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The influence of metabolic profile of obese men on the severity of erectile dysfunction: are metabolically healthy obese individuals protected?

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ABSTRACT

Objective: To determine the prevalence of erectile dysfunction (ED) in metabolically healthy obese (MHO) individuals, and to compare ED severity and hypogonadism prevalence in MHO, metabolically unhealthy obese (MUO) and metabolically healthy non-obese individuals.

Material and methods: ED patients (n=460) were evaluated by standardized protocol, that included clinical evaluation, abridged 5-item version of the International Index of Erectile Function (IIEF-5) questionnaire survey, and Penile Duplex Doppler Ultrasound (PDDU) exam. Patients were classified as obese [body mass index (BMI) ≥30.0 kg/m^2] and non-obese (BMI <30.0 kg/m^2), and metabolic health status was defined by National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) criteria. Statistical analysis was performed and statistical significance was considered at p-level <0.05.

Results: The mean age of the subjects was 56.2±10.5 years. MHO was present in 40% of obese individuals (n=37). MUO had lower mean peak systolic velocity (mPSV) compared to MHO (28.1 cm/s vs. 36.9 cm/s; p=0.005), and IIEF-5 scores were also lower in MUO compared to MHO patients (10.2 vs. 13.1; p=0.018). No statistical differences in IIEF-5 score, mPSV and hypogonadism prevalence between MHO and metabolically healthy non-obese (MHNO) patients were observed.

Conclusion: Our results lead us to conclude that healthy metabolic profile protects obese individuals from severity of ED. The strong association between obesity and ED may be otherwise attributed to metabolic abnormalities present in the obese.

Keywords: Erectile dysfunction; hypogonadism; metabolically healthy obesity; penile duplex Doppler ultrasound

Introduction

Obesity is a complex disorder involving an excessive amount of body fat with increasing prevalence worldwide, and it is predicted to affect more than one billion people by 2030. Obesity is not just a cosmetic concern. It promotes insulin resistance and the occurrence of diseases and health problems such as metabolic syndrome (MetS), type 2 diabetes mellitus and cardiovascular disease, leading to increased risk of premature death and higher all-cause mortality.[1]

Metabolically healthy and unhealthy obesity have been recognized since the 1980's. However, due to the numerous definitions of metabolic health, a wide range of prevalence rates for metabolically healthy obesity (6-40%) have been registered.[2-5] Accordingly, as not the case with all non-obese these subjects have a favorable metabolic profile, some obese people do not present increased risk of health outcomes that are characteristically associated with obesity. In these individuals, who have been described as metabolically healthy obese (MHO), the obese phenotype exists despite the absence of metabolic abnormalities such as dyslipidemia, insulin resistance, hypertension and an unfavorable inflammatory profile.[3,4,6,7] Although many cross-sectional and longitudinal epidemiological studies have reported that

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metabolically healthy obese individuals have not an elevated risk of cardiovascular disease or diabetes[8,9], many others have suggested the opposite.[2,10,11]

Men with obesity-related comorbidities such as type 2 diabetes, cardiovascular disease or MetS, often have erectile dysfunction (ED), most likely due to common biological factors that impair hemodynamic mechanisms of both penile and systemic vascular beds.[12] In subjects with vascular risk factors, penile hemodynamic parameters are impaired and testosterone levels are significantly reduced, changes that are more severe as the number of risk factors increases, reflecting the underlying endothelial dysfunction.[13,14]

Treatment of ED and of obesity is an enormous medical and socio-economic task, that is not always successful. Importantly, MHO individuals may not significantly improve their cardiometabolic risk upon weight loss interventions and in that way not benefit to the same extent as obese patients with metabolic comorbidities from early lifestyle or pharmacological interventions.[15] It is important to identify in a timely manner the obese patient who will benefit most from losing weight and treating their metabolic disturbances (unhealthy obesity) from those who are healthy obese and may not significantly improve their sexual function by obesity treatment strategies. Nevertheless, since MHO is not a static condition, over time, the variables that predict metabolic deterioration in these individuals should be considered.[1,16]

There is a lack of studies demonstrating the impact of the metabolically healthy obesity on erectile function despite the established association between obesity and ED. Thus, we aimed to determine the prevalence of MHO in patients with ED and to compare ED severity and hypogonadism prevalence in MHO, metabolically unhealthy obese (MUO) and metabolically healthy non-obese (MHNO) men.

Material and methods

This transversal, descriptive and analytical study included 460 Caucasian patients followed in our Urology consult for ED within the last four years. Signed informed consent allowing use of their data in this study was obtained from all patients. Exclusion criteria were the presence of any of the following conditions: neurological disease, history of recent coronary artery disease, major psychiatric disorder, hepatic disease, pelvic trauma, thyroid disease, end-stage renal disease and history of drug abuse.

All patients underwent a standardized evaluation protocol that included a health questionnaire, physical examination, biochemical and hormonal blood analysis, International Index of Erectile Function (IIEF-5) questionnaire[17], and Penile Duplex Doppler Ultrasound exam (PDDU).

The health questionnaire was prepared to collect information about past medical history, cardiovascular and metabolic risk factors such as high blood pressure (HBP), diabetes mellitus, abnormalities of total cholesterol (TCho), low-density lipoprotein (LDL) and/or high-density lipoprotein (HDL), and triglycerides (TG). Data concerning current pharmacological treatment, and alcohol and tobacco use were also collected. All patients underwent a standardized physical examination protocol. Anthropometric evaluation, including weight, height and waist circumference (WC) was performed by the same technician with the subjects in light clothing and barefoot. WC was measured using an anthropometric tape (to the nearest 0.1 cm) placed at the level of the midpoint between the upper end of iliac crest and lower end of the 12th rib at the end of normal expiration. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. Patients were classified as obese (BMI ≥30.0 kg/m^2) and non-obese (BMI <30.0 kg/m^2). Systolic and diastolic blood pressures were measured from the right arm using an automatic manometer (DINAMAP Procare 300, GE, UK) after a 10-minute rest period with the patient sitting upright.

Blood analysis was performed using samples of venous blood collected between 8 and 10 a.m., after a 12-hour overnight fasting period. Blood glucose, TCho, LDL, HDL and TG measurements were made using routine laboratory methods. Total testosterone (TT) levels were measured by chemiluminescence method with a commercially available kit (Abbott Diagnostics Division, Princeton, NJ, USA and DSL-Diagnostic Systems Laboratories, Webster, TX, USA) with a normal variation of 280-1100 ng/dL (9.7-38.2 nmoL/L). Free testosterone (FT) levels were determined by radioimmunoassay using a commercial kit (DSL-Diagnostic Systems Laboratories) with a normal range of 5.7-54.7 pg/mL (20-190 pmoL/L). According to the *International Society of Andrology*, *International Society for the Study of Aging Male*, *European Association of Urology*, *European Academy of Andrology*, and *American Society of Andrology* recommendations, hypogonadism was defined as TT below 8 nmoL/L, and when serum TT level was between 8 and 12 nmoL/L, hypogonadism was defined as FT under the lower limit of range.[18]

Patients who were not under acute or chronic use of phosphodiesterase type 5 inhibitors for at least 30 days, underwent PDDU examination, performed by the same investigator and in accordance with the protocol proposed by the *International Society for Sexual Medicine Standards Committee in Standard Practice in Sexual Medicine*.[19] A 12MHz transducer (GE Logic 7 Ultrasound System, UK) was used to evaluate penile vascular flow patterns at 5, 10 and 20 min after the injection of 10 to 20 mcg of commercial prostaglandin E1 (Caverject®) into the

right corpus cavernosum. To allow best possible erection by tactile stimulation, patients were left alone before and in-between evaluations. The mean values of Peak Systolic Velocity (PSV), End-Diastolic Velocity (EDV) and Resistive Index (RI) (accordingly to the formula: RI = [PSV – EDV] / PSV) were obtained from spectral waveform evaluations. Values of PSV ≥35 cm/s, EDV <5 cm/s and RI >1 were considered as normal response. Diagnostic criteria for an abnormal response included arterial insufficiency for PSV <35 cm/s or PSV asymmetry >10 cm/s, cavernous venous-occlusive disease for PSV ≥35 cm/s and EDV ≥5 cm/s, and mixed when 35 <PSV >25 cm/s and EDV ≥5 cm/s. The degree of erectile response was estimated by the same investigator according to a graded scale: 0 (no response), 1 (minimal tumescence and no rigidity), 2 (moderate tumescence and no rigidity), 3 (full tumescence and moderate rigidity), and 4 (full rigidity).

Patients were asked to complete the abridged 5-item version of IIEF-5. ED was classified, based on the IIEF-5 scores (range from 5 to 25) into five categories as severe (5-7), moderate (8-11), mild to moderate (12-16), mild (17-21), and no ED (22-25).

Metabolic health profile was established by using *National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII)* definition.[20] Patients without cardiovascular or metabolic risk factors were considered MHNO if their BMI was below 30.0 kg/m^2, and MHO if BMI was equal zto or higher than 30.0 kg/m^2. MUO category encompassed all men of our sample with obesity and with at least three of the five ATPIII criteria (WC >102 cm; TG >1.7 mmol/L [150 mg/dL] or medication; HDL <1.03 mmol/L [40 mg/dL] or medication; plasma glucose ≥5.6 mmol/L [100 mg/dL]; systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or those under treatment.

Statistical analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences version 22.0 for Windows® (IBM Corp. SPSS., Armonk, NY, USA). The differences between groups were evaluated by unpaired Student's t-test, or Mann-Whitney U test as appropriate, for continuous variables. Multivariate analysis was performed by multivariate linear regression and logistic regression tests for continuous and categorical-dependent variables, respectively. The association of metabolic profile with penile hemodynamics and IIEF-5 score was demonstrated using chi-square test. The software handled missing data automatically: frequencies and cross-tabulations were computed based only in cases with non-missing data; regressions and correlations were computed based on pairs with non-missing data. Statistical significance was considered at a p-level <0.05.

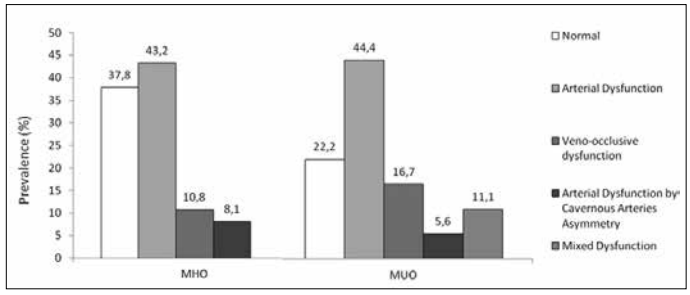

Figure 1. Diagnosis of erectile dysfunction in metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) patients evaluated by penile duplex Doppler ultrasound. No statistical differences were observed in diagnosis of ED by PDDU between MHO and MUO (p=0.151)

Results

The characteristics of the study population are described in Table 1. Mean age and BMI of the patients (n=460) were 56.2±10.5 years and 27.7±4.1 kg/m^2, respectively. In our sample, 19.8% of patients were obese, 31.3% had MetS, and MHO was present in 40% of obese individuals (n=37). Among metabolically healthy individuals, 86% were MHNO (n=238) (Table 2).

Penile hemodynamic parameters evaluated by PDDU were normal in 31.1% of the patients. Arterial dysfunction, veno-occlusive dysfunction, arterial dysfunction were demonstrated by evaluating asymmetry between cavernous arteries, and mixed dysfunction were identified in 41.5%, 13.0%, 8.2% and 6.2% of the patients, respectively. Among obese people, no differences in diagnostic criteria of ED using PDDU were observed between metabolically healthy and unhealthy subjects (p=0.151) (Figure 1). Also, among metabolically healthy individuals, there were no differences in diagnosis of ED by PDDU between those who are obese and non-obese (p=0.639).

The association of penile hemodynamic parameters with the presence of metabolically healthy obesity was also evaluated (Figure 2). MUO had significantly lower mean peak systolic velocity (mPSV) in comparison with MHO (28.1 cm/s vs. 36.9 cm/s, p=0.005). There were no differences in mPSV between MHO and MHNO (36.9 cm/s vs. 36.8 cm/s, p=0.945).

The mean value of IIEF-5 score in all men of our sample was 11.8±4.7. ED assessed by this questionnaire was severe in 20.4%, moderate in 28.4%, mild to moderate in 36.2%, and mild in 11.8% the patients. No ED was verified in 3.2% of men. The association of mean value of IIEF-5 score with metabolic health in obese patients was analyzed. IIEF-5 score was lower in MUO when compared to MHO (10.2 vs. 13.1, p=0.018) (Figure 3), and no differences were verified between MHO and MHNO (13.1 vs. 12.0, p=0.365).

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Table 1. Characteristics of the population in study (n=460)

Variable	Description	Value
Age (years)		56.2±10.5
Waist circumference (cm)		101.9±10.5
Body mass index (kg/m^2)		27.7±4.1
Obesity (%)		19.8
Metabolic Syndrome (%) (NCEP-ATP III criteria)		31.3
Metabolic Syndrome components (%)	Hypertriglyceridemia (≥1.7 mmol/L; 150 mg/dL) or treatment	30.0
	Hyperglycemia (≥6.1 mmol/L; 100 mg/dL) or treatment	34.0
	Low HDL (<1.03 mmol/L; 40 mg/dL) or treatment	25.5
	Systolic blood pressure ≥130 mmHg and/or Diastolic blood pressure ≥85 mmHg or treatment	49.9
	Waist circumference > 102 cm	48.8
Tobacco (%)	Smoker	23.0
	Ex-Smoker	33.4
	Non-Smoker	43.6
Current medical treatment (%)	Antiaggregant agents	26.7
	Beta-blockers	17.3
	Angiotensin receptor blockers	17.3
	Angiotensin-converting enzyme inhibitors	22.5
	Calcium channel blockers	16.8
	Thyazidic diuretics	16.6
	Antidepressants	9.1
	Benzodiazepines	17.9
	Statins	36.4
	Nitrates	4.4
	Fibrates	7.1
	Warfarin	2.9
IIEF-5 Score		11.8±4.7
Hypogonadism (%)	Total testosterone <8 nmol/L 12 nmol/L < Total testosterone >8 nmol/L and Free testosterone <20 pmol/L	18.5 1.5

Data are expressed as mean± standard deviation when normally distributed and as percentages when categorical. NCEP-ATP III: National Cholesterol Education Program, Adult Treatment Panel III; IIEF-5: abridged 5-item version of the International Index of Erectile Function; HDL: high-density lipoprotein

Table 2. Distribution of the population in study

			Body mass index (kg/m^2)	p	
Total population (n=460)	Obese individuals (n=91)	MHO (n=37)	32.9±4.2	0.314	<0.001
		MUO (n=54)	33.7±3.4		
	Non-obese individuals (n=369)	MHNO (n=238)	25.4±2.4*	<0.001	
		MUNO (n=131)	27.0±2.0**		

MHO: Metabolically Healthy Obese Individuals; MUO: Metabolically Unhealthy Obese Individuals; MHNO: Metabolically Healthy Non-Obese Individuals; MUNO: Metabolically Unhealthy Non-Obese Individuals

*p<0.001, MHNO versus MHO and MUO; **p<0.001, MUNO vs. MHO and MUO

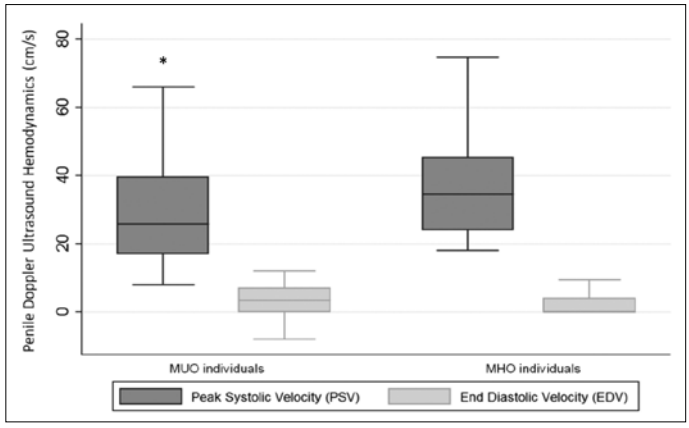

Figure 2. Evaluation of penile hemodynamic parameters in obese subjects in accordance with their metabolic profile
*p<0.05, MUO mPSV versus MHO mPSV. MUO: Metabolically Unhealthy Obese Individuals; MHO: Metabolically Healthy Obese Individuals

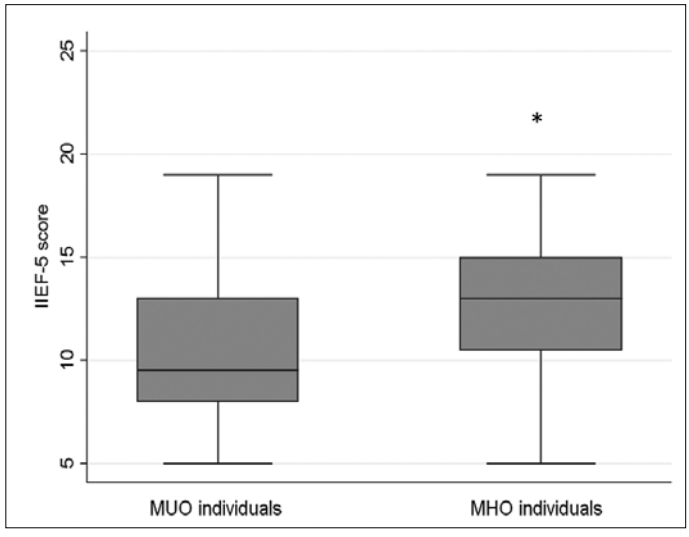

Figure 3. Evaluation of IIEF-5 score in metabolic healthy and unhealthy obese individuals
*p<0.05. IIEF-5: International Index of Erectile Function; MUO: Metabolically Unhealthy Obese Individuals; MHO: Metabolically Healthy Obese Individuals

Hypogonadism was present in 18.5% of men of our sample, of that 36.4% were obese and 15.3% MHO. No differences in prevalence of hypogonadism were verified between MHO and MUO (p=0.058) neither between MHO and MHNO (p=0.189).

Discussion

The association of obesity, MetS and ED has been highly debated in recent years. The increased incidence of ED in obese patients is explained by the several comorbidities associated with the excessive amount of adipose tissue, diabetes, cardiovascular diseases or dyslipidemia. Scientific evidence not only demonstrate that the risk of ED increases with BMI, but also alerts that excessive body weight should be regarded as an independent risk factor for ED.[21] Similarly, MetS is significantly associated with ED prevalence, and its severity increases with the addition of MetS criteria.[14]

A cluster of metabolically healthy obese individuals was thought to diverge from the most recognized obesity-related cardiovascular and metabolic risks. Several studies demonstrated that overweight and obese people without MetS have lower risk of heart failure than normal-weight individuals with MetS.[22-25] Similarly, both cross-sectional and prospective data have showed that MHO men do not have a significantly increased risk of all-cause mortality.[8] However, Twig et al.[26] verified that young MHO men without diabetes are not excempt from the effects of risk factors inducing incident diabetes related with their high BMI. As far as we know, obesity-and MetS-related vasculogenic ED has not been ever evaluated in this population. Thus our study is the first to demonstrate that ED severity is similar in MHO and MHNO.

Due to the lack of an uniform definition of metabolic health status, the prevalence of MHO largely varies depending on which criteria are being used. Phillips[3], compiled and reviewed several studies in this field, in which the single criterion considered to distinguish healthy from at-risk obese subjects was insulin sensitivity. He concluded that the prevalence of MHO which ranged from 6.8% to 30.2%, was higher in women and tended to increase with age. In the present study, NCEP ATPIII criteria, which are based on established cut-off values not dependent on risk distribution in the population under study do not define metabolic health as in some definitions.[27] These criteria are indeed the most commonly used by others, and allowed us to verify that the high proportion of MHO in our outpatients' urology consult was similar to that observed by Meigs et al.[28].

Previous studies indicated that MetS leads to impairment of the hemodynamic parameters of the cavernosal arteries measured by PDDU, with the diminution of mPSV as the number of MetS criteria increase.[14] Herein, MUO patients evidenced that mPSV levels were significantly lower than those observed in MHO subjects. Furthermore, IIEF-5 scores were also lower in MUO than in MHO, showing that individuals with a healthy metabolic profile have milder forms of ED. This is consistent with findings of Demir et al.[29], which demonstrated that the mean value of IIEF-5 score of patients with three or more metabolic risk factors were reduced, emphasizing that severity of ED increases with the accumulation of metabolic risk factors. Additionally, our data also show that no differences on the severity of ED evaluated by IIEF-5 score and PDDU are observed between MHO and MHNO patients. These results suggest that metabolic

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profile, such as hypertension, high blood glucose levels, and dyslipidemia, may have a higher impact on pathogenesis of ED than obesity by itself. It allows us to speculate that maintaining a healthy metabolic profile with a strict control of blood pressure and glycemia, and decrease of total cholesterol, LDL and triglycerides accompanied by an increase in HDL levels, is more beneficial in terms of demonstrating severity of ED than losing weight *per se* which agrees with the findings from Corona et al.[30], that showed that these abnormalities had the greatest impact among obesity-related comorbidities on impairment of penile blood flow parameters in comparison to those verified in patients with simple obesity. In fact, the main pathogenic mechanism underlying ED-related obesity is endothelial dysfunction, mainly caused by comorbid conditions.[12,30]

Given the prevalence of the MHO phenotype in obese populations, emphasis is increasingly placed on understanding the characteristics and potential mechanisms underlying their healthy metabolic profile.[10] There are hormones that play a role in allowing some obese individuals to maintain a healthy profile; and metabolic activity and histological characteristics rather than amount of adipose tissue may partially determine metabolic health among obese individuals. Previous studies suggest that MHO individuals have been obese for fewer years compared with their MUO counterparts, display a lower level of C-reactive protein, high adiponectin concentrations and high levels of insulin sensitivity, despite having a high accumulation of body fat.[3] This favorable profile might reduce their risk of type 2 diabetes, but the risk of CVD is no different with that observed in the MUO.

Testosterone is crucial for male sexual function including erectile function.[21,26] Several studies have shown that age-related decrease in testosterone levels in men is intensified by obesity, MetS and type 2 diabetes. On the other hand, it has been also reported that low testosterone levels can further worsen the metabolic profile and led to development of MetS. Although hypogonadism can exacerbate obesity-associated ED, in the present study there were no differences in the prevalence of hypogonadism between MHO and MUO. This finding reinforces the pathogenic role of high body fat mass not only on circulating testosterone reduction through suppression of sex hormone-binding globulin (SHBG) synthesis, but also in disturbances of insulin and/or leptin metabolism which in turn impair testicular steroidogenesis. In line with previous studies[14], our results suggest that this endocrine abnormality is not decisive for penile hemodynamic impairment.

Despite our interesting findings, some limitations must be acknowledged. Determinants of MHO are unclear, so a consensus on a metabolic health definition is fundamental to improve comparability between groups of patients and studies, as well as to understand the mechanisms by which fat accumulation in obese subjects causes or contributes to metabolic disorders and therefore to ED. It is essential to underscore that the MHO concept presently only addresses the cardiometabolic risks associated with obesity. It is also important to stress out that patients who are MHO are still very likely to present many other obesity-related complications such as altered physical and/or physiological functional status.[1] The definition of hypogonadism based on TT levels is still controversial, as there are no generally accepted lower limits of normal. Although repeating the measurement of TT, and SHBG levels to calculate FT, or evaluating FT by equilibrium dialysis, represent the best options, these accurate and reliable reference assays are expensive, laborious and usually not available in local laboratories. Thus, being able to only display FT levels determined by RIA, is a limitation in our study as it has lower diagnostic sensitivity for hypogonadism.

Considering that MHO may be a stage on the progression of obesity-related pathologies and not just a cluster of patients by itself, prospective studies aiming to determine duration of obesity and transition between metabolic profiles will be necessary to investigate the development of vasculogenic ED. A greater understanding of the MHO phenotype has important implications for therapeutic decision-making, characterization of subjects in research protocols and medicaleducation. In this setting, additional studies focused on MHO-related ED underlying factors and etiological mechanisms and response to lifestyle strategies and pharmacological treatment are also needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Centro Hospitalar S. João, EPE.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.T.; Design – A.M., I.T., N.T.; Supervision – N.T.; Resources – N.T.; Materials – N.T.; Data Collection and/or Processing – A.M., N.T.; Analysis and/or Interpretation – A.M., I.T., N.T.; Literature Search – A.M., I.T., N.T.; Writing Manuscript – A.M., I.T., N.T.; Critical Review – I.T., N.T.

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