spot equidistant to the lower ribcage border and the anterior–superior iliac spine. (2) Height is measured using a metal height measurer graded in centimeters. The results will be converted to meters dividing the result into 10. (3) Body mass index will be calculated applying the formula: weight over square height (kg/height² in meters).
3. **Impedanciometric Measures:** It will be undertaken using a digital 2 electrode impedanciometer (TBF-310GS, Tanita, Japan).
4. **Blood Work Determinations:** After 8–12 hours of fast, levels of cholesterol, triacylglycerides, cHDL, and glucose will be determined using computerized equipment (Human Gesellschaft Biochemica and Diagnostica MBH, Magdeburg, Germany). The time between sample taken and its processing never exceeded 3 months. Low density lipoprotein (LDL) levels will be calculated using the Friedewald formula if triacylglycerides levels are below

400 mg/dL, and if they are above, they will be determined by electrophoresis of lipoproteins in agarose gel and ulterior band densimetry (GS-800 densitometer, Bio-Rad, Hercules, CA).

TRAINING AND GUARANTEE OF QUALITY

Training program

To be able to fully capacitate the personnel, special sessions in filling the medical chart history were necessary, so that the recollection of data like demographics, family, and personal history was indeed accurate. Also, a rigorous preparation was applied to the trainees so that the anthropometric measures could be done swiftly and precisely; this included height, weight, and abdominal circumference. For the physical examination, special sessions on taking of blood pressure were done, so the proper protocol was followed during this particular exam. All of these were supervised by a qualified instructor.

Supervising procedures

Supervision of the data quality was done in all the levels of the processing. The evaluation from each coordinator at each level assured that the data recollection was according to protocol. The monitoring of equipment, including mercury sphygmomanometers, was verified and calibrated periodically throughout the whole project.

Data processing

The arrival and processing of all the data was done within the CIEM. The medical history and various data are physically stored and their information digitalized. The processing personnel were capacitated in the proper use of the programs, and all the data were inserted in duplicates to obtain higher security in the process.

ETHICAL CONSIDERATIONS

The study protocol was designed in compliance with the Helsinki declaration and approved by the Research Ethics Board from the CIEM. Consent was obtained from all participants as mentioned above.

DISCUSSION

In 1999, the consultant group of the World Health Organization published a definition for MS,²⁰ whose

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principal aspect was the biologic and physiologic description of the insulin resistance seen in this illness. It was also recognized in this article that CVD was the primary outcome of the syndrome. Afterward, other MS definitions came to the spotlight, for example, such as The European Group for the study of Insulin Resistance²¹ in 1999, The National Cholesterol Education Program/Adult Treatment Panel III (ATP III) in 2001,²² which was popular due to its simpleness, with the The American Association of Clinical Endocrinologists,²³ and many others. Yet, it was not until 2005 that the International Diabetes Federation founded a consensus group whose purpose was to establish a new definition for MS that could be used in epidemiologic and clinical trials all around the world. They proposed that central obesity is the mandatory requisite that was necessary to make the diagnosis, and for the first time, cut-off values were offered for different ethnic groups.²⁴

Knowing previous statements, "one of the most important observations received by IOF classification reside in its cut-off points for each studied variable . . ." because Latin American countries have no populational studies that could establish the proper cut-off value to numerically separate normal from abnormal, and of course, the attributable risk to each variable. In fact, IDF asks that any investigator in need of such values—for abdominal circumference, for example—to rely on the Eastern Asians cohort data. This simple suggestion is quite delicate because there has been no promotional studies in Latin American, to fully evaluate MS' behavior; so applying Asian data could be wrong in the sense of lack of concordance on each ethnic group. That is why one of the goals of this trial is to shed some evidence on the epidemiologic aspects of MS taking as pattern the IDF and ATP III classifications, and afterward, to be able to set cut-off points in accordance to the peculiarities of our population, but, despite this, several groups have explored the epidemiologic behavior of MS in Hispanic whites and mixed Latin American groups. For instance, in 2005, the Metabolic Syndrome in Active Subjects (MESYAS) study was conducted in 7256 active Spanish workers. They applied the ATP III criteria for MS diagnosis, revealing a prevalence of 10.2%, and it was associated with age, male gender, presence of obesity, hypertension, and/or diabetes mellitus. These results indicate that 1 out of every 10 workers had MS. This particular association needs to be studied in the Latin American population.²⁵

The National Health Survey 2000 in Mexico reported an obesity prevalence of 24%, weighted on age and sex, in a Mexican population over 20 years of age. In the same survey, DM2 prevalence was 11%, and hypertension was 30%. These results indicate a rise from the previous Chronic Disease National Survey in 1993,

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where the prevalence of these conditions were as follows: DM2 7%, hypertension 27%, overweight 61% and obesity 25% in men, and overweight 56% and obesity 15% in women.²⁶ A similar tendency is observed in Talca, Chile, based on a study done in 2007, where high cardiovascular risk factors prevalence compared with what was observed during the National Health Survey of 2003. In the 2007 study, 1007 individuals who were 18–74 years old were used as population sample (with 66% women), showing an elevated percentage of smoking individuals (70.1%), and obese/overweight subjects (45%). High blood pressure was present (37%), along with hypercholesterolemia (44.5%), low cHDL (21.5%), and hyperglycemia (26.3%). This allows us to see that there is an array of environmental factors and life style issues that Latin Americans are living with now that enhances the risk for such disorders.²⁷

Another trial was conducted in Cadiz, Spain, in 2008, based on the prevalence of cardiovascular risk factors, studying 858 adults between 50 and 75 years of age.²⁹ It reported that active smoking habit was 23.7% for men and 7.9% for women, sedentarism was 30.9% and 44.8%, obesity was 54% and 55.9%, diabetes with 29.4% and 26.1%, hypertension with 45% and 52.4%, hypercholesterolemia with 40.9% and 45.1%, and MS diagnosis based on National Cholesterol Education Program/ATP III criteria of 58.8% and 57%, respectively. With the exception of smoking, the prevalence of all the risk factor had risen with age. It was observed that the prevalence of cardiovascular risk factors was extremely high in adults, and that demanded early and appropriate evaluation.²⁸

In Asunción city (Paraguay), the highest overweight population in the southern hemisphere is present.³⁰ The study was done using 1765 adult subjects, between 20 and 74 years of age, with excessive weight values in 64.5% of women and 71.8% of men. The same authors proved that 60% of the population from both sexes had an elevated waist/hip ratio, indicating a very prominent high risk presentation for MS with enhanced metabolic-vascular related illness, and, a higher prevalence of MS-42% of the adult population.³¹

Lipidic variables have the same concerning landscape in our countries. For example, in a study conducted by the Department of Public Health in Mexico (2008) the dyslipidemia prevalence was determined in 1179 individuals between 35 and 65 years of age, who were by all means healthy. Hypertriglyceridemia was present in 57.3% of the subjects, along with hipoalphalipoproteinemia (52.4%), and hypercholesterolemia (48.7%). Of the subjects with obesity (increased waist perimeter), 36.8% had hypertriglyceridemia/hipoalphalipoproteinemia,

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35.2% had mixed dyslipidemia, and 33.4% had hypertriglyceridemia. It was concluded that dyslipidemias are very common in the Mexican population, meaning that a lot of patients are wondering around undiagnosed. This tendency is probably present in all Latin American population, but due to lack of cross-sectional and longitudinal studies that could actually express the epidemiologic behavior of MS is impossible to predict the real risks and in consequence develop accurate health politics in this matter.^{31,32}

There is clear evidence that there is a lack of research and validated values to use as reference in our present populational study. Even though the IDF suggested that when studying Latin American population they should rely on Asian data. Taking into account all that has been exposed here, we strongly believe that the results of this study will help establish globally acceptable criteria for the early detection and intervention of MS in urban population of Venezuela. Moreover, they will provide policy makers, health care providers, and educators from a developing country like Venezuela with an opportunity to guide primary and secondary preventive initiatives at individual and community levels.

Finally, this work will serve as a pilot study for the numerous statistical and epidemiologic investigations that will come afterward, providing first hand accurate evidence on the behavior of the MS and its components in the Venezuelan populace.

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CAPÍTULO II

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Epidemiologic Behavior of Obesity in the Maracaibo City Metabolic Syndrome Prevalence Study

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Abstract

Introduction: Obesity is a worldwide public health issue. Since the epidemiological behaviour of this disease is not well established in our country, the purpose of this study was to determinate its prevalence in the Maracaibo City, Zulia State-Venezuela.

Materials and Methods: A cross-sectional study was undertaken using the data set from the Maracaibo City Metabolic Syndrome Prevalence Study. The sample consists of 2108 individuals from both genders and randomly selected: 1119 (53.09%) women and 989 (46.91%) men. The participants were interrogated for a complete clinical history and anthropometric measurements. To classify obesity, the WHO criteria for Body Mass Index (BMI), and Waist Circumference (WC) from the IDF/NHLBI/AHA/WHF/IAS/ASO-2009 (IDF-2009) and ATPIII statements were applied.

Results: For BMI, obesity had an overall prevalence of 33.3% (n = 701), and according to gender women had 32.4% (n = 363) and men had 34.2% (n = 338). Overweight had a prevalence of 34.8% (n = 733), Normal weight had 29.8% (n = 629), and Underweight had 2.1% (n = 45). Adding Obesity and Overweight results, the prevalence of elevated BMI (>25 Kg/m²) was 68.1%. Using the IDF-2009 WC's cut-off, Obesity had 74.2% prevalence, compared to 51.7% using the ATPIII parameters.

Conclusions: These results show a high prevalence of abdominal obesity in our locality defined by the WHO, IDF-2009 and ATPIII criteria, which were not designed for Latin-American populations. We suggest further investigation to estimate the proper values according to ethnicity, genetic background and sociocultural aspects.

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Introduction

The last five decades have beheld an alarming increase in obesity rates all over the industrialized world. Prevalence estimates of obesity usually are derived from surveys or population studies because systematic data on obesity generally cannot be gathered from medical records or vital statistics [1–2]. Virtually all data on prevalence and trends are derived on indirect body fat measurements based on weight and height (total adiposity) or using regional measures (plicometry) rather than on body fat because of the logistical difficulties involved in measuring body fat in population studies [1–2].

Obesity generally is defined as excess body fat but the definition of “excess”, however, is not clear-cut. Adiposity is a continuous variable not marked by a clear division between normal and abnormal. Moreover, it is difficult to measure body fat directly and consequently, obesity is often defined as excess body weight rather

than as excess of fatness. Thus, in large epidemiologic and clinical studies, two basic approaches have been broadly used: The Body Mass Index calculation (BMI) and the waist circumference measurement (WC) [3].

The World Health Organization (WHO) categorizes obesity in classes according to the different cut-off points in BMI. Similar definitions were recommended by a National Heart, Lung, and Blood Institute (NHLBI) expert committee in the NHLBI Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults [4]. On the other hand, abdominal circumference, albeit essential since it's a surrogate for visceral fat, has been subject to continued modification since central obesity values change according some factors like ethnicity and sex [5].

In Latin America, the epidemiology of obesity has not been studied in depth in most of the countries, but data from large studies from United States of America, Mexico and Brazil

illustrate the magnitude of the problem in the Americas. In the United States, the latest NHANES [6] analyzed data from 2007–2008 in regards to obesity trend through 1999–2008, reporting that obesity is as high as 33.8% overall, 32.2% in men and 35.5% among women, being most prominent among non-Hispanic whites and blacks ethnic groups. In Mexico, the National Health and Nutrition Survey (2006) [7] revealed that central obesity is higher in women than in men using ATPIII criteria, with 60.4% vs. 21.9% respectively. Obesity prevalence in the Mexican population has tripled over the last decade, from 9.8% to 39.3%, with especial concern in the poorer sectors of the economy [8] and adolescents [9]. As for Brazil, there was a 50% increase in obesity prevalence in men and women between 2002–2003, associated with similar frequencies in regards to overweight [10]. This tendency was observed among men in all socioeconomic strata, yet in women the trend was observed among the poorest women [10]. The VIGITEL survey reported that overweight prevalence in Brazil was 47% in men and 39% in women, while obesity was ~11% for both sexes [11].

The epidemiological behavior of this disease is still unknown in the Maracaibo City (Zulia State-Venezuela), therefore we conducted an analysis of the data obtained in the “The Maracaibo City Metabolic Syndrome Prevalence Study” (MMSPS) [12] with the aim of laying the foundations to a broader initiative across our country to establish the epidemiological behavior of this condition among this population.

Materials and Methods

Ethics Statement

All participants signed a written consent before being interrogated and physically examined. The study was approved by the Ethics Committee of the Endocrine and Metabolic Diseases Research Center.

Population Sample

The sample method was already published in the MMSPS cross-sectional proposal [12], yet the main aspects will be mentioned. Using population estimations for the population of Maracaibo (1,428,043 for 2007 according to the National Institute of Statistics), the sample size estimate was calculated to be 1,986 individuals with or above 18 years of age. Moreover, taking into account that in a previous pilot study approximately 10% of the subjects rejected being part of the study (unpublished data), an oversampling number was calculated (198 individuals); the overall number of patients was 2,108 (with 122 subjects –6.15% – added because of the oversampling method) were randomly selected between July 2008 and July 2010 [12]. The only inclusion criterion was to have ≥ 18 years of age. The city of Maracaibo is divided into parishes and each of these was proportionally sampled: Antonio Borjas Romero, Bolívar, Cacique Mara, Caracciolo Parra Pérez, Cecilio Acosta, Cristo de Aranza, Coquivacoa, Chiquinquirá, Francisco Eugenio Bustamante, Idelfonso Vásquez, Juana de Ávila, Luis Hurtado Higuera, Manuel Dagnino, Olegario Villalobos, Raúl Leoni, Santa Lucía, San Isidro, and Venancio Pulgar. The sampling process was undertaken using a 2-phase method: During the first phase, the sorting was random and stratified—where each stratus was represented by sectors from each of the 18 parishes—choosing 4 from each parish. The second sampling was stratified to represent a city block, in which they were selected using a random number generation tool. Once the houses were selected, every adult in the family unit from the selected city blocks was invited to participate in the study and were interviewed on prior written consent, and subjected to a routine

medical examination using the clinical chart provided by the Health and Social Development Ministry of Venezuela as data collecting tool.

Patient Evaluation

A full medical history was obtained using the Venezuelan Popular Powers Health Ministry approved medical chart. Socioeconomic Status was assessed with the Graffar Scale modified by Mendez-Castellano [13], which stratifies subjects into 5 Strata: High Class (Stratum I), Upper Middle Class, (Stratum II), Middle Class (Stratum III), Working Class (Stratum IV), and Lower - Extreme Poverty (Stratum V). In regards of race, the results will be presented as Hispanic whites, American-Indians (Natives), Afro-Venezuelans, Others (which include Arabic or Asian), and Mixed Race. Mixed race is a term applied to denote a group of individuals which have 2 or more (dihybrid or trihybrid) genetic lineages, denoting a complex interethnic crossing, which is a particular characteristic of the Latin American populations [14–15].

Anthropometric Evaluation

Weight and Height measure and BMI Calculation. The WHO classification for Obesity is based upon the Body Mass Index formula [16] $[\text{Weight}/\text{Height}^2]$ expressed in Kg/m^2 . Height was obtained using a calibrated rod, millimeters and centimeters, with the patient barefooted and his/her back facing the wall. Weight was recorded using a digital scale (Tanita, TBF-310 GS Body Composition Analyzer, Tokyo – Japan) with the patient using light clothing and no shoes. The subjects are classified according to the following: Underweight below $18.50 \text{ Kg}/\text{m}^2$, Normal Weight between $18.50\text{--}24.99 \text{ Kg}/\text{m}^2$, Overweight (Pre-obese) between $25.00\text{--}29.99 \text{ Kg}/\text{m}^2$, Obese Class I between $30.00\text{--}34.99 \text{ Kg}/\text{m}^2$, Obese Class II between $35.00\text{--}39.99 \text{ Kg}/\text{m}^2$, and Obesity Class III beyond $40.00 \text{ Kg}/\text{m}^2$.

Waist Circumference. WC was measured using calibrated measuring tapes in millimeters and centimeters, using anatomical landmarks according to National Institutes of Health protocol [17]: 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. The Adult Treatment Panel III (ATP III) [18] defined abdominal obesity according to Waist Circumference (WC), with a cut-off for men of 40 inches (102 cm) and 35 inches (89 cm) for women. The latest International Diabetes Federation/National Heart, Lung and Blood Institute/American Heart Association (IDF/NHLBI/AHA-2009) [19] consensus stated that WC was measured according to Country/Specific values, which for Latin Americans were set equal to South Asians parameters, specifically $\text{WC} \geq 90$ cm for males and ≥ 80 cm for females. Since it was important to compare ATPIII and IDF/NHLBI/AHA criteria for abdominal obesity, we chose to apply the 2009 consensus cut-offs because the 2005 IDF criteria used the same values for abdominal circumference.

Data Analysis

The data was analyzed by using the Statistical Package for the Social Sciences (SPSS) v. 19 for Windows (SPSS Inc. Chicago, IL). Normal distribution was evaluated by using Geary's test. For normally distributed variables the results were expressed as arithmetic mean \pm SD (standard deviation), complemented with the Coefficient of Variation (CV). The differences between them were established using Student's *t*-test (when two groups were compared), analysis of variance (ANOVA), when three or more groups were compared, or proportions Z-test (when proportions between nominal variables were compared). The qualitative

variables were expressed as absolute and relative frequencies, considering the results statistically significant when $p < 0.05$. Age was analyzed only in a descriptive manner, being applied to stratify the population in decennial groups (grouping variable) and it was not used for other calculus. Since this was a randomized sampling cross-sectional study between 18 parishes, we compare the age pyramid obtained from the sample with the country's pyramid, obtaining the same characteristics: a young population which is common in Third World countries, which translates into a transition-type population [20]. Variability was verified using Levent test which rendered not significant except the 18–19 years old group because this decennial group is incomplete. To evaluate BMI, ANOVA was calculated for each gender taking into comparison the mean of each age group and using Tukey for post hoc testing.

Results

General Characteristics of the Population

The sample consisted of 2,108 individuals, of which 46.91% ($n = 989$) were males and 53.09% ($n = 1119$) were females. The average age was 38.68 ± 15.42 years ($CV = 42.04\%$), with a mean average of 36.97 ± 14.94 years old ($CV = 40.41\%$) for males and 40.19 ± 15.67 years old ($CV = 38.99\%$) for females. Stratifying this variable in decennial age groups showed that 8.6% of individuals ($n = 181$) were found in the group of 18–19 years, 27.6% of the individuals ($n = 581$) were in the group 20 to 29 years, 18% of the individuals ($n = 380$) were found in the group of 30–39 years, 20.1% of the individuals ($n = 423$) were found in the group of 40–49 years old, 15.2% ($n = 320$) were found in the 50–59 years group, 7.3% ($n = 154$) were from the 60–69 years group, and finally, 3.3% ($n = 69$) of the individuals were in the group of 70 or more years.

Analyzing the population by Ethnicity, the predominant group was of Mixed race with 75.23% ($n = 1586$), followed by Hispanic whites with 16.17% ($n = 341$). The remaining groups corresponded to American Indians (4.74%, $n = 100$), Afro-Venezuelans (3.13% $n = 66$), and Others (0.71%, $n = 15$). Evaluating the subjects according to socioeconomic status, the largest number

of individuals were placed in Middle class with 838 members representing 39.75% of the total cases, followed by Lower Middle with 751 individuals (35.62%), Upper Middle class with 385 subjects (18.26%), Lower - Extreme poverty with 103 individuals (4.88%), and finally, Upper class with 31 individuals (1.47%).

Obesity Prevalence according to BMI Classification

The BMI distribution matches with a normal distribution, which was confirmed by a Geary's test ($p = 0.08$). Mean BMI was 28.25 ± 6.28 kg/m^2 (95% CI 27.98–28.52, $CV = 22.2\%$), with a minimum value of 14.22 kg/m^2 and a maximum of 68.80 kg/m^2 .

The distribution between age groups, sex and ponderal classification according to BMI is depicted in Table 1 and Figure 1. The prevalence of Obesity (≥ 30 kg/m^2) for both sexes and all ages was 33.3% ($n = 701$), distributed as follow: Obesity Class I 20.4% ($n = 429$), 8.7% ($n = 183$) for Obesity Class II, and 4.2% ($n = 89$) for Obesity Class III. The Underweight prevalence was only 2.1% ($n = 45$), meanwhile Normal-Weight was 29.8% ($n = 629$), and Overweight was 34.8% ($n = 733$). The prevalence of obesity on the female group was 32.4% ($n = 363$) with BMI of 27.87 ± 6.30 kg/m^2 (95% CI 27.50 to 28.24, $CV = 22.6\%$). On the other hand, the prevalence of obesity for the male group was 34.2% ($n = 338$) with BMI of 28.68 ± 6.25 kg/m^2 (95% CI 28.29 to 29.07, $CV = 21.8\%$); arithmetic mean difference was significant between both groups with $p = 0.004$. The BMI results according to age groups (Table 2) were analyzed using ANOVA (Table 3). Women's BMI rises steadily until the 30–39 years and 40–49 years where it stabilizes and progresses without significant difference. Table 2 shows the advancing gain of BMI, reaching a peak at 60–69 years, followed by a decline in the group ≥ 70 yrs old. On the other hand, males show a progressive BMI throughout time, which is significantly different with the youngest age group only.

Obesity Prevalence adjusted by Ethnic Group and Socioeconomic status. Table 4 shows Obesity prevalence adjusted to each racial group and socioeconomic strata. According to ethnics, Mixed Race obtained 1,586 subjects (75.23%), of which 35% were Overweight, 29.6% were Normal-weight and an overall 33% of Obese (≥ 30 kg/m^2) patients. Hispanic Whites group resulted in 341 individuals (16.17%), with

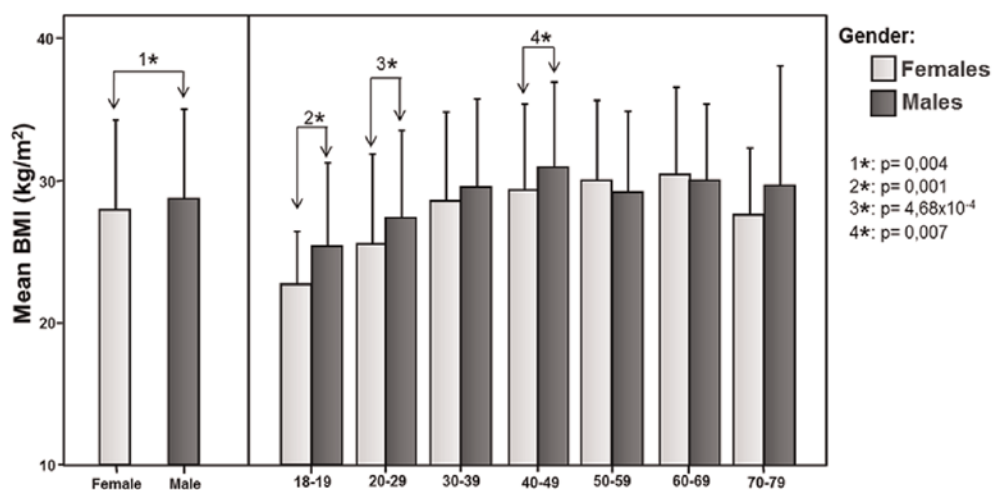


Figure 1. Body Mass Index according to age groups and gender, Maracaibo City 2010. The prevalence of Obesity was 32.4% for women and 34.2% for men. Significant difference (*) was observed between gender and in three age groups: ≤ 19 years, 20–29 years and 40–49 years. doi:10.1371/journal.pone.0035392.g001

Table 1. Distribution of the Population according to BMI, Sex and Age Groups, Maracaibo City 2010.

	Underweight		Normal Weight		Overweight		Obesity Class I		Obesity Class II		Obesity Class III		Obesity		Total	
	<18,5 kg/m ²		18,5–24,9 kg/m ²		25–29,9 kg/m ²		30–34,9 kg/m ²		35–39,9 kg/m ²		≥40 kg/m ²		≥30 kg/m ²		n	%
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Females	30	2,7	378	33,8	349	31,2	215	19,2	99	8,8	49	4,4	363	32,4	1119	100
<20	9	9	69	69	17	17	4	4	1	1	9	3,6	5	5,0	100	100
20–29	16	6,4	126	50,6	63	25,3	24	9,6	11	4,4	9	3,6	44	17,7	249	100
30–39	3	1,6	51	26,4	75	38,9	39	20,2	15	7,8	10	5,2	64	33,2	193	100
40–49	1	0,4	64	25,3	86	34,0	61	24,1	26	10,3	15	5,9	102	40,3	253	100
50–59	0	0	36	19,3	70	37,6	45	24,2	27	14,5	9	4,8	81	43,5	186	100
60–69	0	0	20	20,8	24	25,0	30	31,3	16	16,7	6	6,3	52	54,2	96	100
≥70	1	2,4	12	28,6	14	33,3	12	28,6	3	7,1	0	0	15	35,7	42	100
Males	15	1,5	251	25,4	384	38,6	214	21,6	84	8,5	40	4,0	338	34,2	989	100
<20	7	8,6	29	48,1	22	27,2	7	8,6	3	3,7	3	3,7	13	16,0	81	100
20–29	7	2,1	117	35,2	128	38,6	44	13,3	28	8,4	8	2,4	80	24,1	187	100
30–39	1	0,5	32	17,1	78	41,7	57	30,5	10	5,3	9	4,8	76	40,6	187	100
40–49	0	0	27	15,9	48	28,2	57	33,5	25	14,7	13	7,6	95	55,9	170	100
50–59	0	0	25	18,8	63	47	31	23,1	9	6,7	5	3,7	45	33,6	134	100
60–69	0	0	8	13,8	26	44,8	16	27,6	7	12,1	1	1,7	24	41,4	58	100
≥70	0	0	3	11,1	19	70,4	2	7,4	2	7,4	1	3,7	5	18,5	27	100
Total	45	2,1	629	29,8	733	34,8	429	20,4	183	8,7	89	4,2	701	33,3	2108	100

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34,0% Overweight and an overall 37,8% Obesity. The Amerindian group attained 100 patients, with an overall 24,0% of Obesity and 33% Overweight. Finally, the Afro-Venezuelan group gathered 66 subjects, with an overall Obesity of 28,8% and 39,4% of Overweight. The proportions Z-test showed that there was no significant difference between the adjusted prevalences of obesity within each ethnic group.

As for Socioeconomic status, Middle class prevailed with 838 individuals (39,75%), who obtained 35,6% Overweight and 33,8% of overall Obesity. Following, Lower Middle Class resulted in 751 subjects (33,62%), of which 35,7% were Overweight and an overall 32,8% were Obese. Upper Middle class attained 385 patients, with 35,7% Overweight and 32,7% Obese. It's noteworthy to mention that Extreme Poverty (Level V) obtained patients with Obesity Class I (n = 25, 24,3%), Obesity Class II (n = 6, 5,8%), and Obesity Class III (n = 5, 4,9%). As the previous paragraph, the adjusted prevalence of obesity within the socioeconomic strata showed no differences in the proportions Z-test.

Abdominal Obesity According to IDF/NHLBI/AHA/WHF/IAS/IASO consensus (IDF-2009) and ATPIII criteria

Applying the IDF-2009 (Table 5) classification, Abdominal Obesity was prevalent in Females among the age groups of 60–69 years (94.8%), 50–59 years (94.7%), 40–49 years (89.3%), >70 years (88.1%) and 30–39 years (82.4%). Moreover, Abdominal Obesity frequency in the Male group was among 60–69 years (94.8%), >70 years (92.6%), 50–59 years (88.0%), 40–49 years (84.1%), and 30–39 years (79.7%). With the ATPIII cut-offs (Table 5), the incidence for Abdominal Obesity in the Female group was located in the >70 years (81.0%), 50–59 years (79.7%), 60–69 years (70.8%), 40–49 years (66.4%), and 30–39 years

(61.7%); while, in the Male group, the most prevalent age group was 40–49 years (61.2%), 60–69 years (56.9%), 50–59 years (54.1%), >70 years (44.4%), and 30–39 years (38.0%).

Table 6 shows mean and standard deviation of WC values according to age group. In the female group, a steady rise is observed throughout the years, with a sudden decline at 70 years and beyond. On the other hand, the male group showed peaks at 40–49 years and 60–69 years, not sharing the steady climb seen in their counterparts. ANOVA was applied to each gender group to analyze WC behavior throughout time (Table 7). In the Females, the age group 20–29 years has significant differences between the

Table 2. Body Mass Index distributed according to Age Groups and Gender expressed as mean and standard deviation, Maracaibo City 2010.

Age Groups	BMI (Kg/m ²)			
	Females		Males	
	Mean	SD	Mean	SD
18–19	22,61	3,73	25,28	5,87
20–29	25,54	6,28	27,36	6,10
30–39	28,53	6,23	29,51	6,21
40–49	29,31	6,05	30,91	5,97
50–59	29,93	5,65	29,22	5,61
60–69	30,42	6,11	30,02	5,30
≥70	27,58	4,66	29,65	8,34

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Table 3. p values from ANOVA test when comparing BMI, according to Age Groups and Gender, Maracaibo City 2010.

	≤19 años	20–29 yrs	30–39 yrs	40–49 yrs	50–59 yrs	60–69 yrs	≥70 yrs
<20 yrs	-	0,081	$3,67 \times 10^{-06}$	$1,93 \times 10^{-10}$	$8,64 \times 10^{-05}$	$1,19 \times 10^{-04}$	0,020
20–29 yrs	0,001	-	0,002	$1,45 \times 10^{-08}$	0,044	0,034	0,486
30–39 yrs	$4,02 \times 10^{-13}$	$2,44 \times 10^{-06}$	-	0,301	1,000	0,998	1,000
40–49 yrs	$3,89 \times 10^{-13}$	$2,26 \times 10^{-11}$	0,813	-	0,192	0,960	0,952
50–59 yrs	$3,89 \times 10^{-13}$	$8,01 \times 10^{-13}$	0,230	0,924	-	0,981	1,000
60–69 yrs	$3,89 \times 10^{-13}$	$1,50 \times 10^{-10}$	0,136	0,696	0,995	-	1,000
≥70 yrs	$8,98 \times 10^{-05}$	0,360	0,963	0,569	0,219	0,122	-

The results shown here should be read as follows: the Female age groups are in the White boxes, while the Men age groups are in the Light Gray ones. Each Age group is compared as the table flows onwards. The black boxes represent the same age group which cannot compare with itself. ANOVA is Significant when $p < 0,05$. doi:10.1371/journal.pone.0035392.t003

rests of the decennial groups. Also, difference was observed between groups 30–39 years and 50–59/60–69 years. A similar tendency was observed in the male group, with the <20 years group having significant difference with the rest of the groups, while the 30–39 years only has significant differences with the groups below it and 40–49 years.

Using the WC classification from the IDF-2009, Abdominal Obesity prevalence was 74.2% (n = 1565), compared to 51.7% (n = 1089) using the ATPIII cut-offs. Even though Overweight and Obesity ($\geq 30 \text{ Kg/m}^2$) definitions from BMI criteria are two different categories, they convey information concerning adiposity that allows them to be used as surrogates for adipose disorders. In this light, combining Overweight and Obesity results show a

68.1% prevalence, which mildly correlates with the prevalence obtained using the IDF-2009 criteria (Figure 2).

Discussion

In Latin America, obesity prevalence have tripled in the last 20 years, affecting adults and children throughout the continent [21], being nutritional transition the proposed cause of such phenomena [22–23]. Due to the advancing pace of economics, science, education, politics and other sociocultural topics, the current tendency is the emigration towards industrialized countries, or in this case, to urbanized areas. A large number of these emigrating families are characterized by a common nutritional deterioration owed to a change in their eating habits induced by the socio-

Table 4. Distribution of the Population according to BMI, Ethnic Group and Socioeconomic Status, Maracaibo City 2010.

	Underweight		Normalweight		Overweight		Obesity Class I		Obesity Class II		Obesity Class III		Obesity		Total	
	<18,5 kg/m ²		18,5–24,9 kg/m ²		25–29,9 kg/m ²		30–34,9 kg/m ²		35–39,9 kg/m ²		≥40 kg/m ²		≥30 kg/m ²		n	%
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Racial Group																
Mixed Race	38	2,4	469	29,6	555	35	321	20,2	138	8,7	65	4,1	524	33,0	1586	100
Hispanic White	2	0,6	94	27,6	116	34	80	23,5	31	9,1	18	5,3	129	37,8	341	100
Afro-Venezuelan	2	3	19	28,8	26	39,4	9	13,6	8	12,1	2	3	19	28,8	66	100
Amerindians	3	3	40	40	33	33	15	15	5	5	4	4	24	24,0	10	100
Others	0	0	7	46,7	3	20	4	26,7	1	6,7	0	0	5	33,3	15	100
Total	45	2,1	629	29,8	733	34,8	429	20,4	183	8,7	89	4,2	701	33,3	2108	100
Socioeconomic Status																
Stratum I: High Class	0	0	11	35,5	10	32,3	7	22,6	3	9,7	0	0	10	32,3	31	100
Stratum II: Upper Middle Class	2	0,5	127	33	130	33,8	72	18,7	35	9,2	19	4,9	126	32,7	385	100
Stratum III: Middle Class	23	2,7	234	27,9	298	35,6	163	19,5	75	8,9	45	5,4	283	33,8	838	100
Stratum IV: Working Class	18	2,4	219	29,2	268	35,7	162	21,6	64	8,5	20	2,7	246	32,8	751	100
Stratum V: Extreme Poverty	2	1,9	38	36,9	27	26,2	25	24,3	6	5,8	5	4,9	36	35,0	103	100
Total	45	2,1	629	29,8	733	34,8	429	20,4	183	8,7	89	4,2	701	33,3	2108	100

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Table 5. Distribution of the sample according to IDF2009 and ATPIII classification, Age Groups and Gender, Maracaibo City 2010.

WC	IDF2009				ATPIII			
	Obese		Normal		Obese		Normal	
	≥80 cms ^a ≥90 cms ^b		≥80 cms ^a ≥90 cms ^b		≥89 cms ^a ≥102 cms ^b		≥89 cms ^a ≥102 cms ^b	
<i>Females</i>	877	78,3%	243	21,7%	642	57,3%	478	42,7%
<20	36	36%	64	64%	13	13%	87	87%
20–29	151	60,6%	98	39,4%	91	36,5%	158	63,5%
30–39	159	82,4%	34	17,6%	119	61,7%	74	38,3%
40–49	226	89,3%	27	10,7%	168	66,4%	85	33,6%
50–59	117	94,7%	10	5,3%	149	79,7%	38	20,3%
60–69	91	94,8%	5	5,2%	68	70,8%	28	29,2%
≥70	37	88,1%	5	11,9%	34	81%	8	19%
<i>Males</i>	687	69,5%	301	30,5%	377	38,2%	611	61,8%
<20	26	32,1%	55	67,9%	11	13,6%	70	86,4%
20–29	172	51,8%	160	48,2%	74	22,3%	258	77,7%
30–39	149	79,7%	38	20,3%	71	38%	116	62%
40–49	143	84,1%	27	15,9%	104	61,2%	66	38,8%
50–59	117	88%	16	12%	72	54,1%	61	45,9%
60–69	55	94,8%	3	5,2%	33	56,9%	25	43,1%
≥70	25	92,6%	2	7,4%	12	44,4%	15	55,6%
Total	1565	74,2%	543	25,8%	1089	51,7%	1019	48,3%

*Female's Waist Circumference cut-off.

^bMale's Waist Circumference cut-off.

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cultural influence of the location [24]. Other factors influence this scenario like the reduction of breastfeeding, physical inactivity and easier access to mass media communication which promotes the acquisition of food that at first glance looks more attractive, but it is in fact more expensive and less nutritious [24–25].

In Venezuela, few studies have been conducted to estimate the burden, and those that are published might fail to be reliable due to lack of a proper sample size and statistical analysis; nevertheless since they are current information in regards to the county's situation. In 2003, Campo et al. [26] used 347 subjects to conduct a prevalence study, reporting obesity values in 74% of the men and 56.7% of the women, associating this state with dyslipidemia, hyperinsulinemia, and higher risk for cardiovascular disease. Nuñez et al. [27] evaluated the nutritional status of 360 subjects, reporting that 29.8% of the female and 23.3% of the male subjects were obese, classified as 65.79% in obesity type I, 23.68% as type II, and 10.52% as type III. Ryder et al. [28] published their results on metabolic syndrome components in a sample of 2,716 subjects, reporting that over half of the Hispanic blacks of their study were obese.

The prevalence of Overweight was 34.8% while Obesity was 33.3%. According to ethnic groups, the adjusted Overweight prevalence was predominant in the Afro-Venezuelans (39.4%), followed by Mixed Race (35%) and Hispanic White (34%). Meanwhile, for overall Obesity (≥ 30 Kg/m²), Hispanic Whites prevailed with 37.8%, followed by Mixed Race (33%) and Afro-Venezuelans (28.8%). This disease is most prominent within young and contemporary adults, with 27.8% in the 20–29 age group, 20.1% in the 40–49 years of age and 18% in the 30–39 age group, a trend that is probably related to working status and physical inactivity.

One of the most interesting finding in regards to socioeconomic stratification is the fact that Obesity (class II and III) occurrence is observed in the Extreme Poverty class. Obesity, once considered a disease of the wealthy, is now considered a threat to the lower socioeconomic statuses [29], raising itself as one of the newest paradoxes in the 21st century [30]. The “Poor” and the “Rich” obese do not share the same characteristics; in fact, specific features can be pointed out [31–32]. “The Poor” obese is subject to genomemetic rearrangement (thrifty genotype) which enables him to efficiently store fats when subject to food fluctuation (food insecurity), situation that is fairly common in lower socioeconomic

Table 6. Waist Circumference distributed according to Age Groups and Gender expressed as mean and standard deviation, Maracaibo City 2010.

Age Groups	Waist Circumference (cm)			
	Females		Males	
	Mean	SD	Mean	SD
<20	77,45	9,76	87,40	15,90
20–29	85,11	13,61	92,15	14,57
30–39	92,23	13,48	99,82	14,90
40–49	94,04	13,64	105,33	15,16
50–59	96,75	11,14	103,11	14,38
60–69	97,68	12,78	105,60	13,81
≥70	95,00	11,80	100,50	8,99

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Table 7. p values from ANOVA test when comparing Waist Circumference means, according to Age Groups and Gender, Maracaibo City 2010.

	<20 yrs	20–29 yrs	30–39 yrs	40–49 yrs	50–59 yrs	60–69 yrs	≥70 yrs
<20 yrs	-	0,123	$6,23 \times 10^{-09}$	$2,86 \times 10^{-13}$	$1,71 \times 10^{-12}$	$2,24 \times 10^{-11}$	0,001
20–29 yrs	$9,74 \times 10^{-06}$	-	$2,99 \times 10^{-07}$	$2,87 \times 10^{-13}$	$1,43 \times 10^{-11}$	$3,73 \times 10^{-09}$	0,068
30–39 yrs	$3,89 \times 10^{-13}$	$1,65 \times 10^{-07}$	-	0,007	0,428	0,119	1,000
40–49 yrs	$3,89 \times 10^{-13}$	$6,15 \times 10^{-13}$	0,755	-	0,847	1,000	0,689
50–59 yrs	$3,89 \times 10^{-13}$	$3,89 \times 10^{-13}$	0,010	0,294	-	0,934	0,980
60–69 yrs	$3,89 \times 10^{-13}$	$4,04 \times 10^{-13}$	0,012	0,209	0,997	-	0,748
≥70 yrs	$3,55 \times 10^{-12}$	$7,67 \times 10^{-05}$	0,862	0,999	0,985	0,918	-

The results shown here should be read as follows: the Female age groups are in the White boxes, while the Men age groups are in the Light Gray ones. Each Age group is compared as the table flows onwards. The black boxes represent the same age group which cannot compare with itself. ANOVA is Significant when $p < 0,05$. doi:10.1371/journal.pone.0035392.t007

strata) and is relieved by the tendency to eat highly caloric meals mostly rich in carbohydrates and fat [33]. Meanwhile, the “Rich” obese is known for its sedentary lifestyle, use of motorized transportation and the fair access to junk food [33]. Obesity in low socioeconomic statuses is a rising wave within the Latin American population, especially when poor countries emerge from it strained economic and political situations, and poverty masses migrate toward urban areas [34–35], and these results may very well bear witness to such phenomenon in our city.

In regards to the natural history of weight gain, it can be described using WC's or BMI's progression throughout the years. In the female group, BMI and WC augmented gradually until 30–39 yrs group, suggesting that weight gain is prone to occur during childbearing age due to hormonal changes during pregnancy and nursing, a phenomenon which has been observed in Afro-American women [36]. Also, there seems to be an association between physical activity, number of children, socioeconomic

status and obesity, which is predominant in societies with nutritional transition like Venezuela [37–38]. Meanwhile, male weight gain behavior shows a different pattern. BMI and WC modifications starts very early, probably while entering adulthood, and shows a progressive increase till 40–49 yrs, where it declines slightly yet it climbs again at 60–69 yrs, to finally succumb after 70 yrs of age. These ups and downs could associated with alcohol intake [39] whose effects are severe are earlier if started at an early age, cessation of smoking [40], or the appearance of a cardiovascular event which lead to temporal weight loss [41]. It's worth mentioning that early weight as observed in this cohort is associated with high risk coronary death and myocardial infarction [42]. In both genders, there is a decline in BMI and WC which is usually explained by sarcopenia in senior adults [43–44], but it's important to highlight that muscle loss is worst in those patients who were or are currently obese during this period. Sarcopenic obesity in the elderly is considered a major health

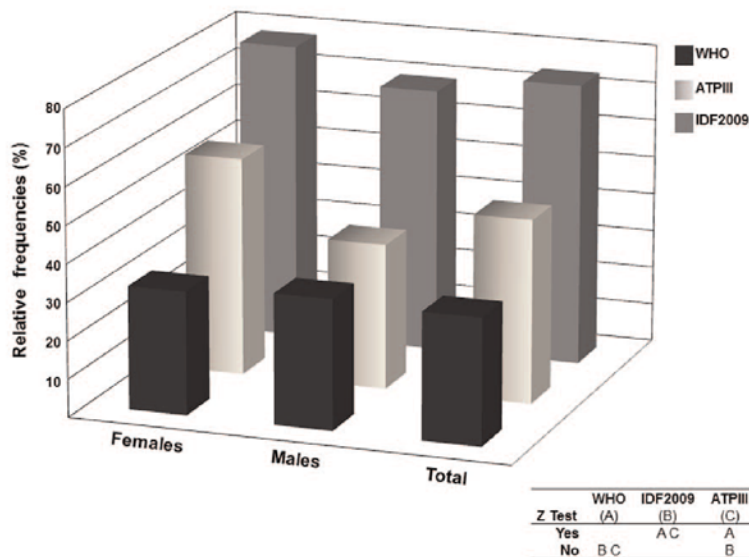


Figure 2. Prevalence of Obesity according to WHO, ATPIII and IDF-2009 criteria, Maracaibo City 2010. Using BMI (WHO) as tool for diagnosis, Obesity was observed in 33% of the sample and in both sexes. Taking waist circumference as reference, ATPIII obtained 51,7% of Obesity, in contrast to 74,2% applying IDF-2009's cut-offs. Using Z Test for proportions, significant differences were observed in between all classifications. doi:10.1371/journal.pone.0035392.g002

problem, because in spite of being stereotypically being considered non-frail adults, they have low relative muscle mass and lower muscle strength [45], which puts them at risk medical complications, including vertebrae and hip fractures.

Applying the IDF-2009 and ATPIII classifications, an increase in Obesity diagnosis was observed using the former WC values, which uses lower cut-offs compared to the latter because they are based on Asian data. Even though IDF-2009 recommends the Asian cut-offs due to lack of appropriate studies and consensus [19], such indication doesn't fit with the Hispanic physiognomy. Asian populations are recognized to have lower BMIs which were enough to suggest that they needed new BMI cut-off points to classify obesity [46]. Moreover, they have higher body fat percentages, especially in the subcutaneous compartment making them prone to generalized obesity despite their non-obese BMIs [47–48], which could be explained by their skeletal dimensions [49]. Asians tend to have shorter legs lengths, smaller WC, longer trunks lengths and less gynecoid fat mass compared to Hispanics [50–51]. It has been previously published [52–53] that WC is a better indicator for cardiovascular risk than BMI in Hispanics, which only enhances the need for appropriate WC reference values in our population.

This study is part of the Maracaibo City Metabolic Syndrome Prevalence Study, a major research study to discover metabolic syndrome's prevalence, risk factors, and related comorbidities. In our country, two recent trials have assessed the associated risk between obesity and cardiovascular disease. In the first trial by Ruiz-Fernández et al. [54], the most prevalent cardiometabolic

factors were low HDL, obesity/overweight, abdominal obesity, hypercholesterolemia, and insulin resistance. In the second trial, Espinoza et al. [55] reported that cardiovascular risk is strongly related to abdominal obesity, especially those with hypertriglyceridemic waist. Both of them used small samples (less than 100 patients) which makes them inappropriate for large population risk predictions.

Our study used a very representative sample from the Maracaibo City population, reporting a high prevalence of obesity using the WHO classification criteria for BMI and the WC's criteria from IDF-2009 and ATPIII. Nonetheless, these cut-off values are not set for ethnic groups like the ones represented in our population sample, which only highlights the need for proper ethnic specific criteria when anthropometric variables are applied. On a final note, it's noteworthy to mention that this study doesn't use self-reported or telephone questionnaires which allows for an accurate assessment of weight and height, without the inherent risk of overestimating or underestimating either of them respectively.

Author Contributions

Conceived and designed the experiments: VJB RPM JLM CC. Performed the experiments: VJB MP JJR RV DC MGP AT. Analyzed the data: VJB MP EBC AT RPM. Contributed reagents/materials/analysis tools: CC. Wrote the paper: JJR MP VJB JLM. Was part of the team that formulated, designed and undertook the current study: EF. Was part of the medical team in situ enrolling the patients: EF RA. Was part of the statisticians team analyzing the data: RA. Helped in the addition of the methodological aspects of the manuscript: RA.

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CAPÍTULO III

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Research Article

Sensitivity and Specificity Improvement in Abdominal Obesity Diagnosis Using Cluster Analysis during Waist Circumference Cut-Off Point Selection

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Introduction. The purpose of this study was to analyze the influence of metabolic phenotypes during the construction of ROC curves for waist circumference (WC) cutpoint selection. **Materials and Methods.** A total of 1,902 subjects of both genders were selected from the Maracaibo City Metabolic Syndrome Prevalence Study database. Two-Step Cluster Analysis (TSCA) was applied to select metabolically healthy and sick men and women. ROC curves were constructed to determine WC cutoff points by gender. **Results.** Through TSCA, metabolic phenotype predictive variables were selected: HOMA2-IR and HOMA2- β cell for women and HOMA2-IR, HOMA2- β cell, and TAG for men. Subjects were classified as healthy normal weight, metabolically obese normal weight, healthy and metabolically disturbed overweight, and healthy and metabolically disturbed obese. Final WC cutpoints were 91.50 cm for women (93.4% sensitivity, 93.7% specificity) and 98.15 cm for men (96% sensitivity, 99.5% specificity). **Conclusions.** TSCA in the selection of the groups used in ROC curves construction proved to be an important tool, aiding in the detection of MOWN and MHO which cannot be identified with WC alone. The resulting WC cutpoints were <91.00 cm for women and <98.00 cm for men. Furthermore, anthropometry is insufficient to determine healthiness, and, biochemical analysis is needed to properly filter subjects during classification.

1. Introduction

Obesity is emerging as an important health issue in Venezuela, particularly in urban areas, paradoxically coexisting with undernutrition [1]. The rising prevalence of overweight and obesity around the world shares a direct correlation with the increasing occurrence of obesity-related comorbidities such as high blood pressure (HBP), metabolic syndrome (MS), dyslipidemia, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD) [2]. Several pathophysiological aspects have been proposed to explain the close relationship

between these diseases, including the degree of adiposity and anatomic fat localization [1–3].

Currently, it is accepted that the majority of individuals who have obesity progressively develop insulin resistance, beta cell failure, and lastly T2DM, proving to be a biological continuum that is undeniably complicated and intricate [2, 3]. However, approximately 10–25% of obese individuals are metabolically healthy, most likely due to preserved insulin sensitivity probably due to genetic factors [4]. On the other hand, visceral adipose tissue inflammation, ectopic fat deposition, and adipose tissue dysfunction have been

proposed as an etiologic triumvirate that mediates insulin resistance in human obesity independently of total body fat mass [3]. Furthermore, it has been reported that around 10–15% of lean subjects may exhibit insulin resistance and other metabolic disturbances like dyslipidemia, dysglycemia, and HBP [5]. This landscape suggests four well-defined phenotypes existence in human beings according to body composition and metabolic status: (a) healthy normal weight (HNW), (b) metabolically obese normal weight (MONW), (c) metabolically disturbed obese (MDO), and (d) metabolically healthy obese (MHO) [6–8].

It has been highlighted that the proposed waist circumference (WC) cut-off points for Latin America, as well as other parts of the world, have relatively low areas under the curve (AUC) and therefore relatively low sensitivities and specificities during COR curves construction [9, 10] when using traditional criteria to classify subjects as healthy or sick, such as the presence of two or more components of the MS criteria as reported by Hara et al. [11]. Recently, our group built ROC curves for WC cutoff-point selection using 2 or more positive MS components to differentiate between healthy and sick individuals, rendering values of 90.25 cm (68.4% sensitivity, 65.8% specificity) for women and 95.15 cm for men (71.1% sensitivity, 67.4% specificity) [12].

Nevertheless, it has been suggested that unusual metabolic phenotypes such as MONW and MHO could influence the accuracy of obesity-centered studies due to difficulties in subject characterization [6–8], and this setback includes sensitivity and specificity from WC cut-offs point selection for obesity diagnosis. The biological traits of these uncommon phenotypes [6–8, 13] result in uncharacteristic grouping of metabolic components which could be difficult to predict. Therefore, the *proof-of-concept* would be that the early detection of these phenotypes prior to WC selection could improve the accuracy of selected WC cutpoints, and their future application in epidemiological studies.

The possibility of detecting MONW and MHO prior to any cut-off point selection method cannot rely on common markers such as WC because they can be misleading, due to the uniqueness of such phenotypes [7, 8]. In this context, the advantage of applying data mining techniques (like Cluster analysis) is that it allows the spontaneous grouping of individuals according to the behavior of metabolic and anthropometric variables, superseding the discriminating capacity of internationally appointed WC cut-off points and other preestablished criteria for metabolic alterations. Since these phenotypes do not behave in the same manner as the common ones, they could be considered as “noise” during the construction of ROC curves and might affect the sensitivity or specificity of the selected cutpoints for WC. Thus, the ability to identify and filter them from the ROC construction process is not only optional, but actually necessary.

Taking all this information into consideration, the purpose of this investigation was to identify subjects with unusual metabolic phenotypes and, afterwards, evaluate their influence during the construction of ROC curves for WC cut-off point selection.

2. Research Design and Methods

2.1. Subject Selection. The Maracaibo City Metabolic Syndrome Prevalence Study (MMSPS) [14] was a cross-sectional research study undertaken in the city of Maracaibo-Venezuela, whose purpose was the identification and analysis of MS and cardiovascular risk factors in the adult population of Maracaibo, the second largest city in Venezuela with 2,750,000 inhabitants. The methodology and randomization during sampling were published elsewhere [14]. Currently, there are 2,230 subjects enrolled [14], out of which 1,902 were selected, therefore excluding those individuals whose serum insulin levels were not determined and those diagnosis with diabetes mellitus; the latter was excluded because pharmacological treatment of these patients would modify the variables used in this research. The study was approved by the Bioethics Committee of the Endocrine and Metabolic Diseases Research Center, University of Zulia, and all participants signed a written consent before being interrogated and physically examined by a trained team.

2.2. Clinical Evaluation. The assessment of blood pressure was done applying the auscultatory technique, and HBP classification was made using the criteria proposed in the VII Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [15]. Mean Arterial Pressure (MAP) [16] was calculated using the equation (Diastolic Pressure + (Systolic Pressure – Diastolic Pressure/3)), expressed in mmHg. Obesity was classified applying the WHO criteria [17] based on the BMI value. Weight was assessed using a digital scale (Tanita, TBF-310 GS Body Composition Analyzer, Tokyo, Japan), while Height was obtained with a calibrated rod, with the patients shoeless and wearing light clothing. WC was measured using calibrated measuring tape in accordance to the anatomical landmarks proposed by the USA National Institutes of Health protocol [18].

2.3. Biochemical Analyses. Fasting levels of glucose, cholesterol, triglycerides (TAG), HDL-C, and hs-CRP were determined using an automatized computer analyzer (Human Gesellschaft für Biochemica und Diagnostica mbH). LDL and VLDL levels were calculated applying the Friedewald formulas [19]. When triacylglycerides were over 400 mg/dL measurement was done using lipoprotein electrophoresis and optical densitometry (BioRad GS-800 densitometer, USA). Insulin was determined using an ultrasensitive ELISA method (DRG Instruments GmbH, Germany, International DRG Division, Inc). The MS diagnosis was done using the IDF/NHLBI/AHA-2009 consensus criteria [20].

2.4. Insulin Sensitivity. This was assessed by the 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. Using ROC curve construction technique, our research team determined that the optimal cutpoint for HOMA2-IR for our population is 2.00 [21].

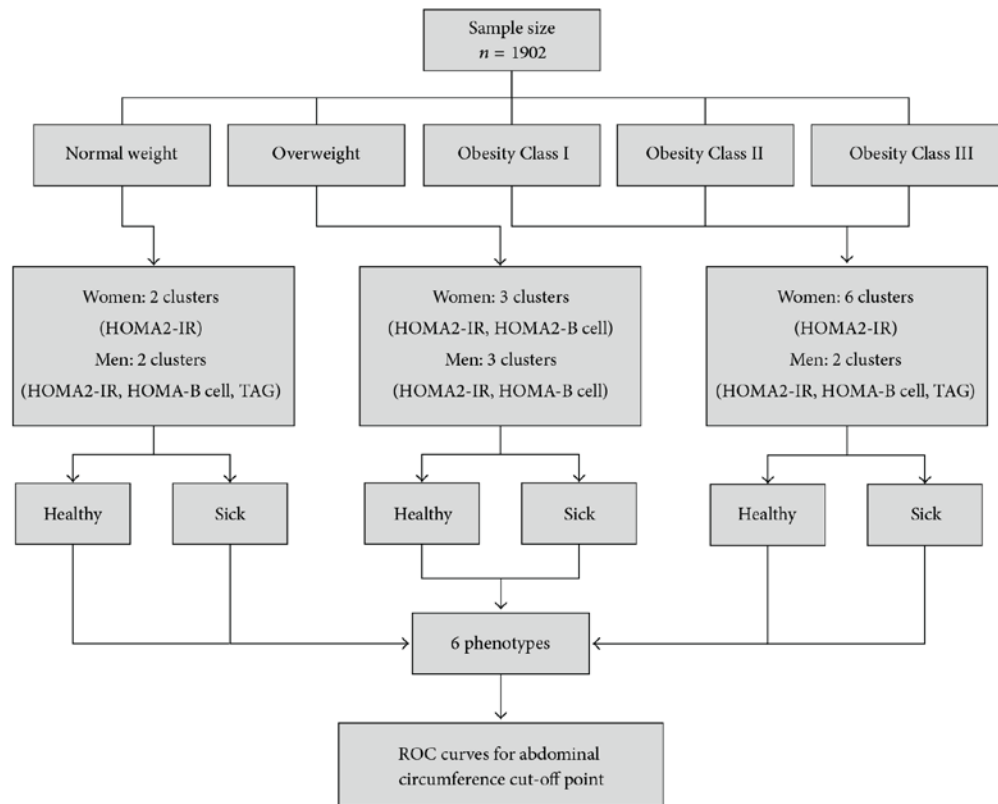


FIGURE 1: Diagram showing the two-stage clustering method to properly categorize the subjects into healthy and sick groups according to the selected predictors.

2.5. Statistical Analysis. Database construction and cluster analysis were done using the Statistical Package for the Social Sciences (SPSS) v19 for Windows (IBM Inc., Chicago, IL), while the ROC curves were constructed using the R Project for Statistical Computing, available at <http://www.r-project.org/>. Normal distribution of continuous variables was assessed using Geary's test; for normally distributed variables, the results were expressed as arithmetic mean \pm SD (standard deviation). Variables without normal distribution were logarithmically transformed, and normal distribution subsequently corroborated. The differences between arithmetic means were assessed using Student's *t*-test (when two groups were compared) or one-way ANOVA (when three or more groups were compared). Qualitative variables were expressed as absolute and relative frequencies.

2.5.1. Cluster Analysis Protocol. Previously to the Two-Step Cluster Analysis, all individuals were classified according to BMI in Normal Weight, Overweight, and Obese. The obese groups were primarily evaluated as a group (Obese, BMI ≥ 30 kg/m²) and according to WHO classification (Class I, Class II, and Class III) [17]; since the results showed similar behavior between them, we decided to use the classification

of Obesity because it allowed us to evaluate the subjects more clearly.

Each BMI category was submitted independently to the cluster analysis, categorizing the subjects as metabolically healthy or sick; see Figure 1. The metabolic variables evaluated as possible metabolic predictors based on their physiological function and biological plausibility were MAP, TAG, total cholesterol, HDL-C, HOMA2-IR, HOMA2- β cell, HOMA2-S, fasting blood glucose, non-HDL-C cholesterol, TAG/HDL-C index, and hs-CRP; WC was excluded because it was the assessed dependent variable. The predictive strength of these variables was analyzed in accordance to cluster ability and quality, ranging from 0.0 to 1.0. The best metabolic predictive variables selected were (a) HOMA2-IR and HOMA2- β cell for normal weight women; (b) HOMA2-IR, HOMA2- β cell and TAG for normal weight men; (c) HOMA2-IR and HOMA2- β cell for overweight women; (d) HOMA2-IR, HOMA2- β cell, and TAG for overweight men; and (e) HOMA2-IR for male and female obese patients (Table 1).

The Two-Step Cluster Analysis for SPSS was conducted in two phases [22]: during the first step (called "precluster"), the subjects are divided into several small subclusters. Then,

TABLE 1: Risk factors aggregation according to Cluster Analysis and derivatives clusters. Maracaibo City Metabolic Syndrome Prevalence Syndrome, 2013.

Phenotypes	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6
Normal-weight females	Size: 7.7% HOMA2-IR = 3.56	Size: 92.7 HOMA2-IR = 1.47*				
Normal-weight males	Size: 15.1% HOMA2-IR = 2.54 HOMA2-Bcell = 172.82 TAG = 180.99	Size: 84.9% HOMA2-IR = 1.15 HOMA2-Bcell = 109.69 TAG = 84.65*				
Overweight females	Size: 24.1% HOMA2-IR = 3.12 HOMA2-Bcell = 195.18	Size: 25.3% HOMA2-IR = 0.97 HOMA2-Bcell = 85.14*	Size: 50.6% HOMA2-IR = 1.69 HOMA2-Bcell = 137.06*			
Overweight males	Size: 18.3% HOMA2-IR = 3.57 HOMA2-Bcell = 212.77	Size: 46.1% HOMA2-IR = 1.80 HOMA2-Bcell = 144.05*	Size: 35.6% HOMA2-IR = 1.09 HOMA2-Bcell = 90.33*			
Obese Class I females	Size: 1.1% HOMA2-IR = 10.30	Size: 4.8% HOMA2-IR = 5.12	Size: 9.0% HOMA2-IR = 3.95	Size: 31.4 % HOMA2-IR = 1.16*	Size: 35.1% HOMA2-IR = 2.06	Size: 18.6% HOMA2-IR = 2.86
Obese Class II females	Size: 1.2% HOMA2-IR = 8.60	Size: 2.4% HOMA2-IR = 8.40	Size: 3.6% HOMA2-IR = 6.37	Size: 34.1% HOMA2-IR = 1.38*	Size: 32.9% HOMA2-IR = 2.52	Size: 25.6% HOMA2-IR = 3.66
Obese Class III females	Size: 4.8% HOMA2-IR = 1.31	Size: 14.3% HOMA2-IR = 4.5	Size: 2.4% HOMA2-IR = 9.0	Size: 14.3% HOMA2-IR = 3.67	Size: 31.0% HOMA2-IR = 2.35	Size: 33.3 % HOMA2-IR = 1.31*
Obese Class I male	Size: 1.0% HOMA2-IR = 8.60	Size: 11.2% HOMA2-IR = 4.60	Size: 19.8% HOMA2-IR = 3.11	Size: 28.3% HOMA2-IR = 2.19	Size: 26.3% HOMA2-IR = 1.59*	Size: 13.6% HOMA2-IR = 0.93*
Obese Class II male	Size: 2.7% HOMA2-IR = 8.10	Size: 16.0% HOMA2-IR = 3.36	Size: 26.7% HOMA2-IR = 3.36	Size: 28.0% HOMA2-IR = 1.71*	Size: 17.3% HOMA2-IR = 2.45	Size: 9.3% HOMA2-IR = 0.70*
Obese Class III male	Size: 2.6% HOMA2-IR = 10.10	Size: 10.3% HOMA2-IR = 7.02	Size: 15.4% HOMA2-IR = 5.83	Size: 20.4% HOMA2-IR = 4.11	Size: 38.5% HOMA2-IR = 2.78	Size: 12-8% HOMA2-IR = 1.52*

The cells with "*" indicate the "healthy" clusters for each phenotype. The cells without "*" represent the "sick" clusters of persons.

HOMA2-IR: Homeostasis Model Assessment-2 for Insulin Resistance; HOMA2-Bcell: Homeostasis Model Assessment-2 for Pancreatic β Cell Function; TAG: triglycerides, expressed in mg/dL.

the obtained subclusters are grouped into a preferred number of clusters; if the desired number of clusters is unknown, the SPSS Two-Step Cluster Component will find the proper number of clusters automatically. Once the program analyzed the subclusters and the characteristics of each BMI category (as described previously), the subjects were categorized in 6 phenotypes: HNW, MONW, healthy and metabolically disturbed overweight, MDO, and MHO.

2.5.2. Cluster Quality Measures. To evaluate the quality of the resulting clusters, the cohesion, separation, and silhouette coefficient were calculated [23–25]. The silhouette coefficient [26] encompasses the ideas of cohesion (the closeness of related objects in a cluster) and separation (the distance

between objects in a cluster), describing the average distances between variables within a cluster and between other clusters, the highest silhouette results being between 0.5 and 1 [23, 26]. The clusters with high cohesion are preferred because it is a guarantee of good quality clustering, demonstrated by high silhouette values and truly clustered variables [23–26].

2.5.3. Cross-Validation Technique. Cluster validation aims to evaluate the differences within a cluster in order to confirm clustering selection to estimate the accuracy of a prediction model [27]. This method requires the division of the data into two groups: one to *train* (training dataset) and the other to *validate* (testing dataset) [27, 28]. The process requires doing several rounds of partitioning and cross-validation,

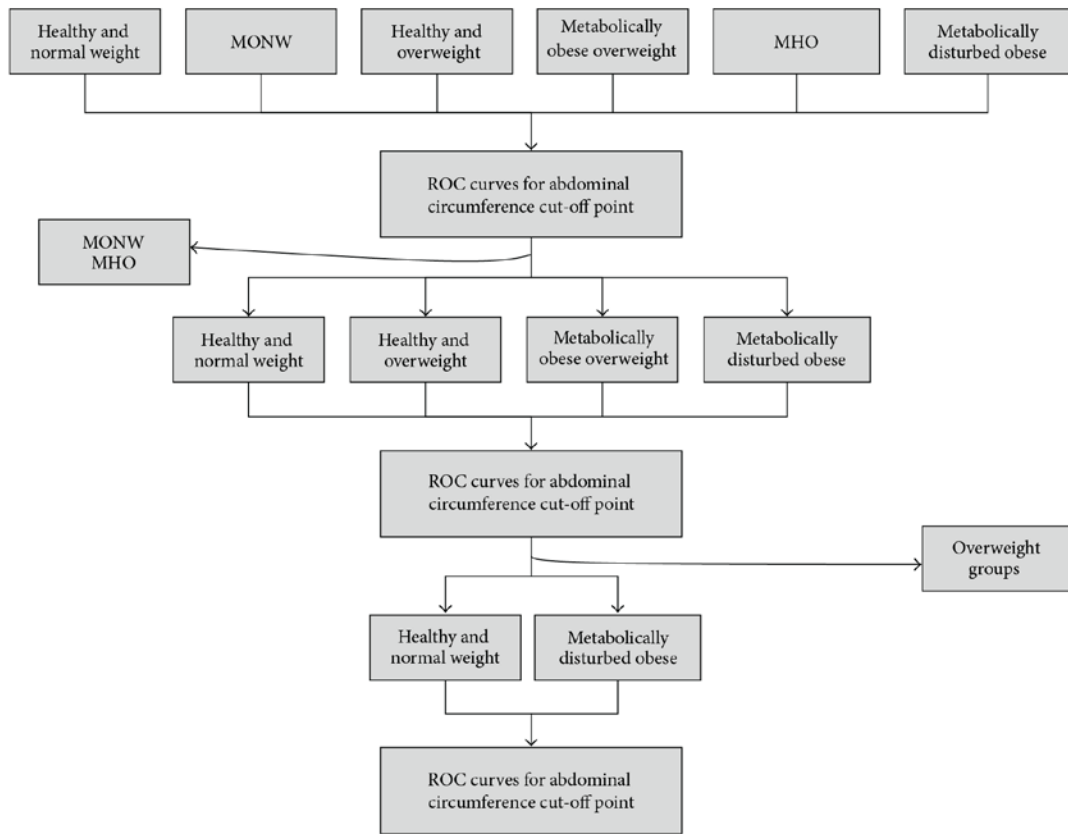


FIGURE 2: Diagram that depicting the selection process during the phenotype analysis and exclusion to determine the proper cut-off point for WC.

where all the analyses are performed on the training set and then validating such analyses in the testing set [27, 28], and agreement was assessed by Cohen's kappa coefficient.

2.5.4. ROC Curves Construction. The Receiving Operating Characteristic (ROC) [29] curves were used to analyze the predictive validity and to determine optimal cut-off values for WC following a series of exclusion steps (Figure 2). Comparison of AUC was calculated with DeLong's Test [30]. Several indexes were calculated to assess the optimal cut-off point on the curve, such as the Youden Index, the distance of the point closest to (0,1) on the ROC curve and Positive Likelihood Ratio were calculated [31]. Nevertheless, sensitivity over specificity was considered when selecting WC cut-off points.

3. Results

3.1. General Characteristics of the Population. An overall 1,902 subjects were studied, out of which 52.15% were women and 47.84% were men. Age arithmetic mean for all participants was 38.70 ± 15.06 years (IC 95%, 38.02–39.08), 37.17 ± 14.54 years for men (IC 95%, 36.85–38.65) and $40.11 \pm$

15.29 years for women (IC 95%, 39.15–41.06). Distribution of the population according to age groups, ethnic groups, BMI, and MS diagnosis is shown in Table 2. For anthropometric parameters, biochemical, and blood pressure results see Table 3.

3.2. Two Steps Cluster Analysis. Using all the information obtained from the clusters, six phenotypes were generated: HNW (28.29%), MONW (3.36%), Healthy Overweight (28.08%), Metabolically disturbed Overweight (7.47%), MHO (11.20%), and MDO (21.60%) (Table 5); note that MONW and MHO subjects represent 14.56% of the total sample. Table 6 shows general biochemical characteristics of the 6 phenotypes built by cluster analysis.

Cluster quality was assessed with the silhouette coefficient, which rendered >0.5 for every cluster, meaning that all clusters were classified as good models. Next, cross-validation was performed, dividing the subjects in two groups: S1 and S2. The S1 group was used as the training set, where centroid-based clustering was calculated using the steps shown in Figure 1. The S2 group was used as the validating set (S2), where clusters were obtained using two methods: (a) normal clustering process (S2-clusters) and (b) clustering based

TABLE 2: General characteristics of the population from Maracaibo City Metabolic Syndrome Prevalence Study, 2013.

	Women		Men		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Age groups						
18-19	87	8.8	70	7.7	157	8.3
20-29	218	22.0	294	32.3	512	26.9
30-39	176	17.7	178	19.6	354	18.6
40-49	230	23.2	164	18.0	394	20.7
50-59	170	17.1	136	14.9	306	16.1
60-69	74	7.5	46	5.1	120	6.3
70 and more	37	3.7	22	2.4	59	3.1
Ethnic groups						
Mixed race	757	76.3	706	77.6	1463	76.9
Hispanic White	162	16.3	138	15.2	300	15.8
Afro-Venezuelan	24	2.4	31	3.4	55	2.9
Amerindian	39	3.9	34	3.7	73	3.8
Other	10	1.0	1	0.1	11	0.6
BMI						
Low weight	29	2.9	11	1.2	40	2.1
Normal weight	335	33.8	227	24.9	562	29.5
Overweight	316	31.9	360	39.6	676	35.5
Obesity grade I	188	19.0	198	21.8	386	20.3
Obesity grade II	82	8.3	75	8.2	157	8.3
Obesity grade III	42	4.2	39	4.3	81	4.3
MS IDF/NHLBI/AHA-2009						
Absence	627	63.2	520	57.1	1147	60.3
Presence	365	36.8	390	42.9	755	39.7
Total	992	100.0	910	100.0	1902	100.0

on centroids and distances obtained from S1 (S2 clusters according to S1). All the resulting S2-derived clusters were compared using Cohen's kappa, resulting in 0.902; $P < 0,00001$ (Table 4).

3.3. ROC Curves

3.3.1. Curves Constructed with the Overall Population (All 6 Groups). We sought to find an appropriate cut-off point for this population sample, applying the 6 phenotypes previously described in a stepwise manner. In Figure 3, ROC curves for men and women are shown. In Figure 3(a), the selected cut-off point for women was 91.25 cm, with an AUC 0.768, sensitivity of 73.3%, and a specificity of 68.5% (Table 7). In the next panel, Figure 3(b), the chosen cut-off point for men was 98.15 cm, with an AUC of 0.786, 74.8% sensitivity, and 69.7% specificity.

3.3.2. COR Curves Construction without MONW and MHO Groups (4 Groups). The following ROC curves were built without the "anomalous signals" derived from the atypical phenotypes, MONW and MHO. In Figure 4(a), the women's ROC curve is depicted, with a selected cut-off point of 91.50 cm, showing an AUC of 0.890, 80.1% sensitivity, and 79.3% specificity. In the following panel, Figure 4(b), the

selected cut-off point for men was 98.15 cm, with an AUC of 0.919, sensitivity of 83.8%, and a specificity of 82.3% (Table 7).

3.3.3. COR Curves Construction Excluding MONW, MHO, and Overweight Groups (2 Groups). The final ROC curves were built without the Overweight groups, leaving only the HNW and the MDO. In Figure 5(a), the women's ROC curve is shown, with a chosen cut-off point of 91.5 cm, characterized by an AUC of 0.982, sensitivity of 93.4%, and a specificity of 93.7%. In Figure 5(b), the men's cut-off point was 98.15 cm, with an AUC of 0.998, sensitivity of 96%, and a specificity of 99.5%; see Table 7. Figure 6 shows all the constructed ROC curves and their DeLong results. Finally, Table 8 shows the metabolic variables of the subjects categorized with the obtained WC cut-off points from this investigation, resulting in significant differences between obese and nonobese subjects in every variable, except in HOMA-2 β cell in the women's group.

4. Discussion

It is imperative to determine accurate WC cut-off values in order to diagnose abdominal obesity, given the progressive and fast rise in the worldwide prevalence of this disease. This growing epidemic has been a driving force for the

TABLE 3: General characteristics of the population according to gender. Maracaibo City Metabolic Syndrome Prevalence Study, 2013.

	Women		Men		Total	
	Mean	SD	Mean	SD	Mean	SD
BMI	27.92	6.25	28.77	6.21	28.32	6.24
WC	91.12	13.96	98.40	15.85	94.57	15.32
FG	98.20	31.01	99.09	32.73	98.62	31.84
Insulin	14.57	9.34	14.83	9.83	14.69	9.58
HOMA2-IR	2.03	1.29	2.08	1.37	2.05	1.33
HOMA2-B cell	136.97	58.67	137.25	65.83	137.10	62.19
HOMA2-S	66.70	42.35	69.11	45.47	67.85	43.88
T-Chol	193.77	44.41	187.32	47.33	190.71	45.92
TAG	117.52	87.44	144.00	114.79	130.08	102.18
HDL-C	46.90	11.89	40.95	11.42	44.08	12.04
SBP	117.69	17.29	121.85	15.98	119.66	16.80
DBP	75.65	10.81	79.03	11.46	77.25	11.25
MAP	89.66	12.17	93.30	12.12	91.39	12.28
Non-HDL-C	146.87	45.08	146.37	47.76	146.63	46.36
TAG/HDL	2.86	3.03	4.03	4.27	3.41	3.72

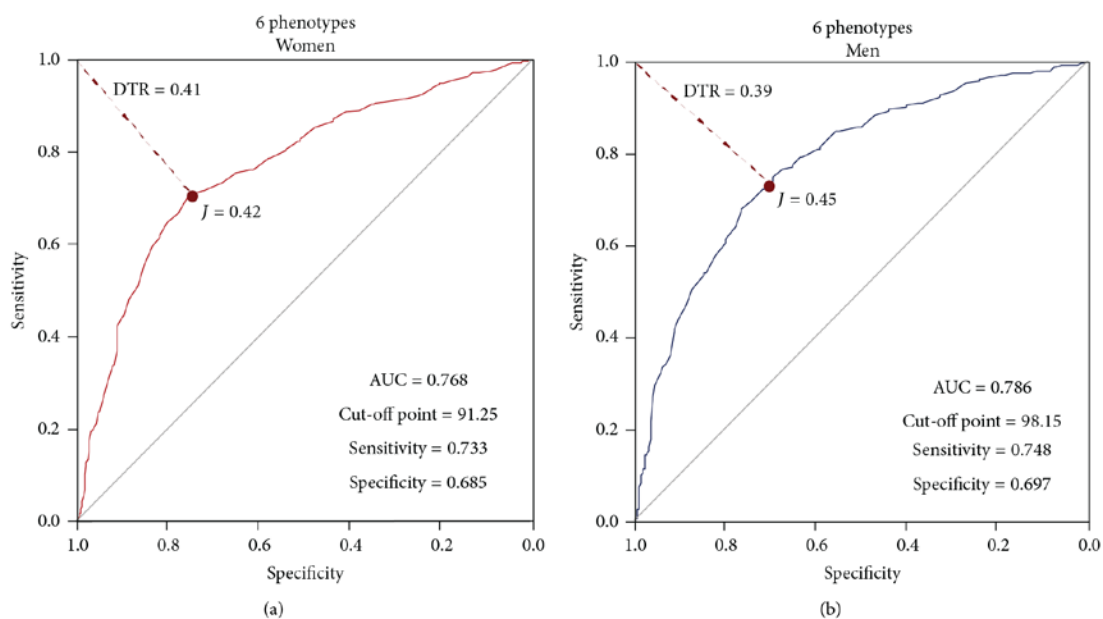


FIGURE 3: ROC curves constructed using 6 phenotypes.

development of improved diagnostic tests to aid physicians in their daily practice to diagnose abdominal obesity associated with metabolic disorders [31]. The search for ethnic-specific values for anthropometric measures requires the application of several techniques, ROC curves being one of the tools available in order to ascertain an appropriate cut-off point [32].

ROC curves approach to determine suitable cut-off points for WC has been extensively used [9–11], especially in populations that are not properly classified in the latest

MS criteria by the IDF/NHLBI/AHA-2009 due to lack of sufficient population-specific data for the WC variable [20]. As opposed to more widespread methodology in these studies [9], the involvement of data mining techniques (cluster analysis) enhances the selection of healthy and sick subjects for the construction of ROC curves because it does not use predetermined variables nor arbitrary cut-off points to decide; instead it allows the program to group the individuals according to their biological characteristics and spontaneous tendencies [22]. This improvement in subject classification

TABLE 4: Distribution of the subjects (training and testing datasets) during cross-validation process.

	Cluster Analysis in S2						Total	
	Cluster 1		Cluster 2		Cluster 3			
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Cluster Analysis in S2 according to S1								
Cluster 1	609	64.0	0	0	31	3.3	640	67.3
Cluster 2	0	0	50	5.3	0	0	50	5.3
Cluster 3	0	0	14	1.5	247	26.0	261	27.4
Total	609	64.0	64	6.7	278	29.2	951	100.0

S1: a subgroup of subjects randomly selected from the database.

S2: a subgroup of subjects randomly selected from the database.

Cohen's kappa coefficient: 0.902 ($P < 0.00001$).

TABLE 5: Distribution of the population according to BMI and Metabolic Health Status. Maracaibo City Metabolic Syndrome Prevalence Syndrome, 2013.

	Women				Total		Men				Total	
	Healthy		Sick*				Healthy		Sick*			
	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Normal weight	336	92.3	28	7.7	364	100.0	202	84.9	36	15.1	238	100.0
Overweight	240	75.9	76	24.1	316	100.0	294	81.7	66	18.3	360	100.0
Obesity class I	59	31.4	129	68.6	188	100.0	79	39.9	119	60.1	198	100.0
Obesity class II	28	34.1	54	65.9	82	100.0	28	37.3	47	62.7	75	100.0
Obesity class III	14	33.3	28	66.7	42	100.0	5	12.8	34	87.2	39	100.0
Total	677	68.2	315	31.8	992	100.0	608	66.8	302	33.2	910	100.0

*The "Sick" term applied here conveys the metabolically disturbed subjects which have metabolic obese profiles.

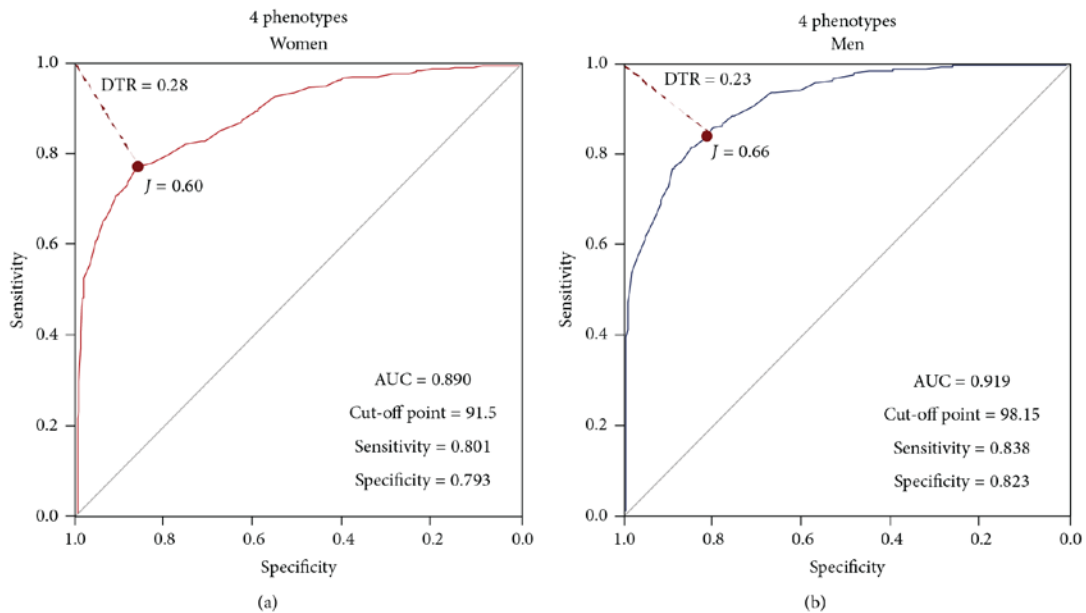


FIGURE 4: ROC curves constructed using 4 phenotypes, after the exclusion of MOWN and MHO groups.

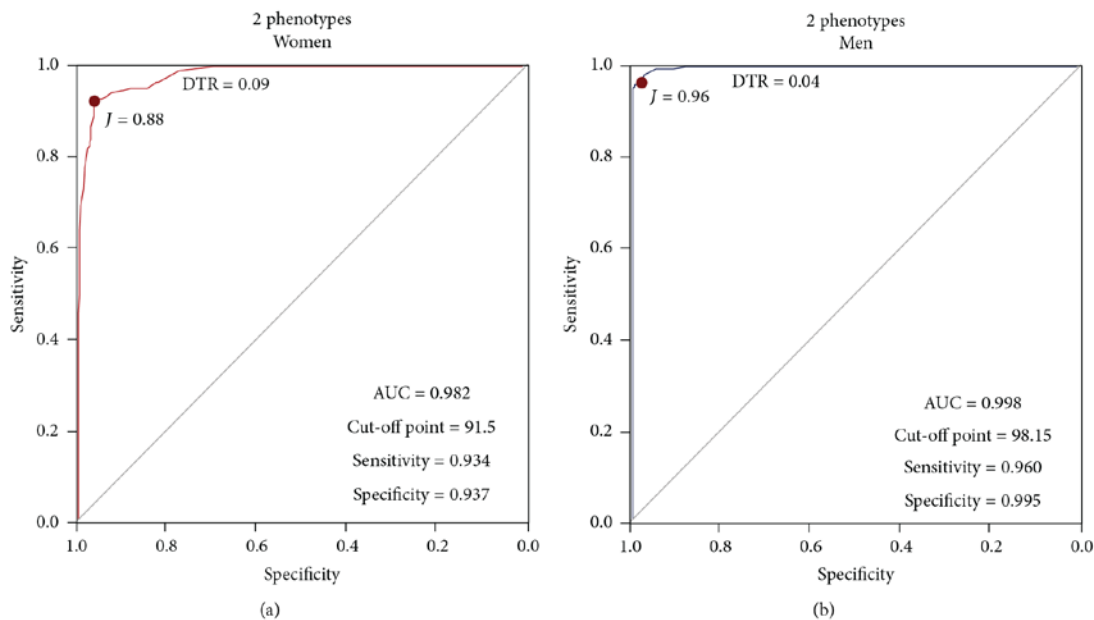


FIGURE 5: ROC curves constructed using 2 phenotypes, after exclusion of Overweight groups.

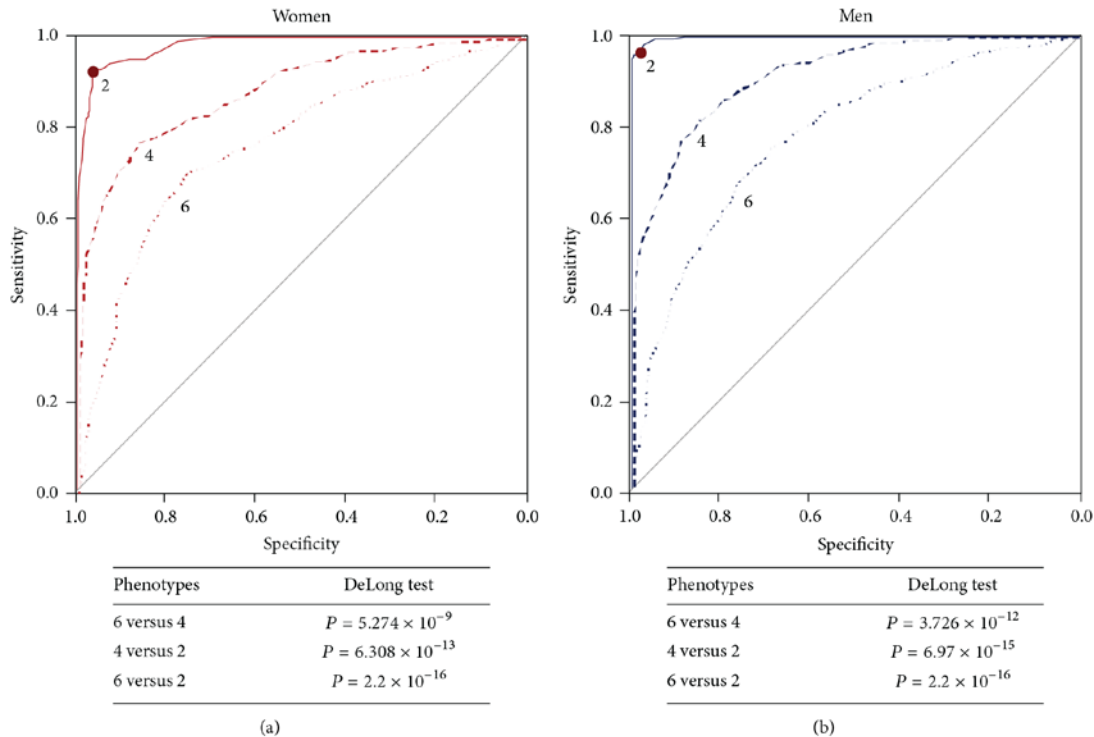


FIGURE 6: Comparison of the ROC curves constructed in the overall stepwise process for both men and women. Notice that the curves get closer to the 1.0 corner as the true healthy and sick subjects are being selected. The DeLong test results are shown as well.

TABLE 6: Metabolic variables behavior of each metabolic phenotype according to sex. Maracaibo City Metabolic Syndrome Prevalence Syndrome, 2013.

	Women		Men	
	Mean	SD	Mean	SD
WC				
HNW	79.27	8.24	81.54	6.87
MONW	77.20	7.07	86.98	7.62
Healthy overweight	89.69	6.88	94.82	6.59
Sick* overweight	90.27	7.59	97.76	6.10
MHO	104.40	10.55	109.17	11.94
MDO	105.50	10.07	116.04	15.32
HOMA2-IR				
HNW	1.47	0.48	1.15	0.44
MONW	3.56	1.36	2.54	1.47
Healthy overweight	1.45	0.51	1.49	0.58
Sick* overweight	3.12	1.14	3.57	1.41
MHO	1.24	0.37	1.40	0.41
MDO	3.14	1.54	3.39	1.42
TAG				
HNW	86.49	52.06	84.65	38.44
MONW	120.61	155.70	180.99	124.76
Healthy overweight	112.97	68.92	131.01	80.97
Sick* overweight	131.32	93.03	173.92	106.29
MHO	120.12	73.96	143.08	118.27
MDO	144.57	95.54	184.60	121.59
HDL-C				
HNW	49.29	11.81	46.00	11.16
MONW	51.61	11.54	39.50	11.84
Healthy overweight	48.17	11.65	41.91	12.88
Sick* overweight	44.43	10.84	38.45	8.39
MHO	45.57	13.01	40.15	9.91
MDO	44.13	11.45	36.71	8.48
MAP				
HNW	83.80	9.60	87.28	9.92
MONW	87.00	13.17	88.28	10.54
Healthy overweight	89.20	11.33	93.44	11.77
Sick* overweight	88.85	10.46	91.45	10.39
MHO	95.78	13.91	96.38	13.17
MDO	95.10	12.07	98.01	12.47

*The "Sick" term applied here conveys the metabolically disturbed subjects which have metabolically obese profiles.

HDL-C, high density lipoprotein, expressed in mg/dl; HOMA2-IR: Homeostasis Model Assessment-2 for Insulin Resistance; MAP: mean arterial pressure, expressed in mmHg; TAG: triglycerides, expressed in mg/dL; WC, waist circumference, expressed in cm.

guarantees cutoff points with superior sensitivity and specificity, which is the ultimate goal in surveys such as ours.

Several studies have suggested that the WC cut-off proposed by the IDF/NHLBI/AHA-2009 consensus seemed to be invalid for certain ethnicities, particularly the Hispanic groups in Latin America [9]. Aschner et al. [10] published their WC cut-off points based on ROC curves using visceral fat area ($\leq 100 \text{ cm}^2$) as the independent variable, with resulting

cut-off values of 94 cm for men (89.9% sensitivity and 80.2% specificity) and 90–92 cm for women (78.9%–72.9% sensitivity and 67.6%–74.5% specificity). However, Aschner's research conveys the use of visceral fat to find an optimal cut-off value of WC which detects subjects at risk of abdominal obesity. A cut-off point of 100 cm^2 was calculated for Japanese population [33], using metabolic criteria cutoffs that are now considered outdated (e.g., fasting glucose $>110 \text{ mg/dL}$). Moreover, Latin-Americans are phenotypically and genetically different from Asians [34], which hinders the possibility of properly extrapolating results from their group onto ours. Despite these shortcomings, this cut-off has been used in several studies as a standard. Currently, Latin America also needs cut-off values concerning visceral fat, especially when ethnic minority groups are included, such as the Amerindians and Afro-Descendants.

Two-Step Cluster Analysis approach enhances sorting of the subjects, allowing for better grouping and evaluation according to biochemical and anthropometric coalescent variables, eliminating the bias observed in predetermined variables and cut-off points. On this reasoning, 6 phenotypes were constructed: Healthy Normal-Weight, MONW, Healthy and Metabolically Disturbed Overweight, MHO, and Metabolically Disturbed Obese. Each group has diverse cardiometabolic profiles which have been widely described in the last decade [5–8, 13]. Evidently, the MONW and MHO are exceptions to rules that have been described traditionally, where first glance examination of an obese or lean patient would automatically classify them as sick or healthy, respectively. Using the selected parameters according to BMI, a proper classification is possible, being demonstrated by the enhancement of sensitivity, specificity, and AUC for abdominal circumference in these groups.

ROC curve programs allow the determination of true positive and negative cases, by providing cut-off points and their corresponding AUC, sensitivity, and specificity; nevertheless, this feature depends on an appropriate sorting of the sample and its accuracy is confirmed with the comparison of curves before and after selection. Eliminating noise during the filtering of information is of paramount importance, since it behaves as phantom signals which derail the evaluation towards inaccurate values. Exclusion of the MONW and MHO categories impedes the use of false data to determine a cut-off point, rendering enough sensitivity and specificity to identify subjects at risk. It is imperative that physicians embrace the advantages offered by both techniques in order to be able to determine valid cutoff points in ethnic-based studies concerning metabolic variables, which are categorized as biological and thus display a continuous behavior.

The other groups that got excluded were the Overweight individuals. The definition of overweight lies between normalcy and obesity, between 25.00 and 29.99 kg/m^2 . This allocation confers this definition a "transition" quality which is based on the possibility of reducing weight and achieving normal weight or augmenting weight reaching obesity levels [35, 36]. Moreover, this also suggests that weight is a continuous biological factor, and the arbitrary classification of overweight is a transition phase in the natural history

TABLE 7: Waist circumference cut-offs based on ROC Curves. Sensitivity, Specificity, Youden's Index, Positive Likelihood, and Distance to the ROC Curve. Maracaibo City Metabolic Syndrome Prevalence Syndrome, 2013.

	WC (cm)	Sensitivity (%)	Specificity (%)	Youden's Index	Distance to ROC	LR+
6 phenotypes						
Women	90.75	75.2	65.3	0.41	0.42	2.16
	91.25 [¶]	73.3	68.5	0.42 [¶]	0.41 [§]	2.32
	91.75	73.3	68.4	0.42 [¶]	0.41 [§]	2.32
Men	97.75	76.5	67.8	0.44	0.40	2.37
	98.15 [¶]	74.8	69.7	0.45 [¶]	0.39 [§]	2.46
	98.40	74.5	69.7	0.44	0.40	2.45
4 phenotypes						
Women	90.75	82.2	75.9	0.58	0.29	3.41
	91.5 [¶]	80.1	79.3	0.60	0.28 [§]	3.86
	92.25	78.4	83.0	0.61 [¶]	0.28 [§]	4.61
Men	97.50	85.7	80.2	0.66 [¶]	0.24	4.32
	98.15 [¶]	83.8	82.3	0.66 [¶]	0.23 [§]	4.73
	98.40	83.5	82.3	0.66 [¶]	0.24	4.71
2 phenotypes						
Women	90.75	94.3	92.6	0.87	0.09 [§]	12.74
	91.5 [¶]	93.4	93.7	0.88 [¶]	0.09 [§]	14.82
	92.5	92.9	94.6	0.88 [¶]	0.09 [§]	17.20
Men	97.00	96.0	98.5	0.95	0.04 [§]	64.00
	98.15 [¶]	96.0	99.5	0.96 [¶]	0.04 [§]	192.00
	98.65	95.5	99.5	0.95	0.05	191.00

6 phenotypes: HNW, MONW, MHO, MDO, and Overweight healthy and sick groups

4 phenotypes: HNW, MONW, and Overweight healthy and sick groups.

2 phenotypes: HNW and MDO.

(¶) Selected cut-off (in cm) based on Sensitivity, Specificity, Youden Index, and Positive Likelihood Ratios (LR+), giving emphasis to highest sensitivity values.

(¶) Cutpoint 1, asserted using the maximum Youden Index.

(§) Cutpoint 2, obtained from the point closet to the ROC (0.1).

TABLE 8: General characteristics of the subjects after categorization using the newly selected WC cutpoints. Maracaibo City Metabolic Syndrome Prevalence Study, 2013.

	Women				P	Men				P
	Abdominal obesity*		Abdominal obesity**			Abdominal obesity**		Abdominal obesity*		
	Absence	Presence	Absence	Presence		Absence	Presence	Absence	Presence	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
BMI (Kg/m ²)	23.84	3.33	32.58	5.58	<0.0001	24.98	3.22	33.30	6.03	<0.0001
WC (cm)	80.84	7.37	102.85	9.26	<0.0001	87.22	7.47	111.60	12.94	<0.0001
FG (mg/dL)	12.67	6.96	16.62	11.04	<0.0001	11.37	7.16	18.66	11.04	<0.0001
Insulin (μUI/mL)	90.29	11.67	98.28	21.81	<0.0001	89.56	12.18	99.99	28.10	<0.0001
HOMA2-IR	146.16	55.94	150.01	62.82	<0.0001	135.45	50.81	165.07	80.20	<0.0001
HOMA2-Bcell	67.59	39.68	56.62	37.36	0.313	79.18	43.15	49.25	35.45	<0.0001
HOMA2-S	1.85	0.96	2.46	1.55	<0.0001	1.67	1.03	2.77	1.57	<0.0001
T-Chol (mg/dL)	185.04	41.95	204.04	45.07	<0.0001	180.75	42.54	196.06	51.89	<0.0001
TAG (mg/dL)	93.86	66.33	136.68	87.99	<0.0001	113.00	73.17	170.87	118.50	<0.0001
HDL-c (mg/dL)	48.80	11.77	45.32	11.86	<0.0001	43.55	12.65	38.14	8.78	<0.0001
SBP (mmHg)	112.12	14.47	122.97	18.34	<0.0001	117.35	14.25	126.74	16.35	<0.0001
DBP (mmHg)	72.03	9.48	79.36	10.99	<0.0001	75.73	10.52	82.65	11.63	<0.0001
MAP (mmHg)	85.40	10.43	93.90	12.46	<0.0001	89.61	10.92	97.34	12.35	<0.0001
Non-HDL-c (mg/dL)	136.24	42.45	158.71	45.09	<0.0001	137.20	42.99	157.92	51.51	<0.0001
TAG/HDL	2.17	2.14	3.38	2.94	<0.0001	2.92	2.41	4.92	4.06	<0.0001

BMI, body mass index; FG, fasting glycemia; HDL-c, high density lipoprotein; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; T-Chol, total cholesterol; TAG, triglycerides; TAG/HDL, TAG/HDL index; WC, waist circumference, expressed in cm. *WC ≥ 91.50 cm; **WC ≥ 98.15 cm.

of obesity [36]. Therefore, since overweight subjects and considered “in transition” were removed them from the final WC ROC curve construction.

It is necessary to emphasize three facts: WC alone cannot recognize MONW or MHO subjects, anthropometry is insufficient to determine healthiness, and relying on the information obtained in other variables is needed for the filtering process. These facts open a new window of opportunity to investigate the establishment of new strategies that can help identify peculiar phenotypes, such as the use of somatotypes constructed with local anthropometric and biochemical data, facilitating the identification of MOWN and MHO subjects.

The chosen cut-off point for the Women’s group was 91.25 cm, very similar to that reported by Herrera et al. [9], suggesting that the females in the sample tend to have higher WC values than the ones set previously both by ATPIII [37] (<88 cm) and IDF/NHLBI/AHA-2009 (<80 cm). This finding is probably explained by differences regarding height, fat distribution, and genetic background [38]. It is noteworthy to point out that, even after the groups were filtered extracting MOWN, MHO, and overweight individuals, the WC cut off point always remained the same, but sensitivity and specificity improved significantly, proving that this approach offers a better way to scrutinize metabolically heterogeneous groups. Women appear to boast higher WC cut-offs, perhaps due to displaying a central fat distribution despite having femoral-gluteal fat distribution tendencies. Regarding males, a similar trend was observed, this time with a selected cut-off of 98.15 cm which is between the cutoff points proposed in IDF/NHLBI/AHA-2009 (<90 cm) and ATPIII (<102 cm).

We have previously published the prevalence of obesity in the city of Maracaibo [1], reporting that the overall prevalence of abdominal obesity using IDF/NHLBI/AHA-2009 criteria [20] was 74.2%, while using the ATPIII criteria [37] rendered a prevalence of 51.7%. Using the cut-off points proposed in this research, the overall abdominal obesity prevalence using the complete sample of MMSPS ($n = 2,230$) is 35.6% ($n = 794$). Thus, the new WC cut-off point reduces the alarming 74.2% obtained with the harmonizing criteria and offers better information to design strategies for primary and secondary prevention.

Lastly, we address two important limitations within this investigation. First, the absence of imaging study confirmation such as visceral fat measurement; this branch of the MMSPS study is currently underway. Second, we used BMI as a method of diagnosis and categorization instead of other obesity diagnostic tools like DEXA for Body Composition [39] due to lack of resources for such endeavor. It has been reported that BMI has limitations in regard to adiposity diagnosis, especially in intermediate ranges of BMI [40]. However, BMI cutoff point of $\geq 30 \text{ kg/m}^2$ should be easily dismissed, since it has been associated with high specificity and positive predictive value for diagnosing obesity in both sexes [40] and strong association with other entities such as arterial hypertension [41], diabetes mellitus [42], stroke [43], premature death [44], and several types of cancer [45].

In conclusion, we propose WC cut-off points of <91.00 cm for women and <98.00 cm for men, both providing an

excellent sensitivity and specificity when concerning the diagnosis of abdominal obesity. The need for ethnic-specific WC cut-off points is paramount, especially when there is an association between WC and mortality prediction [46, 47]. The application of statistical methods that allow the filtering and gathering of accurate information, like Cluster Analysis and ROC curve constructs, will warrantee production of veracious cut-off points that can be applied in large prospective trials.

Conflict of Interests

The authors have are no conflicts of interests to disclose.

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RESULTADOS Y DISCUSIÓN

En la primera publicación de esta tesis se explican los aspectos metodológicos del Estudio de prevalencia de Síndrome Metabólico de la Ciudad de Maracaibo¹¹⁵. Este proyecto de investigación tuvo por objeto estimar la prevalencia de esta condición en nuestra ciudad, ya que para la fecha no se contaba con información sobre el comportamiento epidemiológico de enfermedades crónico degenerativas de alta prevalencia como la obesidad, DM-2, Dislipidemias, Hipertensión Arterial, y de factores de riesgo cardiometabólicos como el sedentarismo, pre-diabetes y tabaquismo, entre otros. Para lograr este propósito se diseñó un estudio transversal, con muestreo aleatorio multietápico en 2.132 individuos de ambos sexos y mayores de 18 años residentes de la ciudad de Maracaibo que permitiera al mismo tiempo conocer la prevalencia de estas entidades¹¹⁶⁻¹²⁰ y obtener los puntos de corte óptimos para la circunferencia abdominal^{121,122} así como de las variables lipídicas¹²³, lipoproteína(a)¹²⁴, HDL y sus subfracciones, perfil oxidativo, TSH, T3L, T4L, anticuerpos anti-peroxidasa tiroidea y anti-tiroglobulina¹²⁵, insulina plasmática en ayuno¹²⁶, HOMA¹²⁷, análisis de polimorfismos de un solo nucleótido e identificación de nuevas mutaciones en genes involucrados en el metabolismo lipídico^{128,129}, así como la calibración de la ecuación de riesgo de Framingham-Wilson para nuestra población¹³⁰⁻¹³². Igualmente, la experiencia recabada en la implantación de los procesos de diseño, muestreo, inmersión en las comunidades, análisis de laboratorio, procesamiento estadístico de datos mediante análisis multivariante avanzado ha servido de base para la preparación de nuevos estudios que permitirán analizar el comportamiento secular y las tendencias de estas enfermedades, en especial, la obesidad. La intención final de este programa será el modelaje de la interacción de los factores de riesgo clásicos y noveles y su contribución en el desarrollo del fenotipo obeso en nuestra localidad.

Este protocolo fue diseñado sobre la base del cumplimiento de la declaración de Helsinki para la investigación en seres humanos y aprobado por el comité de Bioética del Centro de

Investigaciones Endocrino – Metabólicas “Dr. Félix Gómez” (CIEM) de la Facultad de Medicina de la Universidad del Zulia, Venezuela. Se contempló que todos los individuos enrolados en el estudio fueran suficientemente informados de forma verbal y escrita sobre los procedimientos y pasos a seguir durante su evaluación, firmando para este propósito (en caso de ser afirmativa su participación) un consentimiento informado.

Todo el personal proyectado a participar en la realización de las historias clínicas y la recolección de datos en general fueron capacitados en sesiones prácticas y evaluados con la finalidad de estandarizar la adquisición precisa y fiel de los datos de naturaleza demográfica, familiar y de antecedentes personales patológicos. Igualmente se realizó un entrenamiento riguroso en relación a los procedimientos antropométricos y el examen físico, los cuales fueron supervisados por un instructor calificado. Este proceso fue realizado en su totalidad por estudiantes de medicina ó médicos.

Por otro lado, la evaluación de la calidad de los datos obtenidos se planificó para todos los niveles de procesamiento. Para esto se contó con un coordinador responsable de supervisar que dicha recolección correspondiera a cada protocolo de manejo en particular. En vista que la evaluación de los individuos se realizaría a nivel de las comunidades, la información generada en las historias clínicas y las muestras sanguíneas y/o suero, fueron trasladadas al CIEM para su procesamiento en el laboratorio o estadístico. En este último caso, todas las historias clínicas fueron digitalizadas (escaneadas) y guardadas en formato pdf y todos los datos de cada historia fueron transcritos a una base de datos construida en el programa SPSS ver 15, que fue fiel reflejo de un libro de códigos preparado con todas las variables contempladas en el proyecto. Esta base de datos fue auditada en varias oportunidades de forma de evaluar la fidelidad del proceso de transcripción.

De forma de mejorar la comunicación y la participación de los individuos seleccionados se emplearon las siguientes estrategias: 1) Se entregó un folleto sobre los procedimientos y estudios de laboratorio a ser realizados, ofreciendo consulta médica gratuita a todos aquellos que presentaran alguna anomalía en dichos resultados. 2) Se involucró al personal médico de la localidad, particularmente a aquellos de hospitales tipo 1 o ambulatorios urbanos. 3) Se estableció contacto con los líderes de las comunidades y con trabajadores sociales de los centros de salud. 3) Las invitaciones a participar en el estudio fueron enviadas por intermedio de los líderes comunitarios y los trabajadores sociales. 5) Los centros de evaluación fueron escogidos de acuerdo a la localidad en que se estuviese laborando, pudiendo ser escuelas, centro comunitarios o centros de salud de atención primaria. Se contempló que el proceso de muestreo, valoración de pacientes, construcción de la base de datos y procesamiento de los mismos ocurriera ente enero de 2007 hasta Abril de 2009. Las principales variables a ser estudiadas en este proyecto se dividieron en Sociodemográficas (Edad, sexo, grupos etarios, estatus socioeconómico y educativo, parroquia de residencia), hábitos psicobiológicos (Consumo de tabaco, café, bebidas gaseosas, actividad física), variables antropométricas (talla, peso, IMC, CA), Antecedentes patológicos familiares en primer grado, antecedentes patológicos personales, signos vitales, tratamiento farmacológico recibido, antropometría e impedanciometría y variables relacionadas con metabolitos séricos (glicemia e insulina en ayuno, perfil lipídico, usPCR, T3L, T4L, TSH, Abs anti-tiroglobulina y Abs anti-peroxidasa).

A pesar que la construcción de la base primaria de datos, la auditoria de los mismos y el análisis primario de los datos (análisis de la normalidad de los mismos, procedimientos estadísticos descriptivos, tablas de contingencia y pruebas de asociación así como estadísticos univariantes se realizaron con el programa SPSS, debe hacerse notar que los procedimientos estadísticos avanzados, en especial los de naturaleza multivariante y de minería de datos fueron realizados en su

totalidad con el lenguaje de programación R y con el paquete R Studio, cargado con módulos específicos para cada tarea en particular.

En la segunda publicación de esta tesis¹¹⁸, se estudió la prevalencia de obesidad (según el IMC y según la circunferencia abdominal) en la ciudad de Maracaibo, Venezuela utilizando los datos generados en el Estudio de Prevalencia de Síndrome Metabólico de la Ciudad de Maracaibo descrito en la publicación número 1. En este sentido, la muestra estuvo constituida por 2.108 individuos de los cuales el 46,91% (n = 989) fueron hombres y el 53,09% (n = 1119) fueron del sexo femenino y con una edad promedio de $38,68 \pm 15,42$ años (CV = 42,04%). Al estratificar esta variable en grupos de 10 años se encontró que el 8,6% (n = 181) de los participantes se encontró en el grupo de 18 a 19 años, el 27,6% de los individuos (n = 581) se ubicó en el grupo de 20 a 29 años, el 18% (n = 380) en el de 30–39 años, el 20,1% (n = 423) en el grupo de 40–49 años, el 15,2% (n = 320) en el de 50–59 y el 10,6% (n = 223) en el grupo de 60 años y más años. Esta distribución se correspondió cercanamente a aquella observada en la pirámide poblacional de nuestro país.

Al analizar la muestra según su etnicidad, el grupo predominante fue el de raza mezclada con un 75,23% (n = 1586), seguido por los blancos hispánicos con un 16,17% (n = 341). Los grupos restantes correspondieron a indígenas americanos (4,74%, n = 100), afro-venezolanos (3,13% n = 66) y otros (arábigos, orientales) con un 0,71%, (n = 15). Según el estatus socioeconómico, la mayor parte de los individuos se ubicó en la clase media con 838 miembros (39,75%) seguido por el grupo de la clase media-baja con 751 individuos (35,62%), la clase media-alta con 385 sujetos (18,26%), seguido de la clase baja-extrema pobreza con 103 individuos (4,88%), y finalmente la clase alta con solo 31 individuos (1,47%).

En relación al comportamiento del IMC, pudo observarse una distribución normal con una media aritmética de $28,25 \pm 6,28$ kg/m² (95% CI 27,98–28,52, CV = 22,2%), un valor mínimo de

14,22 kg/m² un valor máximo de 68,80 kg/m². Cuando se analizó el comportamiento del IMC según grupos etarios se pudo apreciar su incremento hasta finales de la cuarta década, observándose una estabilización del mismo en los hombres y una ligera caída en las mujeres en la séptima década de la vida. La prevalencia de obesidad de acuerdo al IMC (≥ 30 kg/m²) para ambos sexos y todas las edades fue del 33,3% (n = 701) distribuido de la siguiente forma: a) Obesidad clase I, 20,4% (n = 429). b) Obesidad clase II, 8,7% (n = 183) y c) Obesidad clase III, 4,2% (n = 89), mientras que los individuos con sobrepeso y normopeso y peso normal representaron el 34,8 (n = 733) y el 29,8% (n = 629) respectivamente. La prevalencia de bajo peso fue solo del 2,1% (n = 45). En la estratificación por sexo se observó que la prevalencia de obesidad en las mujeres fue del 32,4% (n = 363) mientras que en los hombres fue del 34,2% (n = 338).

Este estudio también exploró el comportamiento de la CA en la muestra estudiada tomando en consideración los puntos de corte sugeridos para Latinoamérica de la armonización del 2009 (IDF-2009)¹⁰ y los criterios del ATPIII⁵⁴. Esto debido a que para la fecha no se contaba con puntos de corte apropiados para la CA adaptados a nuestra población debido a la ausencia de trabajos en nuestra población, de forma que se encontró que la prevalencia de obesidad abdominal fue del 74,2% (n = 1565) para IDF-2009 y el 51,7% (n = 1089) para ATPIII respectivamente. Cuando se estratificó la circunferencia abdominal por grupos etarios y sexo (IDF-2009) la obesidad fue más prevalente en mujeres del grupo de 60–69 años (94,8%), en el de 50–59 años (94,7%), 40–49 años (89,3%), >70 años (88,1%) y de 30–39 años (82,4%), mientras que en el grupo de los hombres la prevalencia fue mayor en el grupo de los 60–69 años (94,8%), seguido por el grupo >70 años (92,6%), de 50–59 años (88,0%), de 40–49 años (84,1%), y en el grupo de 30–39 años (79,7%). Como era de esperarse, al aplicar los puntos de corte de CA según el ATPIII las prevalencias fueron menores para ambos sexos, observándose las mayores prevalencias en los grupos etarios superiores. Así, la prevalencia en mujeres del grupo >70 años fue del (81,0%), del grupo de 50–59 años

(79,7%), del de 60–69 años (70,8%), de 40–49 años (66,4%), y el de 30–39 años (61,7%); mientras que en los hombres el grupo con mayor prevalencia fue el de 40–49 años (61,2%), seguido por el grupo de 60–69 años (56,9%), el de 50–59 años (54,1%), el de >70 años (44,4%) y el grupo de 30–39 años (38,0%). Para una información mas detallada de dicha distribución pueden consultarse las tablas 6 y 7 de la publicación No 2.

La tercera publicación de esta tesis¹²¹, tuvo el propósito de estimar los puntos de corte de la circunferencia abdominal al mejorar la selección de individuos sanos/enfermos desde el punto de vista metabólico utilizando técnicas de minería de datos, mas concretamente análisis de conglomerados bi-etápicas (Two Steps Cluster Analysis) y al mismo tiempo demostrar que la relativamente baja sensibilidad y especificidad diagnóstica mostrada por la CA (alrededor del 60 al 70% en la mayoría de los estudios)^{133,134,135} podía deberse a la presencia de individuos portadores de fenotipos metabólicos como el MONW y el fenotipo MHO. De hecho, hasta la fecha no se registran estudios que exploren la distribución de estos fenotipos en aquellos estudios con alta especificidad y sensibilidad diagnóstica de la CA en detectar alteraciones metabólicas.

Para lograr estos objetivos se utilizó la base de datos del estudio de prevalencia de SM de la Ciudad de Maracaibo, constituida por 2.230 individuos, de los cuales se seleccionaron 1902 debido a la exclusión de aquellos que no tenían determinación de insulina plasmática en ayuno o que padecían DM tipo 2, ya que el tratamiento farmacológico de esta condición modifica los niveles de insulina plasmática, glucosa en ayuno, TAG y el peso corporal. Previo a la realización del análisis de conglomerados, los participantes se clasificaron ponderalmente según su IMC en normopeso, sobrepeso y obesos (y éstos subdivididos en aquellos con obesidad clase I, clase II y clase III). Luego, a cada grupo ponderal se le aplicó la técnica de clusters bi-etápicas, clasificándolos como metabólicamente sanos o enfermos. Las variables cardio-metabólicas evaluadas como posibles predictores de enfermedad basadas en su función fisiológica y plausibilidad biológica fueron la

presión arterial media, TAG, colesterol total, HDL-C, HOMA2-IR, HOMA2- β cell, HOMA2-S, glucosa en ayuno, colesterol no-HDL, índice TAG/HDL-C y hs-CRP; WC. La potencia predictiva de estas variables fue analizada de acuerdo a la calidad de los conglomerados, siendo las mejores: (a) HOMA2-IR y HOMA2- β cell para las mujeres normopeso; (b) HOMA2-IR, HOMA2- β cell y TAG para los hombres normopeso; (c) HOMA2-IR y HOMA2- β cell para mujeres con sobrepeso; (d) HOMA2-IR, HOMA2- β cell y TAG para los hombres con sobrepeso; y (e) HOMA2-IR para hombres y mujeres obesos. La validación cruzada de los conglomerados se realizó mediante la división de la base de datos en dos grupos: una base de datos de entrenamiento y otra base de datos de validación. El nivel de concordancia entre ambas se analizó mediante la Kappa de Cohen.

Una vez que los individuos fueron clasificados metabólicamente sanos o enfermos se procedió con la construcción de las curvas COR, en primera instancia con los 6 fenotipos metabólicos obteniéndose un punto de corte para la CA en el sexo femenino de 91,25 cm, con un área bajo la curva de 0,768, sensibilidad de 73,3%, y una especificidad de 68,5%. Para el sexo masculino resultó un punto de corte de 98,15 cm, un área bajo la curva de 0,786, 74,8% de sensibilidad y 69,7% de especificidad. Considerando hipotéticamente a los fenotipos MONW y MHO señales anómalas, se construyeron a continuación curvas COR sin estos dos fenotipos. Para este caso, el punto de corte para la CA en mujeres resultó de 91,50 cm, con una mejoría estadísticamente significativa del área bajo la curva de 0,890, y una sensibilidad del 80,1% y especificidad del 79,3%. El mismo comportamiento se observó en las curvas COR para el sexo masculino con un punto de corte de 98,15 cm, una área bajo la curva de 0,919, sensibilidad del 83,8% y especificidad del 82,3% .

Finalmente, se construyeron curvas COR excluyendo a los individuos con sobrepeso, por lo que dichas curvas se construyeron solo con los fenotipos de individuos obesos metabólicamente enfermos y delgados metabólicamente sanos, pues consideramos a los individuos con sobrepeso

(sanos o enfermos) como señales extremadamente similares que no pueden ser discriminados sólo con la CA. En este caso el punto de corte para las mujeres fue de 91,5 cm, con un área bajo la curva significativamente mayor de 0,982, una sensibilidad del 93,4% y especificidad del 93,7%. Para el caso de los hombres, el punto de corte fue de 98,15 cm, con un área bajo la curva de 0,998, sensibilidad del 96% y especificidad del 99,5%. La figura 6 de la publicación 3 muestra todas las curvas COR y el resultado de las comparaciones entre las áreas bajo la curva mediante el test de DeLong, apreciándose en todos los casos una mejoría significativa en las áreas bajo la curva tanto en hombres como en mujeres, así como la sensibilidad y la especificidad de una forma importante, lo que sugiere que este método podría ser de gran utilidad para definir de forma más precisa los puntos de corte de esta variable.

En este sentido, las curvas COR se han utilizado de forma extensa para determinación de los puntos de corte óptimos para CA^{136,137,138}, especialmente en aquellas poblaciones que aun no han sido apropiadamente “clasificadas” debido precisamente a la carencia de datos etno-específicos sobre los puntos de corte para esa variable⁵³. Sin embargo, debe destacarse que antes de aplicar este procedimiento, la población objeto a estudio debe primero clasificarse como sana o enferma (en este caso desde el punto de vista metabólico). El abordaje más común al problema de clasificación de estos individuos ha sido el uso de los criterios diagnósticos de SM –bien sea ATPIII o IDF-2009– excluyendo evidentemente la criterio de circunferencia abdominal¹³⁶. Esta óptica se basa sobre el supuesto (arbitrario) de que los puntos de corte de las variables usadas para la clasificación, es decir, glicemia en ayuno, TAG, HDL y presión arterial se comportan de la misma manera en todas las poblaciones. Cabe preguntarse, si la CA tiene un comportamiento etno-específico, el resto de las mismas no podría tener el mismo comportamiento? Lamentablemente, no se reportan trabajos en los que se hayan utilizado estas variables en un marco étnico-específico. En este sentido, una

recomendación es la determinación de los puntos de corte óptimo para todas estas variables en poblaciones que se encuentren fuera del fondo genético blanco caucásico.

Debido a este argumento y careciendo de datos sobre los puntos de corte, tanto de la CA como del resto de las variables clasificadoras se diseñó un estudio que aprovechara técnicas de minería de datos (análisis de conglomerados) de forma de clasificar a los individuos sin apelar a puntos de corte arbitrarios para nuestra población, de forma que los grupos de individuos sanos y enfermos se pudiesen formar de forma “espontánea” de acuerdo al comportamiento en conjunto de las variables metabólicas seleccionadas para tal fin¹³⁹.

El análisis de clústers bi-etápico mejora la asignación de los sujetos al optimizar la agrupación de los mismos de acuerdo a variables que tienden a agregarse, eliminando el posible sesgo generado por el uso de variables “pre-definidas” o por puntos de corte “predeterminados” y en esencia, arbitrarios. Sobre la base de esta razonamiento se generaron 6 grupos de individuos: sanos con peso normal, enfermos con peso normal (MONW), individuos con sobrepeso sanos y enfermos, obesos metabólicamente sanos (MHO), y obesos metabólicamente enfermos. Cada uno de estos fenotipos tienen perfiles cardiometabólicos diferentes que han sido ampliamente descritos^{57,140}, es evidente que los individuos MONW y MHO son excepciones al comportamiento metabólico habitual, pues no se esperaría que una persona delgada exhibiese problemas metabólicos o que un individuo obeso fuese sano. En este estudio, el uso de las variables clasificadoras sugeridas por el análisis de clusters junto al uso del IMC demostró una mejoría en las áreas bajo las curvas COR, la sensibilidad y la especificidad de los puntos de corte seleccionados. Más aún, la exclusión progresiva de los fenotipos atípicos MONW y MHO mejoró de forma estadísticamente significativa la especificidad y sensibilidad diagnóstica del procedimiento, lo que hace pensar que el análisis de clústers pudo “diferenciar” el ruido de las verdaderas señales de una forma consistente, sistemática y no aleatoria. Por otro lado, la exclusión de los individuos con sobrepeso eliminó un

grupo de transición entre el normopeso y la obesidad cuyo comportamiento biológico es extremadamente heterogéneo y difícil de detectar probablemente porque el valor de los datos dentro de las variables clasificadoras es extremadamente cercano entre el exhibido por los individuos sanos y los enfermos. Una vez más, la exclusión de los individuos con sobrepeso al momento del cálculo de los puntos de corte de CA mejoró de forma estadísticamente significativa las áreas bajo la curva, sensibilidad y especificidad diagnóstica llevándolas alrededor del 95%, un hecho sin precedentes en la construcción de puntos de corte de CA. En la actualidad, se realiza un estudio que dará luces sobre el comportamiento de estas variables en individuos con IMC entre 25 y 29,99 Kg/m².

Por todo lo antes expuesto, es vital enfatizar dos puntos en relación con este trabajo: 1) la circunferencia abdominal aislada no es capaz de distinguir a los sujetos MONW y MHO de los obesos enfermos y los delgados sanos y en realidad dicha identificación deberá finalmente recaer sobre otras variables que los identifiquen como individuos enfermos o sanos. Este hecho abre nuevos horizontes de investigación que puedan permitir el desarrollo nuevas estrategias menos costosas capaces de identificar estos fenotipos, como por ejemplo, el uso de los somatotipos construidos a partir de datos antropométricos locales, y 2) El proceso de filtrado de la señal original (toda la muestra, 6 fenotipos) hacia 4 fenotipos y luego 2 fenotipos no produjo cambios significativos sobre el valor del punto de corte de CA para hombres y mujeres, más si en la sensibilidad y especificidad, hecho que apoya la confiabilidad del análisis de clúster en la identificación de individuos sanos y enfermos.

En la segunda publicación de esta tesis se reportó que la prevalencia de obesidad según el IMC en la ciudad de Maracaibo fue del 33,3%, muy similar a la reportada en el estudio NHANES en los EUA, un dato extremadamente alarmante por las repercusiones sobre la salud pública y los costos asociados al incremento de la prevalencia de sus comorbilidades, hecho que atentaría en un futuro no muy lejano contra el normal funcionamiento del ya mermado sistema de salud

venezolano. Mas preocupante resulta si se analiza la situación desde el punto de vista de la prevalencia de obesidad abdominal, pues utilizando los puntos de corte para CA de la IDF-2009 dicha prevalencia resultó en un 74,2%, advirtiéndonos en este caso que estamos a las puertas de una catástrofe en salud pública. Sin embargo, al emplear los puntos de corte sugeridos en el presente estudio dicha prevalencia se reduce a un 35,6% (muy cercana a la prevalencia de obesidad según el IMC), lo que sugiere fuertemente una sobre-estimación de casos de obesidad abdominal por parte de los puntos de corte propuestos por IDF-2009.

Finalmente, se pueden identificar algunas limitaciones en este estudio. En primer lugar, la ausencia de estudios por imágenes para la medición del TAV de forma de determinar que volumen de este compartimiento se asocia con enfermedad metabólica. En segundo lugar, el uso del IMC como método de clasificación ponderal y de adiposidad en vez de un método orientado a la medición de la grasa corporal total como el DEXA¹⁴¹, ya que varios estudios han resaltado las limitaciones del IMC en relación del diagnóstico de la adiposidad total especialmente a IMC intermedios³¹, aunque hay evidencia suficiente que a niveles ≥ 30 kg/m² se asocian fuertemente con la presencia de otras entidades como, hipertensión arterial¹⁴², diabetes mellitus¹⁴³, enfermedad cerebrovascular¹⁴⁴, muerte prematura¹⁴⁵, y varios tipos de cancer¹⁴⁶. En tercer lugar, este estudio no contempló la distribución de los fenotipos según grupos etarios debido a que no estuvo diseñado con una potencia estadística suficiente para detectar un número importante de individuos delgados metabólicamente enfermos por grupos decenales pues su distribución en nuestra población era desconocida. Queda en el terreno de las hipótesis y abierta a una próxima investigación la sugestiva pregunta de que la proporción de individuos delgados metabólicamente enfermos y obesos metabólicamente sanos varíe en función de la edad, por lo que la capacidad predictiva de la CA, la sensibilidad y la especificidad pueda cambiar en función del grupo etario.

CONCLUSIONES

El Estudio de Prevalencia de Síndrome Metabólico de la Ciudad de Maracaibo ha demostrado ser una experiencia de investigación exitosa que ha permitido la estimación de la prevalencia de enfermedades crónicas no comunicables como la Obesidad, Hipertensión, Diabetes y dislipidemias, así como la determinación de los puntos de corte apropiados para variables lipídicas séricas y la circunferencia abdominal, representando el primer ensayo de esta índole en nuestro país. Este estudio sentará las bases para futuras investigaciones que profundizarán en los factores que influyen en el comportamiento epidemiológico de la obesidad observado en nuestra ciudad.

La prevalencia de obesidad en la Ciudad de Maracaibo mediante la clasificación ponderal basada en el IMC según los puntos de corte propuestos por la OMS ha resultado elevada (33,3 %) y equiparable a la de países donde esta enfermedad se considera un problema de salud pública. Igualmente, la prevalencia de sobre-peso exhibió el mismo comportamiento observándose que el 34,8%) de la muestra estudiada presentaba esta condición, por lo que casi 2/3 de los adultos de nuestra localidad presentan trastornos ponderales por exceso. De la misma forma, la prevalencia de obesidad abdominal se ubicó en un 51,7 y 74,2% al considerar los puntos de corte para la circunferencia abdominal según el ATPIII o IDF-2009 respectivamente. No puede descartarse que esta elevada prevalencia puede ser consecuencia de puntos de corte inapropiados para nuestro trasfondo genético, demográfico y cultural, planteando la imperiosa necesidad de estimar dichos puntos de corte desde una óptica étnico y geo-específica, tal como ha sido sugerido por diversas sociedades científicas.

En este sentido, las técnicas de análisis multivariantes y minería de datos junto con el procedimiento de curvas COR ha permitido seleccionar adecuadamente los diferentes fenotipos metabólicos, en particular, aquellos considerados como atípicos y que son proclives a disminuir la

sensibilidad y especificidad diagnóstica del punto de corte para la circunferencia abdominal. Más aún se ha puesto en evidencia de forma indirecta que la circunferencia abdominal podría no clasificar de forma apropiada (en el mundo real) a 4 de cada 10 individuos con los puntos de corte propuestos, es decir, 91,5 cm para el sexo femenino y 98,15 cm para el sexo masculino.

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