Phenotypic Characterisation of Obesity in an Outpatient Clinic of Atherosclerosis

Caracterização Fenotípica da Obesidade numa Clínica Ambulatória de Aterosclerose

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Abstract

Introduction: Adipose tissue dysfunction is associated with an increased cardiovascular risk, and excess visceral adipose tissue is not confined solely to obese patients. We are now able to accurately assess body fat composition and use it in the definition of obesity.
Objectives: Evaluate the cardiovascular risk according to patient's obesity phenotype.
Material and Methods: An observational, cross-sectional study with adult patients from the Outpatient Clinic of Atherosclerosis and Hypertension at the Department of Internal Medicine of Coimbra´s Healthcare Integrated Delivery System, which were divided into 5 groups: metabolically healthy obese (MHO), metabolically obese normal weight (MONW), normal weight obese (NWO), sarcopenic obese (SO), and normal weight metabolically healthy (NWMH).
Results: A total of 123 patients were included. Each group was composed mainly by males, except for the NWO. The prevalence of diabetes was different between groups ($p < 0.05$) being greater in the NWO. The C Reactive Protein/Albumin Ratio was different between groups ($p < 0.05$), being higher in the MONW, which had the biggest proportion of patients within very high cardiovascular risk.
Conclusions: Our findings contribute to the growing body of evidence supporting the existence of metabolic differences between the proposed obesity phenotypes and supports the importance of integrating body fat distribution into risk assessment.

Keywords: obesity phenotypes; obesity; atherosclerosis; adipose tissue; body fat distribution; body mass index

Resumo

Introdução: A disfunção do tecido adiposo associa-se ao aumento do risco cardiovascular, e o excesso de tecido adiposo visceral não é exclusivo dos indivíduos obesos. Atualmente é possível avaliar a composição em gordura corporal com precisão e usá-la na definição de obesidade.
Objetivos: Avaliar o risco cardiovascular de acordo com o fenótipo individual de obesidade.
Material e Métodos: Estudo observacional, de coorte, com adultos seguidos na Consulta de Aterosclerose e Hipertensão Arterial do Serviço de Medicina Interna da Unidade Local de Saúde de Coimbra, que foram divididos em 5 grupos: *metabolically healthy obese* (MHO), *metabolically obese normal weight* (MONW), *normal weight obese* (NWO), *sarcopenic obese* (SO), e *normal weight metabolically healthy* (NWMH).
Resultados: Foram incluídos 123 doentes. Cada grupo era constituído maioritariamente por indivíduos do género masculino, exceto o NWO. A prevalência de diabetes foi diferente entre os grupos ($p < 0.05$) e maior no grupo dos NWO. O rácio proteína C reativa/albumina foi diferente entre os grupos ($p < 0.05$) e maior no MONW, que também apresentou uma proporção mais elevada de doentes de risco cardiovascular muito elevado.
Conclusões: O nosso trabalho contribui para a evidência crescente que suporta a existência de diferenças metabólicas entre os fenótipos de obesidade propostos e suporta a importância de integrar a distribuição da gordura corporal na avaliação do risco cardiovascular.

Palavras-chave: fenótipos de obesidade; obesidade; aterosclerose; tecido adiposo; distribuição da gordura corporal; índice de massa corporal

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> INTRODUCTION

World Health Organization (WHO) defines obesity as an abnormal fat accumulation, but in clinical practice it is currently diagnosed by calculating the body mass index (BMI), a surrogate measure of body fat based on individual's weight adjusted for their height. [1, 2]

The global epidemic of overweight and obesity represents a rapidly growing health threat to the population

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in an increasing number of countries. [2-4] It is estimated that obesity has been responsible for 5.02 million deaths and 160 million disability-adjusted life years in 2019, making this epidemic a public health target. [5] In Portugal, the first nationwide survey for assessing the prevalence of overweight/obesity in the adult population was conducted in 1995-1998 demonstrating that 49.6% of the study sample was overweight or obese. [6] In the first study that aimed to assess general and abdominal obesity prevalence in Portugal the results found an overall prevalence of obesity of 22.3%, being significantly higher in women (24.3%), and a prevalence of pre-obese of 34.8%, being significantly higher in man (38.9%). Furthermore, the prevalence of abdominal obesity in adults was 50.5%, being significantly higher in man (62%). [7]

Adipose tissue, now recognized as an endocrine organ, comprises two main types: brown and white, the latter including the subcutaneous and the visceral fat. [1, 8-10] Visceral adipose tissue is insulin-resistant and proinflammatory, contributing to local and systemic inflammation. [1, 8-10] Dysfunctional adipose tissue leads to an imbalance in adipocytokine production, oxidative stress, and ectopic fat deposition in organs such as the liver, the heart and the skeletal muscle. This is linked to atherosclerosis, endothelial dysfunction, and cardiometabolic diseases, which increase the risk of coronary artery disease, heart failure, and mortality. Notably, visceral adipose tissue can accelerate atherosclerosis, even in individuals with normal weight, underscoring its significant health implications. [1, 8-10]

Although it is important to consider anthropometric measures in estimating the risk of visceral adiposity, they should not be used in isolation to replace BMI as an adiposity metric, but rather be added to the information provided by the BMI. [8, 9, 11] However, there is no category-specific waist circumference for a given BMI category across different ages, sex and ethnicity, and there is only a modest correlation between visceral adiposity measured through image and anthropometric measures of abdominal obesity, which limits its clinical use. [8, 9, 11] With imaging development, we are now able to precisely assess body composition and use body fat percentage in the definition of obesity. [8, 12]

Acknowledging that we are moving from obesity to obesities, A. Vecchié *et al* focused on describing different obesity phenotypes, trying to explain their association with distinct cardiovascular profiles. [1, 8, 9] They proposed four phenotypes of obesity with different association with cardiovascular risk within the same BMI category: the metabolically healthy obese (MHO), the metabolically obese normal weight (MONW), the normal weight obese (NWO) and the sarcopenic obese (SO). Individuals with MHO phenotype are characterized by high BMI, lower visceral adipose tissue, a healthy metabolic profile with high insulin sensitivity and low pro-inflammatory cytokine levels, and a greater cardiorespiratory fitness. These subjects have a lower risk of cardiovascular disease and mortality compared to normal weight subjects. [1, 3, 13] The MONW phenotype is characterized by higher visceral fat mass and an unhealthy metabolic profile, with lower insulin sensitivity, high pro-inflammatory cytokine levels, greater incidence of type 2 diabetes and a higher risk of developing heart failure. The NWO phenotype refers to subjects that have a body fat mass over 30% despite their normal BMI. [1, 12] Individuals with SO phenotype are characterized by combination of low skeletal muscle mass and function and high fat mass. [1]

With our work we aim to assess the cardiovascular risk of the adult patients followed at Outpatient Clinic of Atherosclerosis and Hypertension at the Department of Internal Medicine of Coimbra´s Healthcare Integrated Delivery System, according to their phenotype as proposed by A. Vecchié *et al*, and raise new evidence regarding this current topic.

> MATERIAL AND METHODS

Study Participants

We conducted an observational, cross-sectional study, developed at the Outpatient Clinic of Atherosclerosis and Hypertension at the Department of Internal Medicine of Coimbra´s Healthcare Integrated Delivery System. The project was approved by the Ethics Committee of Coimbra´s Healthcare Integrated Delivery System, Coimbra, Portugal.

Patients were included according to the following inclusion and exclusion criteria.

Inclusion criteria:

– Individuals aged 18-years-old or older, followed at the Atherosclerosis and Hypertension Outpatient Clinic of the Internal Medicine Department of Coimbra's Hospital and University Centre.

Exclusion Criteria:

– Pregnant women;
– Individuals with pacemakers;
– Individuals with a history of limb amputation;
– Individuals who refused or were unable to sign the informed consent form.

Measurement of Demographic and Health Factors

Age, gender, smoking and drinking habits were assessed by self-report. Height was assessed by self-report and weight was measured by asking each participant to stand barefoot on the top of a digital scale. Seated systolic and diastolic blood pressures were measured using validated automated blood pressure measuring devices. Bioelectrical impedance analysis results (body fat mass, skeletal muscle mass, visceral fat area) were used resorting to LookinBody120® software. Medical comorbidities (diabetes, dyslipidaemia, hypertension, heart failure, chronic kidney disease, atrial fibrillation, cerebrovascular disease, and acute coronary syndrome) and results of other complementary diagnostic tests (total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, lipoprotein(a) (Lp(a)), apolipoprotein B (ApoB), creatinine, uric acid, albumin, C reactive protein, the presence of carotid plaques on neck's doppler ultrasound and hepatic steatosis on abdominal ultrasound) were collected from the patient´s electronical health records.

Phenotype Categories and Cardiovascular Risk

There is not a standard definition of body phenotypes. For the present study, patients were grouped according to the obesity phenotypes proposed by Vecchié *et al* [1] into metabolically healthy obese (MHO), metabolically obese normal weight (MONW), normal weight obese (NOW) and sarcopenic obese (SO), and a new category called normal weight metabolically healthy (NWMH) was created. To assess visceral fat area, body fat percentage, and muscle mass, the LookinBody120® device was used. Patients with a BMI equal to or greater than 30 kg/m² and a visceral fat area below the age-adjusted reference values were classified as belonging to the MHO group. Patients with a BMI between 18.5 and 24.9 kg/m² and a visceral fat area equal to or greater than the age-adjusted reference values were classified as belonging to the MONW group. Patients with a BMI between 18.5 and 24.9 kg/m² and a body fat percentage equal to or greater than 30% were classified as belonging to the NWO group. Patients with a body fat percentage above the age-adjusted reference values and muscle mass below the age-adjusted reference values were classified as belonging to the SO group. Patients with a BMI between 18.5 and 24.9 kg/m², a body fat percentage below 30%, and a visceral fat area below the age-adjusted reference values were classified as belonging to the NWMH group. Patients were also classified in different cardiovascular risk groups according to the *2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice*. [2]

Statistical Analysis

Descriptive statistics, such as absolute and relative frequencies, mean, standard deviations, and medians, were used to summarize univariate variables. Two sample z-test and test of proportion were used to assess the differences between two groups. Multivariate test of means was used to assess the differences between the groups means.
A *p*-value of 0.05 or less was considered statistically significant. Statistical analysis was performed using STATA v16 (StataCorp LLC, College Station, TX).

> RESULTS

Sample Characterisation

A total of 123 patients were included, which corresponds to 15% of the total number of patients followed at the Outpatient Clinic of Atherosclerosis and Hypertension at the Department of Internal Medicine of Coimbra´s Healthcare Integrated Delivery System.
Fourteen patients (11%) were classified as being MHO, sixteen patients (13%) were classified as being MONW, twenty-seven patients (22%) were classified as being NWO, thirty-eight patients (31%) were classified as SO, and the remaining twenty-eight (23%) fell into the newly created category of NWMH patients.
Table I shows that the NWMH group had an average age of 57 years, were mostly male (n = 18; 64.3%), with an average Lp(a) of 28.3 mg/dL, Apolipoprotein B of 95.2 mg/dL, and a C Reactive Protein/Albumin (CRP/A) Ratio of 41.3. Twenty-two of the NWMH patients (78.6%) were classified into high or very high cardiovascular risk. The MHO group had an average age of 63.1 years, were mostly male (n = 8; 57.1%), with an average Lp(a) level of 35.6mg/dL, ApoB level of 127 mg/dL, and a CRP/A Ratio of 24.2. Eight patients (85.7%) of the MHO individuals were classified into high or very high CV risk. The MONW group had an average age of 61.16 years, with mostly male subjects (n = 11; 68.8%), an average Lp(a) level of 22.2mg/dL, ApoB level of 72.8mg/dL, and a CRP/A Ratio of 54.5, with 87.6% (n = 14) of the patients classified into high or very high CV risk. The NWO group had an average age of 60.18 years, and were almost entirely female patients (n = 26; 96.3%), with an average Lp(a) of 50.6mg/dL, ApoB of 131.5mg/dL, and a CRP/A Ratio of 41.9, with 70.4% (n = 19) of the subjects classified into

Table I - Global characteristics of the sample size.

Variable	*Normal Weight Metabolically Healthy* (N = 28)	*Metabolically Healthy Obese* (N = 14)	*Metabolically Obese Normal Weight* (N = 16)	*Normal Weight Obese* (N = 27)	*Sarcopenic Obese* (N = 38)
Age – Mean, in years (DP)	57 (16)	63 (13)	61 (16)	60 (18)	63 (11)
Masculine Gender – N (%)	18 (64.3%)	8 (57.1%)	11 (68.8%)	1 (3.7%)	20 (52.6%)
Dyslipidaemia – N (%)	28 (100%)	13 (92.9%)	15 (93.8%)	23 (85.2%)	35 (92.1%)
Hypertension – N (%)	16 (57.1%)	9 (64.3%)	11 (68.8%)	12 (44.4%)	33 (86.8%)
Diabetes – N (%)	8 (28.6%)	2 (14.3%)	10 (62.5%)	2 (7.4%)	22 (57.9%)
Chronic Kidney Disease – N (%)	3 (10.7%)	0	0	3 (11.1%)	5 (13.2%)
Heart Failure – N (%)	0	0	1 (6.3%)	4 (14.8%)	7 (18.42%)
Atrial Fibrillation – N (%)	0	1 (7.1%)	2 (12.5%)	1 (3.7%)	2 (5.26%)
Stroke – N (%)	2 (7.1%)	0	2 (12.5%)	3 (11.1%)	2 (5.26%)
Acute Coronary Syndrome – N (%)	2 (7.1%)	0	0	1 (3.7%)	2 (5.26%)
Secondary Prevention – N (%)	4 (14.2%)	0	2 (12.5%)	4 (14.8%)	4 (10.53%)
Lp(a) – Mean (SD)	28.3 (26.5)	35.6 (27.7)	22.2 (32.6)	50.6 (51.8)	31.1 (45.7)
ApoB – Mean (SD)	95.2 (37.9)	127 (52.4)	72.8 (37.9)	131.5 (86.6)	108.1 (34.8)
LDL – Mean (SD)	97.3 (50.9)	109.3 (38.9)	87.4 (31.5)	124.6 (97.7)	101.2 (45.8)
Albumin – Mean (SD)	4.4 (0.3)	4.5 (0.3)	4.3 (0.3)	4.3 (0.4)	4.3 (0.3)
C Reactive Protein – Mean (SD)	0.3 (0.3)	0.6 (0.9)	0.2 (0.1)	0.9 (1.7)	0.4 (0.4)
CRP/Albumin Ratio – Mean (SD)	41.4 (36.9)	24.4 (18.9)	54.5 (50.8)	41.9 (48.4)	22.5 (18.8)
Carotid Plaques – N (%)	9 (32.1%)	5 (35.7%)	7 (43.8%)	10 (37.0%)	13 (59.1%)
Steatosis – N (%)	6 (21.4%)	3 (21.4%)	6 (37.5%)	7 (25.9%)	11 (73.3%)
Cardiovascular Risk (ESC) Low Moderate High Very High	 4 (14.3%) 2 (7.1%) 10 (35.7%) 12 (42.9%)	 7 (14.3%) 0 7 (50%) 1 (35.7%)	 1 (6.3%) 1 (6.3%) 5 (31.3%) 9 (56.3%)	 5 (18.5%) 3 (11.1%) 4 (14.8%) 15 (55.6%)	 4 (10.5%) 2 (5.3%) 12 (31.6%) 20 (52.6%)
% of Body Fat – Mean (SD)	22.3 (5.4)	29.4 (9.6)	32.1 (8.2)	36.7 (4.1)	22.3 (5.4)
Visceral Fat Area – Mean (SD)	59.3 (27)	103.5 (35.9)	212.7 (131.7)	109.0 (39.8)	56.3 (26.9)

ApoB - Apolipoprotein B. CPR - C Reactive Protein. LDL - Low-density lipoprotein. Lp(a) - Lipoprotein(a). SD - Standard Deviation.

high or very high CV risk. The SO group had an average age of 63.11 years, with an equal gender distribution (52.6% males, n = 20), with an average Lp(a) level of 31.1mg/dL, ApoB level of 108.18mg/dL, and a CRP/A Ratio of 22.5, with 84.2% (n = 32) of the individuals classified into high or very high CV risk.

Regarding the differences observed comparing the five groups in Table I, the CRP/A Ratio means were statistically different between the five groups ($p < 0.05$), being highest in the MONW group. The prevalence of diabetes varied between the groups ($p < 0.05$) and was higher in NWO patients. Nonetheless, there were no significant differences in ApoB or Lp(a) levels between all the groups.

Tables II to IV highlight the differences in metabolic profiles across the groups. Specifically, the comparison between MONW and NWO aimed to explore the combined impact of visceral fat area and body fat percentage. The analysis of MHO versus NWO focuses on the role of body fat percentage, while the comparison between MHO and MONW sought to clarify differences primarily driven by visceral fat area.

Comparison Between Metabolically Obese Normal Weight and Normal Weight Obese

When comparing MONW with NWO (Table II), we observed statistically significant gender differences (68.8% *vs* 3.7%, $p < 0.05$), with almost all the patients in the NWO group being female. Statistically significant differences were also seen between the prevalence of diabetes (62.5% *vs* 7.4%, $p < 0.05$), the mean Lp(a) level (22.2 *vs* 50.6, $p < 0.05$), and the mean ApoB level (72.8 *vs* 131.5, $p < 0.05$).

Comparison Between Metabolically Healthy Obese and Normal Weight Obese

Concerning Table III, when comparing MHO with the NWO, statistically significant differences were only observed between the gender, with the group of NWO being mostly female (57.1 *vs* 3.7%, $p < 0.05$).

Comparison Between Metabolically Healthy Obese and Metabolically Obese Normal Weight

As shown in Table IV, where we compared MHO with MONW patients, statistically significant differences have been observed between the prevalence of diabetes (MHO 14.3% vs MONW 62.5%, $p < 0.05$), the mean ApoB level (127 *vs* 72.8, $p < 0.05$), the mean CRP/A ratio (24.4 *vs* 54.5 $p = 0.03$), and the mean visceral fat area (103.5 *vs* 212.7, $p < 0.05$).

Table II - Comparison between Metabolically Obese Normal Weight and Normal Weight Obese.

Variable	*Metabolically Obese Normal Weight* (N = 16)	*Normal Weight Obese* (N = 27)	*p*-value
Age – Mean, in years (DP)	61 (16)	60 (18)	0.850
Masculine Gender – N (%)	11 (68.8%)	1 (3.7%)	0.000*
Dyslipidaemia – N (%)	15 (93.8%)	23 (85.2%)	0.395
Hypertension – N (%)	11 (68.8%)	12 (44.4%)	0.121
Diabetes – N (%)	10 (62.5%)	2 (7.4%)	0.000*
Chronic Kidney Disease – N (%)	0	3 (11.1%)	0.167
Heart Failure – N (%)	1 (6.3%)	4 (14.8%)	0.401
Atrial Fibrillation – N (%)	2 (12.5%)	1 (3.7%)	0.274
Stroke – N (%)	2 (12.5%)	3 (11.1%)	0.890
Acute Coronary Syndrome – N (%)	0	1 (3.7%)	0.436
Secondary Prevention – N (%)	2 (12.5%)	4 (14.8%)	0.833
Lp(a) – Mean (SD)	22.2 (32.6)	50.6 (51.8)	0.027*
ApoB – Mean (SD)	72.8 (37.9)	131.5 (86.6)	0.000*
LDL – Mean (SD)	87.4 (31.5)	124.6 (97.7)	0.044*
Albumin – Mean (SD)	4.3 (0.3)	4.3 (0.4)	1
C Reactive Protein – Mean (SD)	0.2 (0.1)	0.9 (1.7)	0.033*
CRP/Albumin Ratio – Mean (SD)	54.5 (50.8)	41.9 (48.4)	0.424
Carotid Plaques – N (%)	7 (43.8%)	10 (37.0%)	0.659
Steatosis – N (%)	6 (37.5%)	7 (25.9%)	0.423
Cardiovascular Risk (ESC) Low Moderate High Very High	 1 (6.3%) 1 (6.3%) 5 (31.3%) 9 (56.3%)	 5 (18.5%) 3 (11.1%) 4 (14.8%) 15 (55.6%)	 0.265 0.601 0.199 0.9644
% of Body Fat – Mean (SD)	32.1 (8.2)	36.7 (4.1)	0.036*
Visceral Fat Area – Mean (SD)	212.7 (131.7)	109.0 (39.8)	0.002*

ApoB - Apolipoprotein B. CPR - C Reactive Protein. LDL - Low-density lipoprotein. Lp(a) - Lipoprotein(a). SD - Standard Deviation.

> DISCUSSION

The proportion of MHO individuals in our sample (11.4%) is in accordance with the estimated prevalence of European obese adults (between 10 to 30%). [3] In our work, the MHO sample had an equal gender distribution and had a lower proportion of individuals in the very high CV risk group (35.7%). One study conducted in seven European countries that raised additional evidence on the variation of the prevalence of MHO across different populations, demonstrated a higher prevalence of women and younger subjects within this phenotype [3] Although one study from NHANES (National Health and Human Nutrition Examination Survey) showed that 51.3% of overweight and 31.7% of obese adults were metabolically healthy, to the extent of our knowledge, there are no data on the prevalence of MHO in the Portuguese population. [13]

When studying the association between MHO and cardiovascular disease and mortality there are inconsistent results, which are attributed to the inadequate adjustment for potential confounders

Table III - Comparison between Metabolically Healthy Obese and Normal Weight Obese.

Variable	*Metabolically Healthy Obese* (N = 14)	*Normal Weight Obese* (N = 27)	*p*-value
Age – Mean, in years (DP)	63 (13)	60 (18)	0.541
Masculine Gender – N (%)	8 (57.1%)	1 (3.7%)	0.000*
Dyslipidaemia – N (%)	13 (92.9%)	23 (85.2%)	0.475
Hypertension – N (%)	9 (64.3%)	12 (44.4%)	0.227
Diabetes – N (%)	2 (14.3%)	2 (7.4%)	0.480
Chronic Kidney Disease – N (%)	0	3 (11.1%)	0.195
Heart Failure – N (%)	0	4 (14.8%)	0.130
Atrial Fibrillation – N (%)	1 (7.1%)	1 (3.7%)	0.631
Stroke – N (%)	0	3 (11.1%)	0.195
Acute Coronary Syndrome – N (%)	0	1 (3.7%)	0.466
Secondary Prevention – N (%)	0	4 (14.8%)	0.130
Lp(a) – Mean (SD)	35.6 (27.7)	50.6 (51.8)	0.227
ApoB – Mean (SD)	127 (52.4)	131.5 (86.6)	0.836
LDL – Mean (SD)	109.3 (38.9)	124.6 (97.7)	0.476
Albumin – Mean (SD)	4.5 (0.3)	4.3 (0.4)	0.072
C Reactive Protein – Mean (SD)	0.6 (0.9)	0.9 (1.7)	0.460
CRP/Albumin Ratio – Mean (SD)	24.4 (18.9)	41.9 (48.4)	0.099
Carotid Plaques – N (%)	5 (35.7%)	10 (37.0%)	0.935
Steatosis – N (%)	3 (21.4%)	7 (25.9%)	0.750
Cardiovascular Risk (ESC) Low Moderate High Very High	 7 (14.3%) 0 7 (50%) 1 (35.7%)	 5 (18.5%) 3 (11.1%) 4 (14.8%) 15 (55.6%)	 0.735 0.195 0.016* 0.227
% of Body Fat – Mean (SD)	29.4 (9.6)	36.7 (4.1)	0.002*
Visceral Fat Area – Mean (SD)	103.5 (35.9)	109.0 (39.8)	0.654

ApoB - Apolipoprotein B. CPR - C Reactive Protein. LDL - Low-density lipoprotein. Lp(a) - Lipoprotein(a). SD - Standard Deviation.

and the lack of a standard definition of MHO, which makes the comparison between studies difficult. [3, 9, 13] Furthermore, it is suggested that MHO should be viewed as a transient state for most individuals with obesity rather than a permanent one as, over the long term, it does not appear to represent a benign condition. [9, 11, 14] Additionally, it is argued that MHO should be considered a risk condition, similar to pre-diabetes, and that treatment should be started early in order to prevent the development of metabolic abnormalities. [12]

In our work the proportion of MONW was 13%, which is in accordance with the estimated prevalence in the United States (between 7 and 20%). [13] This group had the highest proportion of patients with very high CV risk (56.3%), and also the highest CRP/A ratio (54.5). The CRP/A ratio has been recently recognised and used as a more reliable inflammatory marker than albumin and CPR alone. [15-18]

When comparing MONW and NWO, there were statistically significant differences between gender (male gender 68.8% *vs* 3.7%, $p < 0.05$), C reactive protein (0.2 *vs* 0.9, $p = 0.033$), Lp(a) (22.2 *vs* 50.6, $p = 0.027$) and ApoB (72.8 *vs* 131.5, $p < 0.05$) mean values. This effect was not seen neither by the percentage of individuals in secondary prevention (12.5% *vs* 14.8%, $p = 0.833$), nor by differences in the cardiovascular risk group. This difference between gender was observed in other studies. [13] Furthermore, when comparing MHO and MONW, there are statistically significant differences in visceral fat area (mean 103.5 *vs* 212.7, $p = 0.002$) which may influence the differences also seen in the proportion of patients with diabetes (14.3 *vs* 62.5, $p = 0.007$) and in the CPR/A ratio (24.4 *vs* 54.5, $p = 0.028$). Although it is already known that obesity is strongly associated with elevated levels of CRP alone, studies on the CRP/A ratio are still lacking. [19] Our results demonstrate promising use of CRP/A ratio as an inflammatory marker in obese patients.

The early recognition of the MONW phenotype is crucial for initiating timely lifestyle interventions and pharmacologic treatment, even before they are recommended based on conventional risk stratification, which may underestimate the cardiovascular risk associated with visceral obesity. [1] In our study, 12.6% of patients were classified as having low or moderate CV risk. Despite having the lowest mean levels of both Lp(a) and ApoB, this group had the highest CRP/Albumin ratio, reflecting a heightened inflammatory state, as well as the greatest mean visceral fat mass. These findings underscore the potential benefits of early intervention for these patients. The 2021 European Society of Cardiology Guidelines on Cardiovascular Disease Prevention in Clinical Practice already

Table IV - Comparison between Metabolically Healthy Obese and Metabolically Obese Normal Weight.

Variable	*Metabolically Healthy Obese* (N = 14)	*Metabolically Obese Normal Weight* (N = 16)	*p*-value
Age – Mean, in years (DP)	63 (13)	61 (16)	0.706
Masculine Gender – N (%)	8 (57.1%)	11 (68.8%)	0.507
Dyslipidaemia – N (%)	13 (92.9%)	15 (93.8%)	0.921
Hypertension – N (%)	9 (64.3%)	11 (68.8%)	0.794
Diabetes – N (%)	2 (14.3%)	10 (62.5%)	0.007*
Chronic Kidney Disease – N (%)	0	0	1
Heart Failure – N (%)	0	1 (6.3%)	0.339
Atrial Fibrillation – N (%)	1 (7.1%)	2 (12.5%)	0.623
Stroke – N (%)	0	2 (12.5%)	0.171
Acute Coronary Syndrome – N (%)	0	0	1
Secondary Prevention – N (%)	0	2 (12.5%)	0.171
Lp(a) – Mean (SD)	35.6 (27.7)	22.2 (32.6)	0.224
ApoB – Mean (SD)	127 (52.4)	72.8 (37.9)	0.001*
LDL – Mean (SD)	109.3 (38.9)	87.4 (31.5)	0.093
Albumin – Mean (SD)	4.5 (0.3)	4.3 (0.3)	0.069
C Reactive Protein – Mean (SD)	0.6 (0.9)	0.2 (0.1)	0.098
CRP/Albumin Ratio – Mean (SD)	24.4 (18.9)	54.5 (50.8)	0.028*
Carotid Plaques – N (%)	5 (35.7%)	7 (43.8%)	0.651
Steatosis – N (%)	3 (21.4%)	6 (37.5%)	0.337
Cardiovascular Risk (ESC) Low Moderate High Very High	 7 (14.3%) 0 7 (50%) 1 (35.7%)	 1 (6.3%) 1 (6.3%) 5 (31.3%) 9 (56.3%)	 0.467 0.339 0.297 0.239
% of Body Fat – Mean (SD)	29.4 (9.6)	32.1 (8.2)	0.411
Visceral Fat Area – Mean (SD)	103.5 (35.9)	212.7 (131.7)	0.002*

ApoB - Apolipoprotein B. CPR - C Reactive Protein. LDL - Low-density lipoprotein. Lp(a) - Lipoprotein(a). SD - Standard Deviation.

highlight the role of ectopic fat in obesity management, recommending anthropometric measures such as waist circumference. [20]

This common recommendation of weight loss through moving more and eating less has been shown to be an oversimplification, as its impact varies significantly depending on the patient's individual phenotype. [3, 8] For SO subjects, such recommendations may have an unintended catabolic effect on muscle mass, leading to a loss of lean body mass. This highlights the importance of a treatment strategy combining moderate energy restriction with regular exercise, which better preserves muscle mass while promoting fat loss. [1, 12]

For patients with elevated visceral adipose tissue, such as those with the MONW phenotype, improving cardiorespiratory fitness and reducing waist circumference are desirable outcomes, even in the absence of significant weight reduction. [8, 11, 12, 21] Physicians should place greater emphasis on cardiorespiratory fitness, as it is strongly correlated with overall health and serves as a robust predictor of cardiovascular risk. [9, 12]

In addition, patient´s phenotype may assist physicians in determining the most appropriate pharmacological treatment or even in the choice of patients that should underwent restrictive or malabsorptive surgery, as it has been proven that it significantly reduces visceral adipose tissue. [8, 9]

Our work has some limitations, namely the retrospective design, the number of patients included and the fact that almost all patients had dyslipidaemia, and were undergoing pharmacological treatment, which might underestimate the real differences between the phenotypes and may change the lipid profile, since the association between visceral adipose tissue and higher ApoB levels was not found in our sample. Furthermore, the most widely used methods in research for assessing body composition and obesity phenotypes (computed tomography and magnetic resonance imaging) have important limitations to their use in clinical practice, such as the exposition to radiation and its limited assess, which is the reason why dual-energy x-ray absorptiometry (DXA) is being used as a lower-cost, lower-radiation alternative. [9] However DXA is hardly feasible in clinical practice as it requires specialized radiology equipment, being replaced by bioelectrical impedance analysis (BIA), due to its

simple, non-invasive and low-cost usage, emerging as an alternative method of measuring body composition. [22-24] BIA's major limitation is the assumption of fixed hydration, which is the main reason for not being the standard method for assessing body composition. [23, 24] Nonetheless, we used a 8-electrode segmental system that is more accurate, increasing the validity of our results. [24]

> CONCLUSION

In a world of precise and personalized medicine, one-size does not fit all, and it is important to understand that BMI is an inaccurate measure of adiposity and that reducing BMI should not be the primary target for physicians. Our findings contribute to the growing body of evidence supporting the existence of metabolic differences between the proposed obesity phenotypes and, although further studies are necessary to draw definitive conclusions, it reinforces the importance of a thorough understanding of the metabolic profile beyond the conventional anthropometric measurements. The importance of this understanding in a specialized clinic is to adapt lifestyle recommendations and pharmacological treatment not only according to individual´s cardiovascular risk, but also in consonance with patient's phenotype. Considering our results, for the MONW and NWO patients, an early intervention may be appropriate, even before there is a formal recommendation by international guidelines. Furthermore, as resources to manage obesity are limited, attention should be focused on high-risk phenotypes, such as individuals with excess visceral and ectopic fat with elevated cardiovascular risk.

In summary, our work supports the importance of integrating body fat distribution into risk assessment and current treatment paradigms, and emphasizes the need for a multidisciplinary approach, assuring adequate treatment for individuals who are most likely to benefit from it. <

Conflicts of Interests and Sponsorships/*Conflitos de Interesses e Patrocínios*

The authors declare that they have no conflicts of interest or sponsorships./*Os autores declaram a inexistência de conflitos de interesses e de patrocínios.*

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