ORIGINAL ARTICLE

# Eccentric Vascular Remodeling: Its Relationship with Metabolic Disorders and Increased Body Mass

## *Remodelado vascular excéntrico: su relación con trastornos metabólicos y el incremento de la masa corporal*

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## ABSTRACT

**Background:** Recent evidence would establish muscle hypoperfusion as the primary cause of metabolic disorders in response to overfeeding. This centripetal concept on the development of metabolic disorders could involve not only alterations in the microvasculature, but also affect the conductance arteries.
**Objectives:** The aim of this study was 1- to determine the association between baseline brachial artery diameter (BAD) and flow-mediated vasodilation (FMVD), 2- To analyze the association of both parameters throughout the increase in body mass, 3- To evaluate associations between BAD/FMVD with components of the metabolic syndrome (MS) and 4- To evaluate the independent association of both variables with MS
**Methods:** A total of 3493 patients were evaluated. Patients <18 and >80 years old, those with previous cardiovascular disease, chronic kidney disease (CKD), collagenopathies, or treated with statins were excluded from the study. Blood pressure (BP), anthropometric parameters and metabolic profile were determined, and the subjects were classified according to the presence of MS conforming ATP-III criteria. BAD was measured in mm and FMVD as percentage. The linear association between BAD and FMVD was assessed, and both variables were analyzed according to deciles of body mass index (BMI). Associations between BAD/FMVD with BP, glucose (Glu), triglycerides (TG) and high-density cholesterol (HDL-C) levels were evaluated. Two logistic regression analyses were performed with MS as dependent variable and BAD or FMVD plus age, gender, BMI, and coronary risk factors (CRF) as independent variables.
**Results:** A total of 1995 patients (48.2±11 years, 56% men) were admitted in the study. An inverse correlation was found between BAD and FMVD (r= -0.42; p <0.0001). BAD increased according to deciles of BMI (p <0.000001), while FMVD showed an inverse relationship with increasing deciles of BMI (p <0.000001). BAD exhibited a direct correlation with BP, Glu and TG; and an inverse relationship with HDL-C (p <0.05 in all cases). FMVD presented an inverse correlation with BP, Glu and TG; and a direct correlation with HDL-C (p <0.05 in all cases). BAD was independently associated with MS adjusted for age, gender, BMI and CRF (OR 1.42, p=0.0019), while FMVD was not (OR 0.98, p=0.217).
**Conclusion:** Eccentric vascular remodeling was associated with vascular adaptation to increased blood flow demand and with metabolic alterations throughout the increase in body mass. Thus, the dynamic compromise of vasculature could play a decisive role in the development of metabolic alterations occurring synchronously with weight gain.

**Keywords:** Vascular remodeling -Metabolic syndrome -Obesity -Flow-mediated vasodilation

## RESUMEN

**Introducción:** Existe evidencia reciente que establecería a la hipoperfusión muscular como causa primaria de trastornos metabólicos en respuesta a la sobrealimentación. Esta concepción centrípeta del desarrollo de trastornos metabólicos podría implicar no sólo alteraciones en la microvasculatura, sino también afectación en las arterias de conductancia.
**Objetivos:** 1- Determinar asociación entre diámetro basal de la arteria humeral (D-Hum) y la vasodilatación mediada por flujo (VDMF) 2- Analizar la asociación de ambos parámetros conforme aumenta la masa corporal 3- Evaluar asociaciones entre el D-Hum/VDMF con componentes del síndrome metabólico (SM) 4- Evaluar la asociación independiente de ambas variables con el SM
**Material y métodos:** Se evaluaron 3493 pacientes. Se excluyeron pacientes <18 y > 80 años, con patología cardiovascular previa, insuficiencia renal crónica (IRC), colagenopatías, y tratados con estatinas. Se determinó presión arterial (PA), parámetros antropométricos y perfil metabólico, y se clasificó a los sujetos de acuerdo con la presencia de SM según el ATP-III. Se midieron D-Hum en mm y VDMF en %. Se analizó la asociación lineal entre D-Hum y VDMF y se analizaron ambas variables según decilos de índice de masa corporal (IMC). Se evaluaron asociaciones entre D-Hum/VDMF con la PA, glucemia (Glu), triglicéridos (TG) y colesterol de alta densidad (HDL-C). Se realizaron dos regresiones logísticas con SM como variable dependiente y D-Hum o VDMF más edad, sexo, IMC y factores de riesgo coronario (FRC) como independientes.

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**Resultados:** Ingresaron 1995 pacientes (48,2±11 años, 56 % hombres). El D-Hum y la VDMF presentaron una asociación inversa (r= -0,42; p<0,0001). El D-Hum aumentó según decilos del IMC (p < 0,000001); la VDMF mostró relación inversa con los decilos crecientes de IMC (p < 0,000001). El D-Hum presentó correlación directa con PA, Glu y TG; e inversa con HDL-C (p<0,05 en todos los casos). La VDMF mostró correlación inversa con PA, Glu y TG; y directa con HDL-C (p<0,05 en todos los casos). El D-Hum se asoció en forma independiente con el SM ajustado por edad, sexo, IMC y FRC (OR 1,42, p=0,0019), mientras que la VDMF no (OR 0,98, p=0,217). **Conclusión:** El remodelado vascular excéntrico se asoció con un compromiso en la adaptación vascular ante aumentos en la demanda de flujo sanguíneo y con alteraciones metabólicas a lo largo del incremento de la masa corporal. Así, el compromiso dinámico de la vasculatura podría tener un rol determinante en el desarrollo de alteraciones metabólicas en forma sincrónica con la ganancia de peso.

**Palabras clave:** Remodelado vascular -Síndrome metabólico - Obesidad -Vasodilatación mediada por flujo

## INTRODUCTION

The increase in body mass observed in overweight and obese subjects is associated with hemodynamic alterations, the most important being the increase in plasma volume and vascular dysfunction. From a pathophysiological point of view, different endocrine alterations act concurrently and synergistically in the development of these circulatory alterations.

With the increase in body mass - particularly in obese people - the increase in water and sodium reabsorption prompted by insulin through the activation of the sodium-hydrogen exchanger in the proximal convoluted tubule, (1) hyperreninemia derived from increased sympathetic outflow, (2) decreased tubular flow rate and stimulation of tubuloglomerular feedback, (3) in addition to increased autonomous secretion of aldosterone in dysfunctional adipocytes (4) promotes a circulatory state characterized by increased cardiac output and eccentric remodeling of the cardiac chambers and conductance arteries, which coexists with enhanced tone of the precapillary sphincters and development of peripheral hypoperfusion. Since the delivery of macronutrients to metabolically active organs, such as skeletal muscle and adipose tissue, is largely dependent on adequate perfusion, the inability to increase blood flow during the postprandial period can be associated with metabolic alterations in overweight and obese subjects. As an example, blocking insulin-mediated muscle blood flow reduces glucose consumption in the muscle by 40% according to the euglycemic-hyperinsulinemic clamp technique. (5) In this scenario, the alterations in the structure and function of the conductance arteries that participate in muscle perfusion (which consume 75 to 80% of the total body glucose) (6) added to the increase in peripheral resistance disorders could jointly induce metabolic disorders as a peripheral starting point with the progressive increase in body mass.

## METHODS

A total of 3493 patients from the metabolic database of the CARFARE registry (CARDIOMETABOLIC RISK FACTORS REGISTRY), carried out for a cardiovascular prevention program of the Officia Cardiometabolic Unit, from the Cardiology service of Hospital Universitario Austral from July 2016 to January 2020, were evaluated .These patients underwent a structured, sequential evaluation, on the same date, consisting of laboratory analyses that included urine metabolites and peripheral blood assessments after 12-hour fasting. Subsequently, medical interrogation with data collection on cardiovascular risk factors (CRF) and clinical-cardiological history, weight and height measurements with body mass index (BMI) calculation, baseline blood pressure (BP) (at rest, 3 determinations), and performance of different imaging studies were performed.

For practical purposes, data on the pathological history, CRF, metabolic profile measurements - glucose (Glu), HDL cholesterol (HDL-C) and triglyceride (TG) levels in peripheral blood and flow-mediated vasodilation (FMVD) were used. Obesity was defined according to the World Health Organization (WHO) as BMI ≥ 30 kg/m$^2$, and metabolic syndrome (MS) according to the IDF Joint Interim Statement and 2019 AHA/NHLBI (7) as the presence of 3 of the following criteria: TG >150mg /dL, HDL <40 mg/dL in men and <50 mg/dL in women, BP >130/85 mm Hg, glucose >100 mg/dL, and treatment for diabetes mellitus (DM), hypertension (HTN) or dyslipidemia.

A high-resolution vascular ultrasound machine (Phillips HD7 XE, Koninklijke Philips N.V) equipped with a 10 MHz linear array probe was used for FMVD. This procedure was performed on the brachial artery, in a quiet environment, at 22°C, with 12-hour fasting, without medication intake, during the morning, and in the absence of antihypertensive drugs for a period of 12 hours. The calculation was performed using the following formula: FMVD = [(baseline BAD in mm - post-ischemia BAD in mm) / baseline BAD in mm] × 100. Ischemia was induced through 30 mm Hg supra-systolic compression with a cuff placed on the brachial artery of the left arm, 3 to 5 cm above the elbow crease for 3 minutes. The data on baseline BAD and FMVD were collected in mm and percentage, respectively.

For the present analysis, patients aged <18 and >80 years, those with a history of ischemic heart disease (chronic stable angina, unstable angina, acute myocardial infarction), heart failure, chronic arrhythmia or significant arrhythmic events, transient ischemic stroke, stroke or peripheral vascular disease, stage III or higher chronic kidney disease, known rheumatological diseases and decompensated chronic diseases, as well as incomplete data, were excluded. Patients treated with statins or β2 adrenergic agonists, due to their effect on endothelial function, were also excluded from the analysis.

A linear relationship between BAD and FMVD was analyzed, and each of these variables (BAD and FMVD) was subsequently evaluated according to BMI levels. Linear associations between BAD and FMVD with constituent variables of MS (BP, GLu, TG and HDL-C) were evaluated. Two logistic regression analyses were performed to explore the independent association of both variables with MS.

### Statistical analysis

Baseline characteristics are expressed as mean and standard deviation for continuous variables, and as number of cases and percentage for categorical variables. Linear correlation is expressed with the Pearson r coefficient in the case of normally distributed variables and Spearman's rho in those with a non-normal distribution. BMI levels were obtained through stratification into deciles. The analysis of variables according to deciles was carried out using ANOVA in those with a normal distribution, and the Kruskall Wallis test in those with a non-normal distribution. Given the probable collinearity of BAD and FMVD, two logistic regressions were carried out: 1- with MS as the dependent variable and BAD, age, gender, BMI and CRF (dyslipidemia, HTN, DM, smoking, sedentary lifestyle) as independent variables, and 2- with MS as the dependent variable and FMVD, age, gender, BMI and CRF (dyslipidemia, HBP, DM, smoking, sedentary lifestyle) as independent variables. A value of $p < 0.05$ was considered statistically significant. The analysis was performed with MedCalc 20.2.17 statistical software package.

### Ethical considerations

The study was carried out in accordance with the Declaration of Helsinki and was approved as part of the Carfare Registry by the Ethics Committee of our institution (19-044).

## RESULTS

A total of 1995 patients were included in the study (48.2±11 years, 56% male, BMI 27.9±5.89 kg/m$^2$, MS 20.3%). The population presented patients with low prevalence of smoking, dyslipidemia and DM (Table 1).

In the univariate analysis, BAD and FMVD showed a significant inverse relationship (r: -0.42, $p<0.0001$). BAD increased across BMI deciles ($p <0.000001$) (Figure 1) and, conversely, FMVD presented a progressive reduction across BMI deciles ($p <0.000001$) (Figure 2). A direct correlation was found between BAD and BP ($r=0.26$, $p <0.001$), Glu ($r=0.25$, $p <0.001$) and TG ($r=0.26$, $p <0.001$) and an inverse correlation with HDL-C ($r= - 0.35$, $p <0.001$). On the other hand, FMVD presented weaker inverse associations with BP ($r= -0.15$, $p<0.001$), Glu ($r= - 0.11$, $p <0.001$) and TG ($r= -0.12$, $p <0.001$) and a direct correlation with HDL-C ($r= 0.14$, $p <0.001$).

In the first logistic regression analysis, BAD was independently associated with MS, with OR 1.42 (95% CI 1.14-1.77, $p=0.002$), adjusted for age, gender, BMI, dyslipidemia, smoking, DM, HTN and sedentary lifestyle [Hosmer-Lemeshow test $p=0.12$, area under the ROC curve 0.77 (95% CI 0.75-0.79)] (Table 2).

In the second logistic regression analysis, FMVD did not show a significant association with MS, with OR 0.98 (95% CI 0.97-1.007, $p=0.217$) when adjusted for the same variables [Hosmer- Lemeshow test $p=0.15$, area under the ROC curve= 0.77 (95% CI 0.75-0.79)] (Table 3).

## DISCUSSION

Eccentric vascular remodeling, characterized in this study as an increase in baseline BAD, was associated with the development of MS components with the progressive increase in body mass. Thus, the inverse relationship between vascular remodeling (BAD) and FMVD (mechanism that increases vascular flow in situations of high metabolic demand, such as exercise and the postprandial period) could be linking hemodynamic dysfunction with metabolic alterations in the context of weight gain. Although the impact of metabolic alterations on vascular structure and function is unobjectionable, it is highly probable that at some point in the evolutionary continuum, the alterations in vascular dynamics contribute, in a vicious circle, to the development/enhancement of those metabolic imbalances.

Thus, eccentric remodeling would represent an attempt to ensure adequate muscle perfusion in response to both the increase in intravascular volume and the oversupply of high-energy substrates. Actually, sugars such as glucose (8) or fructose (9) increase the activity of the sympathetic system, with increased cardiac output - a cause of eccentric vascular remodeling - and increased tone of the precapillary sphincters with muscle hypoflow. These adjustments are associated with a drop in the consumption of energy substrates - glucose and triglycerides - and finally with the development of peripheral metabolic alterations. Effectively, different drugs that share sympatholytic/vasodilatory effects such as moxonidine (10), rilmenidine (11) and azelnidipine (12), or nitric oxide donors such as sodium nitroprusside (13) induce improvements in the glycemic and lipid profile in subjects with obesity, MS, or DM.

The association between the observed increase in BAD and its relationship with metabolic alterations does not seem to be a generalized phenomenon with the increase in body mass. In fact, and as an example, 1 in 3 obese people exhibit a “metabolically healthy” phenotype in which no evident metabolic alterations are manifested. (14) These subjects apparently present as distinctive characteristics an adequate subcutaneous lipid reservoir capacity, normally functioning adipocytes, and low levels of inflammation, all in the context of adequate muscle perfusion and microvascular function.

**Table 1.** Baseline characteristics (n=1995)

| Variable | |
|---|---|
| Age, years (mean ± SD) | 48.2 ± 11.2 |
| Male gender (%) | 56 |
| BMI, kg/m$^2$ (mean ± SD) | 27.9 ± 5.9 |
| HTN (%) | 26 |
| Smoking (%) | 14 |
| DM (%) | 4 |
| Dyslipidemia (%) | 25.9 |
| Sedentary lifestyle (%) | 33 |

BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension; SD: Standard deviation

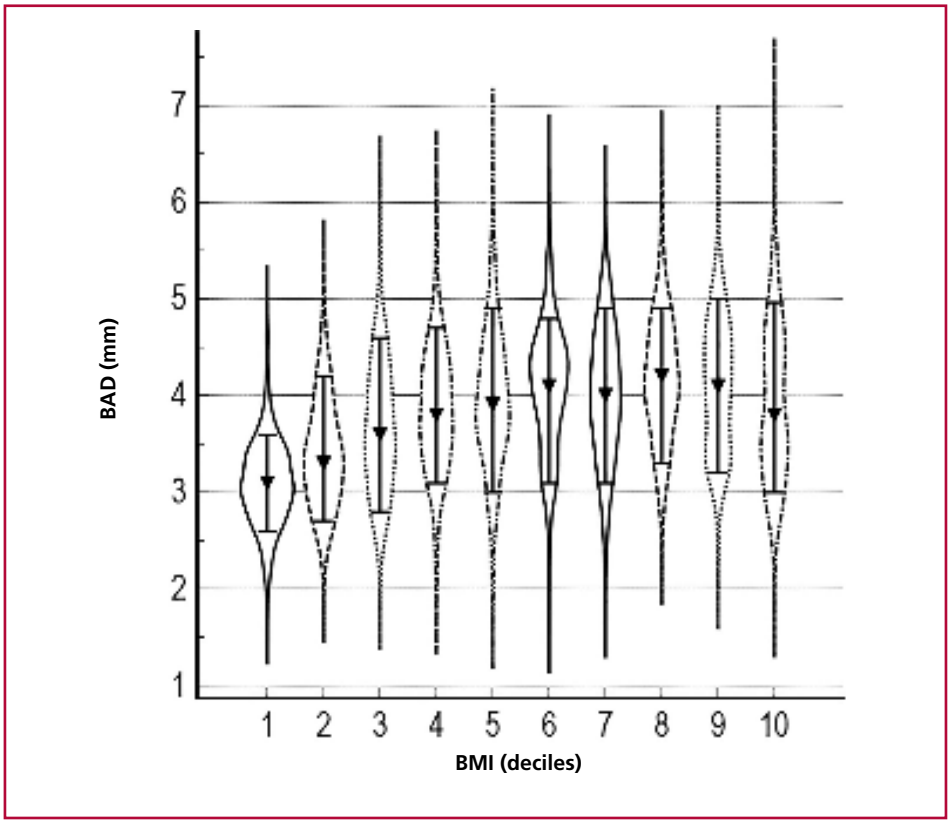


**Fig. 1.** Brachial artery diameter according to deciles of body mass index.

Kruskall Wallis test, p <0.000001. Values expressed as median (10-90% CI).
BAD: Baseline brachial artery diameter. BMI: Body mass index

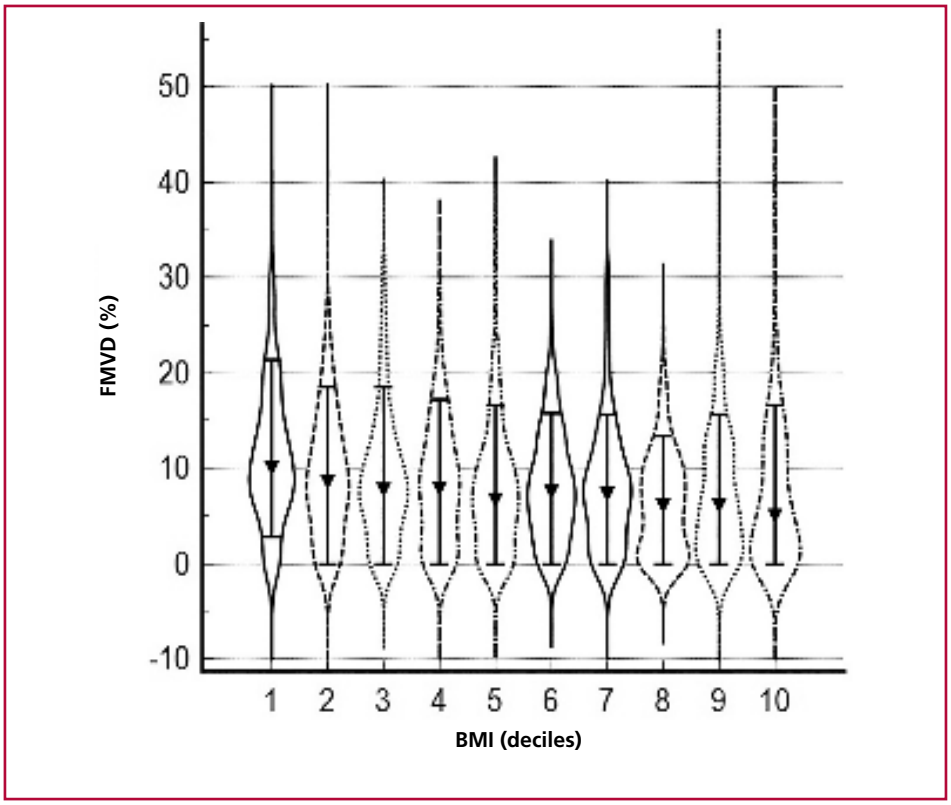


**Fig. 2.** Flow-mediated vasodilation according to deciles of body mass index.

Kruskall Wallis test, p <0.000001. Values expressed as median (10-90% CI)
FMVD: Flow-mediated vasodilation. BMI: body mass index

**Table 2**. Adjusted brachial artery diameter and its relationship with metabolic syndrome (MS).

| Variable | Beta coefficient | Standard error | p | OR | 95% CI |
|---|---|---|---|---|---|
| Age | 0.009 | 0.006 | 0.125 | 1.01 | 0.99-1.02 |
| Male gender | 0.325 | 0.169 | 0.054 | 1.38 | 0.99-1.92 |
| BMI | 0.115 | 0.013 | <0.0001 | 1.12 | 1.09-1.15 |
| **BAD** | **0.350** | **0.112** | **0.002** | **1.42** | **1.14-1.77** |
| DLP | 0.384 | 0.134 | 0.004 | 1.47 | 1.12-1.91 |
| SMK | -0.119 | 0.179 | 0.503 | 0.88 | 0.62-1.26 |
| DM | 0.630 | 0.263 | 0.016 | 1.87 | 1.12-3.14 |
| HTN | 0.773 | 0.132 | <0.0001 | 2.16 | 1.67-2.80 |
| Sedentary lifestyle | 0.134 | 0.143 | 0.347 | 1.14 | 0.86-1.51 |

BMI: Body mass index; BAD: Baseline brachial artery diameter; DLP: Dyslipidemia; DM: Diabetes mellitus; HTN: Hypertension; SMK: Smoking

**Table 3**. Relationship between adjusted flow-mediated vasodilation and metabolic syndrome (MS).

| Variable | Beta coefficient | Standard error | p | OR | 95% CI |
|---|---|---|---|---|---|
| Age | 0.012 | 0.005 | 0.024 | 1.01 | 1.01 – 1.02 |
| Male gender | 0.641 | 0.135 | <0.0001 | 1.89 | 1.45 – 2.47 |
| BMI | 0,122 | 0.013 | <0.0001 | 1.13 | 1.10 – 1.15 |
| **FMVD** | **-0.011** | **0.009** | **0.217** | **0.98** | **0.96 - 1.00** |
| DLP | 0.345 | 0.134 | 0.010 | 1.41 | 1.08 – 1.83 |
| SMK | -0.122 | 0.180 | 0.497 | 0.88 | 0.62 – 1.26 |
| DBT | 0.662 | 0.261 | 0.011 | 1.93 | 1.16 – 3.24 |
| HTN | 0.772 | 0.132 | <0.0001 | 2.16 | 1.67 – 2.81 |
| Sedentary lifestyle | 0.103 | 0.143 | 0.472 | 1.10 | 0.83 – 1.46 |

BMI: Body mass index; DLP: Dyslipidemia; DM: Diabetes mellitus; FMVD: Flow-mediated vasodilation; HTN: Hypertension; SMK: Smoking

This observation would be in line with recent studies suggesting that adipose tissue oxygenation, determined by the balance between oxygen supply and oxygen consumption, could be a key factor in determining the adipose tissue phenotype in obese subjects. (15,16)

It is highly probable that alterations in vascular function could be linked to the development of modifications in the metabolism of both carbohydrates and lipids in metabolically complicated subjects. Recent studies show that vascular insulin resistance secondary to high-fat diets compromises even short-term skeletal vascular flow. These data suggest that the alteration of blood flow in the skeletal muscle microvasculature is a primary event that would precede whole body insulin resistance in the development of type II DM. (17)

In the same sense, in a large prospective population-based study conducted in middle-aged subjects, the elevated baseline levels of 2 markers of endothelial dysfunction (sE-selectin and sICAM-1) were significantly associated with the risk of developing type II DM, especially sE-selectin, which was found to be a strong independent predictor of incident DM after adjusting for obesity, other clinical parameters and lifestyle in both men and women. (18)

Concomitantly, evidence has emerged that seems to link fatty deposit hypoperfusion with the development of total body insulin resistance. The inverse association between postprandial increase in adipose tissue perfusion with the degree of insulin resistance suggests that adipose tissue hypoperfusion may affect whole-body insulin sensitivity. Thus, the drop in the supply of glucose, lipids and oxygen to the adipose tissue would generate a decrease in the uptake of energy substrates at the level of subcutaneous fatty deposits, with ectopic accumulation of lipids in viscera and muscle, adipocyte hypoxemia and central and peripheral insulin resistance. (19)

From our point of view, we have observed an interesting association between alterations in the vascular structure and function of the conductance vessels and metabolic abnormalities with weight gain. However, these associations should be interpreted with caution due to the inherent limitations of the study. Actually, with a design which does not allow causality to be imputed, the absence of an objective

measurement of fat mass, and the fact that FMVD was not measured during the postprandial period or adjusted for drugs limit the interpretation of the results. However, it is probable that dynamic alterations in vascular flow behave as inducers of metabolic disorders, particularly during the postprandial period. Recent evidence shows that a fundamental difference between metabolically healthy obese subjects and those with MS lies in a preservation of FMVD during the postprandial period in those metabolically uncomplicated, with an endothelial response similar to that of subjects with normal weight and without metabolic alterations. (20) These findings are reinterpreting the function of the vascular endothelium as a fundamental actor in the control of glucose and carbohydrate metabolism. (21) We must also point out that in the present study the adjustment of hemodynamic variables for each of the drugs was not performed, with the intention of not making the analysis more complex. The study was carried out without the morning administration of the patients' usual medication, which would at least limit the immediate effect of high plasma drug levels.

Finally, it is not possible to completely rule out the fact that the increase in arterial conductance is mainly linked to anatomical modifications secondary to the increase in body mass. Effectively, in a study by Dalli et al. (22) a significant relationship was evidenced between BAD and the arm perimeter. However, the persistence of the association between BAD and MS adjusted by BMI, a parameter closely related with body surface area and, therefore, with arm circumference, would suggest an association independent of anthropometry in this relationship.

## CONCLUSIONS

In the present study we have evidenced a relationship between vascular structure and function alterations in conductance arteries with metabolic disorders through increased body mass. A prospective study with the purpose of evaluating insulin-vascular resistance and hemodynamic-metabolic causality with weight gain in subjects prior to the development of MS could help clarify these associations.

### Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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