Obesity Complications and Challenges

Chapter 2

"Obesity Phenotype and Its Characterization"

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1. Introduction

Obesity is a chronic disease characterized by hyperplasia and hypertrophy of adipocytes. It has a multifactorial and complex etiology, involving genetic (most common polygenic inheritance), behavioral, cultural, neuroendocrine, and environmental factors. Among various causes, there is an increase in caloric consumption, a decrease in energy expenditure, or both, resulting in an energy imbalance between consumed and expended calories [1,2].

It is considered a global epidemic that covers all age groups and socioeconomic classes and presents high prevalence in urban areas of developing countries [1,3]. In recent decades there has been a significant increase in individuals with obesity. In 1995, there were approximately 200 million adults with obesity in the world, in 2000 it increased to values above 300 million individuals [2]. This proportion tends to increase, and it is estimated that by 2030 approximately 60% of the world population will have excess total body mass.

Although considered a chronic disease and not just a risk factor for other diseases, some researchers suggest the term "benign obesity phenotype" or "metabolically healthy obesity (MHO)" to describe obesity developed without Systemic Arterial Hypertension (SAH), Cardiovascular Disease (CVD), Insulin Resistance (IR), type 2 diabetes mellitus (T2DM), dyslipidemia or Metabolic Syndrome (MS) [4]. In contrast, individuals with MHO that have some degree of metabolic impairment are classified as "Metabolically Unhealthy Obesity" (MUHO).

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Therefore, the concept of MHO emerged from the observations of Jean Vague, in the 1950s, of the existence of individuals MHO, even with obesity, had a lower predisposition to T2DM and atherosclerosis, compared to what was expected in view of their excess adiposity, which may be related to the distribution of body fat. Since then, MHO has been described in clinical observations and epidemiological, prospective cohort and intervention studies [5]. Although the existence of individuals with obesity and without metabolic and cardiovascular complications is already well established, there is a debate in the scientific literature about the extent to which MHO represents a distinct and stable phenotype and whether there is clinical relevance to predict the risk of T2DM and future CVDs [6].

The MHO concept can serve as a model to better understand the mechanisms that link obesity to cardiometabolic diseases. However, one of the biggest challenges in the MHO study is its inconsistent and contradictory definition. While the World Health Organization defines obesity as excessive accumulation of fat, diagnosed by a Body Mass Index (BMI) ≥30 kg/m², which can harm health, how could there be a healthy obesity phenotype? Furthermore, considering the absence of a standardized consensus for its definition, the MHO remains surrounded by several criteria that make it even more difficult to understand its real meaning: is the MHO a healthy phenotype or just a transitional period in the progression from health to disease? And during this chapter the authors will clarify some of these questions.

Definition and Criteria for Classification of the Metabolically Healthy Obesity Phenotype

It is important to point out that there is no unified definition of MHO. Despite the consensus that a BMI ≥30 kg/m² is a prerequisite for it, more than thirty different definitions of metabolic health are used in clinical studies. In general, MHO has been defined by the absence of diseases and/or metabolic alterations, such as CVD, T2DM, dyslipidemias, SAH, MS, Atherosclerotic Cardiovascular Disease (ACVD) and preserved insulin sensitivity. However, the numerous criteria available in the scientific literature differ in relation to the metabolic parameters considered as risk factors, as well as the cut-off points adopted, and the number of changes tolerated to classify the individual as healthy. Thus, there are criteria that tolerate one, two or even three parameters outside the cut-off points and still consider the individual healthy, however, there are more conservative ones, a more recent trend, where no change in the adopted parameters is tolerated.

The heterogeneity in the definition of MHO represents an important limitation for the interpretation of studies that report a wide range of associations between this phenotype, CVD, mortality, and the risk of metabolic diseases [5,7]. Furthermore, differences in diagnostic criteria can define MHO subpopulations that have only little overlap in key cardiometabolic parameters. For example, more than 40% of National Health and Nutrition Examination Survey (NHANES) III participants were classified as MHO using the National Cholesterol Education

Program (NCEP) Adult Treatment Panel (ATP III) criteria for MS [8], but only 20% fall into the MHO category using cut-off points for insulin sensitivity parameters. These uncertainties in the MHO definition may imply that the phenotype does not biologically represent a distinct subgroup of obese individuals.

`The need for standardized MHO criteria was addressed by the BioShare-EU project and by Lavie et al [9]. According to the Healthy Obese Project, which included data from 10 population-based cohort studies from seven countries (Estonia, Finland, Germany, Italy, the Netherlands, Norway, and the United Kingdom), 17% of the 163.000 individuals evaluated were with obesity (11.465 men and 16.612 women, aged between 18 and 80 years). In the study, the main clinical and metabolic characteristics commonly used to define MHO were evaluated and compared.

A harmonized definition of MHO in adults was proposed based on the diagnosis of obesity (BMI ≥ 30kg/m²) associated with the following criteria:

- Serum triglycerides: ≤ 1.7 mmol/L (≤ 150 mg/dL),
- HDL-cholesterol: > 1.0 mmol/L (> 40 mg/dL) (in men) or > 1.3 mmol/L (> 50 mg/dL) (in women),
- Systolic blood pressure ≤ 130 mmHg, Diastolic blood pressure ≤85 mmHg, without antihypertensive treatment as an alternative indicator,
- Fasting blood glucose: ≤ 5.6mmol/L (≤ 100mg/dL), without drug treatment with hypoglycemic drugs.

These MHO definitions appear to be more easily applicable compared to previous attempts using parameters of insulin sensitivity (eg, euglycemic-hyperinsulinemic clamps, HOMA-IR, Matsuda index) or systemic inflammation (eg, C-reactive protein [CRP]). In contrast to the origins of the MHO concept (which may have included patients with SAH or T2DM), more recent definitions exclude individuals MHO meet only one of the MS criteria. Table 1 describes the criteria most used in the scientific literature to define the MHO phenotype.

It is important to emphasize that the MHO concept can only be applied to individuals MHO that meet the cardiometabolic criteria described above and should not be misinterpreted as a subgroup of individuals with obesity without health problems [6]. In addition to metabolic diseases (eg, T2DM, dyslipidemia, Metabolic Associated Fatty Liver Disease [MAFLD]) and CVD (eg, SAH, myocardial infarction, stroke), obesity is associated with osteoarthritis, back pain, asthma , depression, cognitive impairment, some cancers (eg breast, ovarian, prostate, liver, kidney, colon), all of which can have an impact on reduced quality of life, unemployment, lower productivity, and social disadvantages [10]. Therefore, the diagnosis of ‘obesity’ should

remain an indication for the initiation of interventions for its control - even in those individuals without any cardiometabolic alteration at the time of diagnosis.

World epidemiology of the obesity phenotype

Data on the prevalence of MHO have been inconsistent, with variations of 10 to 30% depending on the criteria used for their classification, which are diverse and heterogeneous.

A meta-analysis that included 12 cohort studies and 7 intervention studies found a prevalence of 35% of MHO with significant regional differences [27]. In general, MHO appears to be more prevalent in women than in men and decreases with age. Large regional and gender-related variation in MHO prevalence was found in the BioSHaRE-EU Healthy Obesity Project, which estimated the age-standardized prevalence of MHO at approximately 12% across all cohorts.

In an analysis conducted with 10 independent cohorts from different European countries, a variation in the prevalence of MHO was observed from 7 to 28% in women, and from 2 to 19% in men, depending on the country evaluated. The biggest difference between genders was found in the United Kingdom study, with a prevalence of MHO of 9% in men compared to 28.4% in women, on the other hand, the prevalence of MHO was similar in men (19%) and women (21.1%) in a cohort from Italy.

It is important to emphasize that MHO prevalence estimates can only be compared in different cohorts or studies if the same criteria are used to define it. For example, the 68% prevalence of MHO observed in a large study of 3.5 million men and women from the Health Improvement Network is likely to be overestimated, due to the definition of the MHO phenotype that did not consider cut-off points for glucose parameters, blood pressure or lipids [30].

MHO was also observed in Asian and African populations with a prevalence (depending on diagnostic criteria and based on a BMI ≥25 kg/m² cut-off for obesity) ranging from 4.2% in a Chinese cohort to 13.3 % among Asian Indians and 28.5% among African Americans. Among 1.054 Hispanic American participants in the IR Study, 19% were classified with the MHO [31,32]. Data from the NHANES III program suggests a prevalence of MHO of approximately 17% in Americans of European or African descent.

Regarding the Brazilian population, in a study with individuals included in the Longitudinal Study of Adult Health (ELSA-Brazil), it was observed that, among the 21.2% classified with obesity, 5.6% fit the MHO phenotype. Women and younger individuals stood out for having a higher prevalence of the phenotype [33]. The criteria used for this classification followed those recommended by Ortega et al, namely: BMI ≥ 30 kg/m² and absence of any

parameters among the four indicators of MS, except for altered waist circumference.

In children and adolescents, MHO may be a more frequently observed condition. In a cross-sectional study from Canada, which included girls aged 8-17 years and boys with a BMI ≥ 85th percentile, the prevalence of MHO was 21.5% when cardiometabolic risk factors (blood pressure, serum lipids, glucose) were considered and 31.5% when IR parameters were applied to define MHO. In children and adolescents from the Korea National Health and Nutrition Survey, the prevalence of MHO was between 36.8% (for a definition based on cardiometabolic risk factors) and 68.8% (for IR criteria) [34].

In a study with 418 Brazilian adolescents with obesity, the estimated prevalence of MHO varied according to the criteria used, as expected. When applying the criteria proposed by the International Diabetes Federation (IDF), which is based on the absence of any cardiometabolic risk factors (except altered waist circumference), 43.1% of the phenotype were identified. For the second form of classification, the authors added the HOMA-IR assessment to the criteria proposed by the IDF, and 12.7% of the adolescents were classified as MHO, as they did not present alterations in any of these parameters [35].

According to the national and international data presented, it is possible to perceive that regardless of the definitions used and the remarkable regional and of gender, MHO does not seem to be a rare condition [9].

Characterization and determinants for the metabolically healthy obesity phenotype

The mechanisms that explain why there are individuals with obesity do not develop classic alterations of this condition are not yet well established in the literature. However, factors such as adipose tissue distribution, inflammatory parameters, insulin sensitivity, oxidative stress, cardiorespiratory fitness, and lifestyle have been constantly cited as involved in this issue. Advancement in knowledge about such factors is essential so that assertive strategies for controlling obesity can be traced, with the aim of reducing health risk and prolonging the healthy phenotype, reducing, for example, the probability of transition to MUHO.

Biological Mechanisms Underlying Metabolically Healthy Obesity

Despite the debate about the clinical implications of the MHO as a “diagnosis” [6,36], obesity without cardiometabolic abnormalities provides a unique human model system, and it is necessary to study the mechanisms that link the factors that promote weight gain and fat accumulation to obesity-related cardiometabolic complications.

In recent years, several biological mechanisms and phenotypic characteristics have been identified that differentiate individuals with MHO from those with MUHO **(Figure 1)**.

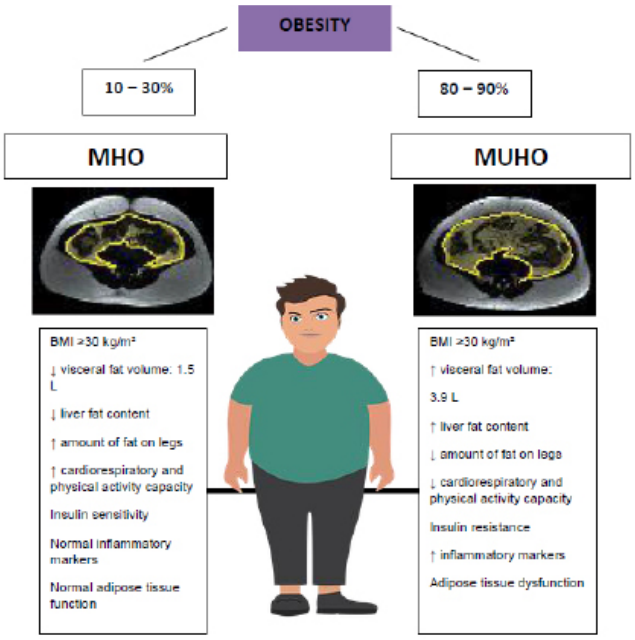

Figure 1: Characteristics of MHO and MUHO phenotypes. MHO: Metabolically Healthy Obesity; MUHO: Metabolically unhealthy obesity.

In a large cohort stratified by BMI, Stefan et al [36] linked high hepatic fat and predominantly abdominal (including visceral) adiposity to MUHO, while greater insulin sensitivity, better insulin secretion, cardiorespiratory fitness, and lower body subcutaneous fat mass were associated with the MHO phenotype. Certainly, these associations do not resolve the question of which features are truly protective against cardiometabolic abnormalities and which are merely a consequence of the MHO phenotype. It is important to emphasize that the biological correlates of the MHO were similarly associated with metabolic health in the entire range of BMI from normal weight, passing through overweight and even obesity [36].

In this context, it was recently shown that the greater amount of fat in the trunk in postmenopausal women of normal weight is associated with an increase in the incidence of ACVD, while a greater amount of fat in the legs predicts a lower risk of ACVD [37]. These data further support the notion that the distribution of fat in the abdominal region and ectopic fat, such as accumulation in the liver or skeletal muscle, has a greater power to determine metabolic health compared to total volume of body fat mass [36].

The distribution of fat, with increased visceral and hepatic deposition and low fat mass in the legs may be the result of an impaired expansion capacity of healthy subcutaneous adipose tissue reserves [38]. In analogy to human lipodystrophy, MUHO may be the result of an inability of the subcutaneous adipose tissue to expand further after a chronic positive energy balance. Impaired adipose tissue function may, in fact, mechanically link the long-term energy imbalance between too many calories consumed and too few calories expended and damage to endogenous organs, causing the installation and development of MAFLD, T2DM, and ACVD.

To further elucidate the potential role of adipose tissue function in defining metabolic

health despite obesity, studies were conducted with individuals that had the MHO phenotype were matched for age, sex, and BMI, but were sensitive to insulin or resistant in euglycemic-hyperinsulinemic clamps. In addition to greater visceral and hepatic fat and the presence of IR, it was shown that individuals with MHO with preserved insulin sensitivity had less infiltration of immune cells into visceral fat depots, a smaller mean adipocyte size, and a favorable pattern of adipokine secretion.

On the contrary, a pattern of pro-inflammatory, diabetogenic and atherogenic secretion may contribute to the development of the MUHO phenotype. Therefore, the results support the explanation that ectopic fat and adipose tissue dysfunction may lead to systemic IR, lipotoxicity, and a pro-inflammatory state, and thus may play a causal role in the transition from MHO to MUHO. Furthermore, a distinct pattern of circulating signaling molecules associated with MHO was found.

Individuals with MHO and preserved insulin sensitivity are characterized by high concentrations of adiponectin and neuroregulin [39] and low concentrations of CRP, progranulin, fetuin-A, retinol-binding protein-4 (RBP4), dipeptidyl peptidase-4 (DPP4) [40] compared to individuals with obesity and IR. Interestingly, MHO can be better predicted based on macrophage infiltration into visceral adipose tissue and serum adiponectin concentrations. Signs of adipose tissue can include peptide hormones (adipokines), immune cells, and metabolites, which, specifically or in a pattern, contribute to the development of T2DM, MAFLD, endothelial dysfunction, and CVD.

In an unbiased cluster analysis of 12 signaling molecules, adiponectin, Adipocyte Fatty Acid Binding Protein (AFABP), chemerin, and fibroblast growth factor (FGF) 21 showed the strongest associations with metabolic health parameters [41]. However, it remains an open question for prospective epidemiological studies whether circulating parameters can predict conversions from MHO to MUHO. Alterations in the signaling of molecular signatures may directly affect the target tissue through receptor-mediated mechanisms (eg, effects of leptin in regulating satiety in the brain) or contribute indirectly (eg, modulation of insulin secretion through acid release). Free fatty acids from visceral fat deposits) to increase cardiometabolic diseases.

Role of Adipose Tissue in Metabolic Regulation

Inflammatory processes in adipose tissue are now considered to be contributors to obesity-related metabolic disorders. Excess energy in adipose tissue has been shown not only to induce pro-inflammatory responses, but also to cause endoplasmic reticulum stress, hypoxia, mitochondrial defects, and finally systemic IR [42]. The increase in lipid and carbohydrate substrates results in increased demand on the mitochondrial electron transport chain. The increased demand for nutrient oxidation together with increased hypoxia, due to insufficient vas-

cularization of the TA, generate abnormally high amounts of reactive oxygen species (ROS). Oxidative stress leads to the activation of key inflammatory kinases, such as c-Jun N-Terminal Kinase (JNK), p38 mitogen-activated protein kinases (MAPK) and inhibitor of kappa B kinase (IKK), which can directly interfere with insulin signaling, or indirectly through the induction of activated B kappa light chain enhancer nuclear factor (NF ^{k} B) cells, and increased production of pro-inflammatory cytokines and chemokines [43].

White adipose tissue plays a key role in mediating the systemic inflammation seen in certain obesity phenotypes. Chronic nutrient overload results in excessive fat accumulation and implies hyperplasia (increased number of adipocytes) and adipocyte hypertrophy (increased cell size) [44]. The increasing size of adipocytes requires constant remodeling in the extracellular matrix of the adipose tissue, which, if insufficient, will lead to vascularization and innervation deficits.

Studies have shown that the MHO phenotype was associated with smaller adipocytes compared to controls with MUHO. O'Connell and colleagues reported a significant increase in the mean size of omental adipocytes in MUHO when compared to MHO. Adipocyte size is strongly correlated with metabolic parameters, such as IR, triglyceride levels, hepatic steatosis, and fibrosis [45].

Advanced degree of steatosis was found in MUHO (43%) than in MHO (3%). The size of adipocytes was suggested to be more relevant than the actual size of the fat deposit. In a later study, O'Connell revealed that adipose tissue in individuals with MHO had lower levels of preadipocyte factor-1 (Pref-1), a known inhibitor of preadipocyte differentiation, and a more favorable inflammatory profile, with lower macrophage numbers, lower levels of tumor necrosis factor alpha (TNF-α), Monocyte Chemotactic Protein-1 (MCP1) and higher levels of adiponectin [45].

The importance of adipocyte size can potentially be explained by the expandability hypothesis, which suggests that adipocytes have a limit for storing lipids. When this threshold is reached, a reminiscence of fatty acids begins to "spill over" to ectopic sites such as muscles, heart or liver, leading to CVD and metabolic risk (eg, hepatic insulin resistance) [10]. In general, the ability to recruit new or small adipocytes seems to be associated with a better state of metabolic health [45].

Regarding macrophages in adipose tissue, adipocyte hypertrophy, followed by increased release of pro-inflammatory cytokines, promotes adipose tissue infiltration by immune cells and phenotypic alterations in resident immune cells [46]. An increase in pro-inflammatory macrophages in the adipose tissue of individuals with obesity, accompanied by overexpression of TNF-α, Interleukin-6 (IL-6), inducible nitric oxide synthase, transforming growth factor 1, and CRP, among others.

In contrast, MHO has been associated with a low degree of inflammation, with reduced leukocyte counts and low levels of TNF-α, IL-6 and CRP identified in plasma. Normal adipocyte function associated with lower infiltration of immune cells in adipose tissue and a normal pattern of adipokine secretion has been reported in individuals with MHO [47].

Insulin Resistance, Low-Grade Inflammation, and Body Adiposity

Regardless of the criterion, the cardiometabolic risk factors considered for the classification of the obesity phenotype have one characteristic in common: they have all been associated with IR. Although there is still no consensus, this observation suggests a substantial contribution of this condition to the installation of metabolic losses observed in obesity [33,35].

Therefore, insulin sensitivity has been continuously cited as one of main determinants of the MHO [35,48]. The explanation for the difference in insulin action between individuals with MHO and MUHO is still unclear, but some mechanisms have recently been recently suggested in the scientific literature, and are based on adipose tissue functionality, body composition and inflammatory profile, for example.

In fact, excessive accumulation of adipose tissue, mainly visceral, is related to adipocyte dysfunction, leading to increased production of pro-inflammatory action, such as TNF-α and IL-6. In obese animals, it has already been observed that the neutralization of TNF-α, which was elevated, promoted a significant increase in peripheral glucose uptake and insulin action, suggesting an important role in the regulation of hormone action [49]. Molecular studies indicate that TNF-α is associated with impairments in insulin receptor signaling function, by inducing serine phosphorylation reactions, inhibiting tyrosine phosphorylation, necessary for the insulin signaling cascade. In addition, TNF-α itself is associated with the propagation of the inflammation state, stimulating the increase in the production of pro-inflammatory adipokines and inhibiting those with anti-inflammatory action. IL-6, in turn, appears to be related to IR by promoting increased expression of the suppressor of cytokine signaling (SOCS)-3, a protein that inhibits the insulin receptor and also promotes its degradation [49]. In addition to these, other factors, such as angiotensinogen, plasminogen activator inhibitor-1 (PAI-1), MCP-1, are also associated with inflammation and IR and are produced mainly by visceral adipose tissue.

Another point also associated with impaired insulin action is the intense lipolysis characteristic of visceral adipose tissue. The constant release of free fatty acids into the bloodstream promotes an increase in IR at the hepatic level, for example, in addition to other hormonal and inflammatory disorders, such as increased cortisol, angiotensinogen and stimulation of lipogenesis in hepatocytes [48].

With such a scenario in view, it is possible to assume the probable link between meta-

bolic phenotypes, body adiposity, and inflammation/IR. And, in fact, more and more studies suggest the distribution of body fat as a key role in worsening the inflammatory state and promoting IR.

Individuals with MUHO have a greater accumulation of visceral and hepatic adipose tissue, which, in turn, are related to increased production of pro-inflammatory cytokines and local macrophage infiltration, constituting a state of subclinical and chronic inflammation that is associated with impaired insulin sensitivity to adipose tissue [36,48]. Although the results are still conflicting on which cytokines are altered according to the phenotype, evidence indicates that individuals with MHO have a less exacerbated inflammatory state and insulin sensitivity when compared to MUHO, and these findings are mainly attributed to the lower visceral fat content [48].

In addition to visceral accumulation, the pattern of subcutaneous fat distribution also appears to influence insulin action and inflammatory status. Higher concentration of adipocytes at the abdominal level, compared to the gluteofemoral level, was associated with higher production of cytokines with pro-inflammatory stimulus. In addition, a higher percentage of fat in the gluteofemoral region has already been associated with greater insulin sensitivity and lower risk of CVD. As already mentioned, individuals classified as MUHO apparently have a greater accumulation of abdominal fat and fewer gluteofemoral fats, compared with MHO.

Another factor related to the inflammatory profile and insulin action, according to the metabolic phenotype of obesity, is oxidative stress [48]. Although this approach is still more recent and there is no consensus, studies show that people classified as MUHO may present higher free radical production and lower antioxidant capacity, with the installation of oxidative stress [49,50]. The accumulation of free radicals, in turn, results in dysfunction and alteration of B cell proliferation and growth of B cells and impaired insulin signaling capacity, for example [49].

Therefore, it can be observed that recent literature suggests a different profile of inflammation and insulin action according to metabolic phenotype, and the main hypotheses are based on the different distribution of body fat between MHO and MUHO.

Effect of Aging and Sex Hormones Signaling on Body Fat Distribution

Studying the distribution of body fat during aging may be an important key to understanding the pathophysiological mechanisms that link the distribution of fat and cardiometabolic risks to the installation of the MUHO phenotype.

Ghaben and Scherer discussed data that showed that a decrease in adipogenic potential during aging was associated with the presence of senescent preadipocytes. These senescent

preadipocytes release pro-inflammatory cytokines that induce IR in the adipose tissue [51]. This IR induction results in increased lipolysis in the adipose tissue and, finally, in a lower capacity of adipocytes to effectively store lipids [52].

To better understand how aging induces a redistribution of adipose tissue, it is also important to study the effects of sex hormones on adipose tissue function. Premenopausal women have a higher amount of total body fat mass, which is predominantly driven by the increase in gluteofemoral fat mass, and they have a lower visceral fat mass than men of similar age. These differences are believed to partly explain the low age-adjusted cardiometabolic risk of premenopausal women compared with men [53].

In premenopausal women, the ratio of antilipolytic α2-adrenergic receptors to β1-1 and β1-2 adrenergic receptors in subcutaneous adipocytes is higher than in men and is lower in visceral adipocytes than in subcutaneous adipocytes.

Although many signs and symptoms are commonly observed during the aging process, it is worth mentioning those associated with hyperandrogenism, found in women after menopausal amenorrhea [54,55]. Menopause is the phase associated with the greatest redistribution of adipose tissue from the gluteal and abdominal region. During menopause, estrogens decrease by more than 50%. Furthermore, estrogens are not only considered to promote adipose tissue hyperplasia, but also to regulate adipocyte lipolysis [53].

The presence of testosterone and estradiol receptors in the adipose tissue and the imbalance in the relationship between these hormones after menopause are associated with a change in the distribution of body fat, with an increase in abdominal and visceral fat, corresponding to the android profile [55]. The accumulation of visceral fat is closely related to changes in lipid metabolism, especially in the levels of free fatty acids, resulting from the lipolysis of triglycerides. Since the serum concentrations of this component are high, there are important changes in the activity of some enzymes, such as lipoprotein lipase and lecithin-cholesterol acyltransferase, promoting an increase in LDL-c levels, a reduction in HDL-c and contributing to the development of atherosclerosis and other cardiometabolic complications [55,56].

Therefore, differences in the distribution of adrenergic receptors may explain part of the presence of fat accumulation in visceral deposits in menopausal women and men and consequently the presence of the MUHO phenotype.

Hormonal change and its association with MHO

The most important hormones associated with the pathogenesis of obesity are leptin, insulin, Cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), Peptide YY (PYY), ghrelin, and adiponectin [57]. **Figure 2** shows several hormonal changes and their association with

MHO.

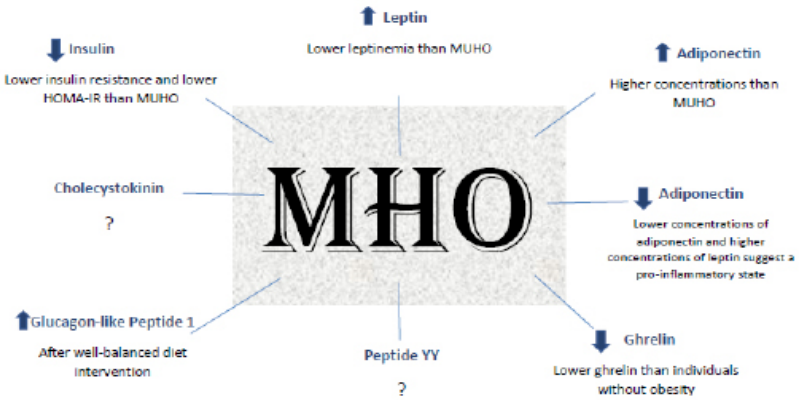

Figure 2: Major hormones associated with the pathogenesis of obesity and their associations with the MHO phenotype. Abbreviations: HOMA-IR: homeostasis model assessment of insulin resistance index; MHO: metabolically healthy obesity; MUHO: metabolically unhealthy obesity.

Leptin

Leptin is a protein produced primarily by white adipose tissue and one of the main regulators of weight homeostasis and body fat content [57]. This hormone crosses the blood-brain barrier, binds to receptors in the hypothalamus, negatively regulating appetite stimulators.

The human body's ability to secrete Leptin is proportional to the number of adipocytes. Therefore, due to the accumulation of adipose tissue, people with obesity have high concentrations of leptin, but this does not exert its action properly. Therefore, the anorectic and stimulating effects of body energy expenditure, which would promote weight loss in eutrophic individuals, for example, do not occur in obesity, conferring a situation of resistance to leptin. However, the pro-inflammatory action of excess hormone is maintained in this condition, being associated with metabolic damages [58]. Some mechanisms raised to explain leptin resistance in obesity are possible structural changes in its molecule, altered expression, changes in transport across the blood-brain barrier, and deterioration of its receptor signaling function. Furthermore, some forms of obesity can be characterized by a "selective resistance to leptin", limited to favorable metabolic effects, i.e., satiety and weight loss, while its sympathoexcitatory effects on the cardiovascular system are maintained, leading to arterial hypertension.

Leptin or leptin receptor deficiency also results in obesity, due to impaired signaling, regulation of food intake, energy expenditure, and other functions. Leptin plays a crucial role as a biomarker of cardiometabolic diseases and affects vascular structure, leading to hypertension, angiogenesis, and atherosclerosis [22]. Studies also suggest that leptin can predict myocardial infarction and elevated leptin levels may be related to increased cardiovascular risk.

Regarding the metabolic phenotype, there are few studies that address the leptin profile; however, it seems that MUHO individuals have higher concentrations of the hormone, with higher associated inflammatory stimulus, compared to MHO, and their circulating levels are correlated with the phenotype [22,59,60].

Adiponectin

Adiponectin is a 247 amino acid adipokine produced by white adipose tissue. It is secreted mainly by visceral rather than subcutaneous adipose tissue. The decrease in adiponectin production in obesity is responsible for improving gluconeogenesis and reducing glucose uptake, generating hyperglycemia, and contributing to IR and T2DM. Low levels of adiponectin can also cause hyperlipidemia, which contributes to CVD.

It has already been shown that metabolically healthy individuals have higher plasma adiponectin than metabolically unhealthy individuals, both in the obese group and in the normal weight group. Another study observed that adiponectin concentrations were reduced in the MHO and slightly lower in the MUHO group.

In this benign phenotype, the altered adipokine profile with higher levels of leptin and lower levels of adiponectin suggests a pro-inflammatory state [22,59,61].

Insulin

Insulin is an endocrine peptide hormone that regulates blood glucose levels. It is produced and secreted by pancreatic beta cells (β cells) and exerts its physiological effects by binding to the insulin receptor on the plasma membrane of target cells.

Insulin is responsible for the glucose uptake mediated by the translocation of the Glucose Transporter Type 4 (GLUT4), and responsible for the decrease in food intake by binding to the hypothalamus receptor [62].

One of the main mechanisms for the development of T2DM is the increase in the endocrine workload of the pancreas, which can lead to β-cell decompensation. Obesity-associated IR may occur because of complex mechanisms (decreased surface insulin receptor content and decreased insulin signal transduction) generating a state of hyperglycemia and causing micro and macrovascular damage [62].

A recent study demonstrated that HOMA-IR and insulin values were lower in metabolically healthy class III individuals with obesity compared to metabolically unhealthy ones. In addition, IR gradually increased from individuals with MHO phenotype to low HDL-c and to MUHO. This suggests that insulin and HOMA-IR may be predictors of the development of metabolic alterations in these individuals [48].

In a study with 96 individuals, classified as MHO (n=26), MUHO (n=51) and healthy eutrophic (n=19), the euglycemic-hyperinsulinemic clamp, the gold standard for assessing insulin action, was performed. observed that MHO individuals showed greater sensitivity to the hormone, compared to MUHO. However, MHO showed lower insulin sensitivity compared

to the healthy eutrophic group. These data suggest that the healthy phenotype already shows impairments in the action of the hormone, although characterized by lower IR, when compared to the unhealthy.

Ghrelin

Ghrelin is a gastric peptide hormone produced by a subset of cells in the stomach, the hypothalamus, the pituitary, and other tissues. These 28 amino acid peptides promote the secretion of Growth Hormone (GH), the stimulation of appetite and food intake, the modulation of pancreatic secretions, gastric motility, and gastric acid secretion. It has been shown that ghrelin secretion is reduced in obesity, leading to hyposecretion of GH [63].

A recent study evaluated ghrelin levels in MHO and MUHO groups. In this study, both groups had a lower level of ghrelin. However, despite the results suggesting a small reduction in ghrelin in the MUHO group when compared to the MHO, there was no statistically significant difference [64].

Little is known about the involvement of ghrelin in obesity phenotypes. However, reduced levels of the hormone have already been associated with the presence of MUHO in adult men [59].

Peptide YY

Peptide YY (PYY) is a 36 amino acid peptide that is synthesized and released from the distal gastro-intestinal tract cells called L cells. It has two circulating forms, PYY1-36, and PYY3-36 (predominant) and belongs to the same

family as neuropeptide Y (NPY) and Pancreatic Polypeptide (PP). This peptide acts on the hypothalamus to reduce intestinal motility, gastric emptying and gallbladder secretion, decreasing appetite and increasing satiety [57].

Despite some contradictory results, it has been shown that, in humans, there is a negative effect on the association between circulating PYY and adiposity markers. It was also reported that attenuated postprandial PYY release observed in subjects with obesity was associated with impaired satiety, which reinforces the association of this hormone with appetite regulation and obesity. In contrast, there is no study with PYY in individuals with MHO, demonstrating an area that still needs to be explored.

Glucagon-like Peptide 1

Another intestinal peptide is the Glucose-Like Peptide 1 (GLP-1), released by the intestine in response to food intake, as is PYY. It works by stimulating insulin secretion, growth, and survival of β cells, preventing the release of glucagon and reducing appetite [57]. This has

demonstrated that functional deficits in GLP-1 signaling caused by weight gain can maintain the obesity phenotype. Furthermore, altered GLP-1 signaling has been suggested to be considered as a risk factor for the development of obesity. There are also results that suggest that GLP-1 inhibits thrombosis, prevents atherogenesis, protects against oxidative stress and vascular damage, acting as a cardiovascular protective agent. Therefore, the impairment of GLP-1 in people with obesity has several implications in these individuals.

An intervention study evaluated the effectiveness of body weight reduction induced by a low-calorie diet in 103 individuals with the MHO phenotype. They observed a significant increase in GLP-1 after 2 months of a well-balanced diet. Therefore, the intervention improved metabolic rates in the MHO and reinforced the hypothesis that these individuals would benefit from a weight reduction program by adopting lifestyle changes [20].

In an observational study of 129 people with obesity and 24 without obesity, it was observed that those with MHO, according to HOMA-IR, had higher concentrations of GLP-1 at 90 and 120 minutes postprandial, compared to MUHO [65].

CCK

CCK was the first hormone associated with reduced appetite. It affects the secretion of exocrine pancreatic enzymes, gastrointestinal motility, and the secretory function of the gallbladder, promoting satiety. There are a few forms of CCK, such as CCK-5, CCK-8 (potent neurotransmitters) and CCK-22, CCK-58, CCK-33 (the most prevalent form found in plasma and intestines). People with obesity have reduced CCK levels. The interaction of CCK with leptin (which promotes greater inhibition of food intake) is also disrupted in obesity [66].

The use of CCK has been considered a therapeutic strategy for the treatment of obesity through appetite regulation [50]. Furthermore, reduced sensitivity to CCK has been shown to be associated with low HDL-C concentrations in individuals with obesity, which may be associated with increased cardiovascular risk. However, there is no available study evaluating CCK in individuals with MHO, demonstrating a research gap.

Transitions between metabolically healthy and unhealthy obesity

Obesity has been considered a recurrent and progressive chronic disease [67], a definition that is probably also applicable to the MHO. In fact, individuals in long-term obesity control programs may go through cycles of weight loss and recovery, accompanied by their phenotype shifting from MUHO to MHO and back to MUHO. These transitions between metabolic states are not specific to obesity and have also been identified in children and adolescents. Furthermore, nearly 50% of participants in the Multiethnic Atherosclerosis Study (MESA) were defined as MHO at baseline and developed metabolic abnormalities during the

approximately 12-year follow-up period. This finding is supported by a meta-analysis of 12 studies that included more than 5.900 individuals with a follow-up of 3 to 10 years, which shows that almost half of the participants classified as MHO developed at least one metabolic abnormality [27].

Individuals with MHO can be found at any age, but in groups with increasing age, the prevalence of this phenotype has been consistently lower. A lower prevalence of postmenopausal MHO compared to premenopausal women and a 30% transition from MHO to MUHO during menopause [68] suggest that changes in sex hormones may play a role in the transition to an unhealthy phenotype. Among prospective Pizarra study participants, approximately 30% of subjects diagnosed with MHO at baseline converted to MUHO at the 6-year follow-up investigation.

It is important to emphasize that the transition from MHO to MUHO is not necessarily a one-way street, as with the necessary individual interventions, there is the possibility of reversing in the opposite direction. In a large UK study of over 380.000 subjects, approximately 27% of MHO subjects became MUHO at a median follow-up of 4 years, while 21% of MUHO transitioned to MHO over the same period.

Interestingly, in this same study, individuals who remained MHO during follow-up had a similar risk of developing CVD and all-cause mortality compared to healthy eutrophic individuals. On the contrary, those MHO who transitioned to MUHO were at increased risk. These data bring to light the paramount importance of identifying the phenotype and maintaining its healthy state for the preservation of the individual's health.

In addition, data from 3,743 women (51%) and adult men (≥ 18 years) from the Northwest Adelaide Health Study show that conversion from MHO to MUHO occurred without significant differences between genders, in 16% of participants within 10 years of follow-up. Persistence of MHO was related to younger age, lower sustained waist circumference, peripheral fat distribution in women, and lower CVD outcomes. An analysis of the Clinical Practice Research Datalink (CPRD), a large-scale UK primary care database that contains data from 231,399 patients with a reported BMI of ≥35 kg/m², suggested that men are more likely to transition from MHO to MUHO [69].

Finally, 30-year follow-up data from 90.257 Nurses Health Study participants robustly confirmed the frequent transition from MHO to MUHO and demonstrated a decline in metabolic health with age across the entire BMI range [5]. During this long observation period, it could also be shown that there are individuals maintaining their MHO status, which did not translate into a reduction in CVD risk at the level of metabolically healthy lean participants. Taken together, longitudinal studies demonstrate that metabolic health is not a stable condition, it does not depend solely on the state of obesity and deteriorates with aging. On the other

hand, the MUHO phenotype can also be considered a temporary trait that can be reversed in MHO by targeted interventions.

METABOLLICALLY HEALTHY OBESITY: how plausible is this condition?

The finding of heterogeneity of metabolic risks has provoked debates regarding the existence of the MHO phenotype. This controversy is based on the absence of a single criterion for its diagnosis, as well as an established consensus of the variables that are used for its definition. Since there is great diversity among them, favoring contradictory results among the available studies and little possibility of replicating them [70,71].

In this sense, the number of studies questioning the applicability of the phenotype in clinical practice is growing, suggesting that the use of the term "healthy" does not really characterize an individual with obesity, in addition to causing confusion and being able to impair the control of this condition.

However, a fact that has already been confirmed in several studies, mainly epidemiological, is that the MHO phenotype represents only a temporary state. Over time, risk factors appear to become more present, increasing the risk of cardiometabolic events [5]. Thus, evidence indicates that, if there is no intervention, MHO can transition to MUHO in a period of approximately 5 to 10 years, which reinforces that this is not a stable condition [72].

Systematic reviews and meta-analyses carried out between 2013 and 2020 demonstrate that, in fact, MHO, compared to healthy eutrophy, is associated with a higher risk of CVD and mortality, whether from all causes or cardiovascular disease. For example, in a meta-analysis of twenty-three prospective cohorts and approximately 4.5 million participants, an increased Relative Risk (RR) for CVD and all-cause mortality was observed (RR= 1.58, CI: 1 .34-1.85; RR=1.59, CI: 1.02-2.47, respectively) in the MHO, when compared to healthy eutrophic individuals [73]. However, compared to MUHO, the risk in MHO is reduced.

In a large study carried out in the United Kingdom with approximately 380.000 participants, for example, it was observed that, compared to healthy eutrophic, the RR to develop T2DM for MUHO was 12.86 (CI: 11.71 -14.12) [74], meanwhile, for MHO, this was 5.15 (4.66-5.69). Such data reinforce that the healthy phenotype should not be interpreted as the absence of health risks compared to adequate weight, but a condition, in the context of obesity, that favors a lower health risk than expected.

In this context, another controversial topic is the definition of which reference group should be used to compare subjects with MHO, regarding risk estimates and clinical characteristics. The current questioning considers several aspects, with emphasis on the following questions: should it be the general population without obesity or a more selected subgroup of

healthy individuals and without obesity, as well as normal weight individuals with a metabolically healthy phenotype?

This issue needs further discussion to better guide studies on metabolic phenotypes. If a very healthy reference group is selected, most other groups will be at increased risk, but if the general population is used as a reference, the comparison more closely resembles the real-world experience. We leave here a question to be thought about, and with new findings, we try to advance in the perspective of answering it.

It is also worth mentioning that, although the MHO presents greater health impairment than healthy eutrophy, the risk is lower compared to MUHO, as evidence indicates. Therefore, these data reinforce the existence of the phenotype and its applicability in clinical practice, allowing the early selection of individuals MHO who do not yet have pronounced metabolic impairment, and the adoption of interventions to avoid the development and transition to MUHO.

METABOLIC PHENOTYPES: perspective of obesity control

The concept of metabolic phenotypes must be considered for the determination of the management of obesity treatment. First, it is important to emphasize that the intervention, depending on the case, does not necessarily require a focus on weight loss. Health improvement can and should be a target of treatment and follow-up, and often better than the extent of weight loss per se. Thus, prior to determining the strategy to be used, for a more assertive conduct, it is essential to properly assess the degree of impairment of the individual's health and their respective metabolic phenotype.

In addition to the criteria used to classify the phenotype, other tools can be applied in clinical practice, to obtain a more integrative assessment of the condition. The Edmonton Obesity Staging System (EOSS), for example, suggests a classification based on clinical assessments of health and functional status. For an individual with MUHO without functional impairment (EOSS stage 0), it would be recommended to avoid weight gain, but the health benefits of an aggressive weight loss program are considered marginal [75].

The extent of weight-loss-dependent improvements in health parameters and outcomes have been described, for example, in the Action for Health in Diabetes (Look AHEAD) trial and appear to also apply to individuals with MHO as well [76]. A moderate weight loss of around 10% may be sufficient to change an obesity phenotype with cardiometabolic abnormalities in MHO [36]. There are currently no randomized controlled trials of obesity treatment comparing cardiometabolic outcomes between individuals with MHO and MUHO that would support any treatment stratification depending on the phenotype status.

It is important to emphasize that individuals classified as MUHO present greater health

impairment and the conduct should be directed not only to the control of obesity, but also of the associated metabolic alterations, aiming at attenuation or preventing them from progressing to more serious damages.

However, the MHO should not be neglected. It could even be argued that MHO have high treatment priority because they can benefit the most from preserving metabolic health. This suggestion is supported by data from bariatric surgery interventions that show that shorter duration and better hyperglycemia parameters are the main determinants of diabetes remission and metabolic health [77].

That is, interventions are also extremely important in this case, even if for reasons other than MUHO. After all, this phenotype has a transitory profile and, therefore, its early detection and the development of conducts is extremely advisable, to prevent the individual from progressing to the unhealthy phenotype.

In view of the importance of inflammatory processes for the metabolic damage of obesity, as discussed, considering this aspect is essential for nutritional management, whether to prevent progression between phenotypes or in the care of patients already classified as MUHO. Evidence indicates that a higher score for the Dietary Inflammatory Index, a tool used to assess the potential for stimulating inflammation in the dietary pattern, was positively associated with the presence of the MUHO phenotype. Furthermore, a more inflammatory diet was considered a potential risk factor for the development of this phenotype and, among MUHO individuals, it seems to contribute to the increase in all-cause mortality [78].

Another important aspect regarding the treatment of obesity and its metabolic phenotypes is the fight against a sedentary lifestyle. Increasing physical activity and preserving cardiorespiratory fitness are well established interventions to reduce obesity related to T2DM and CVD. In both children and adults, increased physical activity and cardiorespiratory fitness were recognized as important correlations of the MHO phenotype. Importantly, a higher fitness level in MHO compared to MUHO can also be an indicator for a healthier lifestyle and does not exclude other behavioral factors underlying MHO.

However, in some cases, the treatment of obesity can be challenging and conservative strategies, aimed at behavioral changes or pharmacological intervention, may have modest effects, with weight loss in the range of 3-10% and little success regarding long-term maintenance. deadline. In this sense, bariatric and metabolic surgery is being increasingly performed for the treatment of obesity, which is considered the most effective intervention for this condition, in severe cases. Regarding metabolic phenotypes, bariatric surgery interventions have been shown to be as effective in MHO compared to MUHO patients in relation to cardiometabolic outcomes, contradicting a stratification of obesity based on MHO status [9].

However, not all individuals classified as obese are eligible for surgery. Furthermore, in view of its complexity and costs, it is impractical to apply large-scale surgery, which follows the intense prevalence of obesity in the world population. Therefore, this should not be the solution to this problem in all cases, but for the most serious ones.

Thus, from a public health perspective, individuals with MHO may have a lower priority for early access to treatment and more aggressive weight loss strategies. It is essential to reiterate that the goals of obesity treatment should not focus only on weight loss, but rather on health parameters. Maintaining favorable cardiometabolic health can be easier to achieve and may require only moderate weight loss in people with MHO.

Final considerations and future prospects

Recently, standardized definitions of MHO have been proposed, which are relevant to clinical research on differences in obesity-related morbidity and mortality between MHO and MUHO.

Whether the MHO has additional implications for the clinical management of obesity remains unclear, but individual treatment decisions must consider metabolic and cardiovascular abnormalities to reduce the risk of premature mortality, CVD, DM, and various cancers in all obese individuals. The concept of MHO, as a human model system, can provide important information to unravel the mechanisms of how fat accumulation, more noxious fat distribution, and TA dysfunction can cause metabolic and cardiovascular abnormalities. In this context, the role of individual factors that reflect or cause the MHO phenotype, such as higher fat content in the legs, higher cardiorespiratory fitness and physical activity, insulin sensitivity, lower levels of inflammatory markers and others, still need to be investigated.

It is also important to note that timely treatment of obesity should also be recommended for people with MHO, because the risk of developing cardiometabolic diseases is still higher than in metabolically healthy people with adequate weight.

Future research should value the positive aspects related to the MHO phenotype as a model to understand how obesity, adipose tissue, cell composition, and dysfunction contribute to obesity-associated cardiometabolic diseases. In addition, both in clinical practice and in scientific research, the definition of metabolic health must be harmonized. Further epidemiological studies may identify modifiable determinants and risk factors to better prevention of MHO to MUHO conversions and cardiometabolic disease manifestations. In addition, genetic factors that potentially contribute to the MHO phenotype, in addition to the expected effects of fat distribution, body composition and subcutaneous TA expansibility, should be explored.

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