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Review Article

Emerging concepts in metabolically healthy obesity

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Abstract: Obesity is a major risk factor for noncommunicable diseases that is responsible for more than 70% of early deaths in the world. In the 1980's decade, some studies started to describe a "benign" obesity phenotype, named "metabolically healthy obesity" (MHO), which represents obesity without comorbidities such as hypertension, cardiovascular diseases, insulin resistance, diabetes, dyslipidemia or metabolic syndrome. However, it is still unclear if this "benign" obesity phenotype is really favorable or just a transition status to unhealthy obesity and if these subjects presented subclinical levels of cardiovascular risk that are not commonly detected. To further elucidate these issues, the investigation of pathophysiological mechanisms that can increase cardiovascular risk in MHO individuals, such as hormones and cytokines, may offer some responses. In parallel, the evaluation of subclinical cardiovascular derangement, using the systemic microcirculation as a proxy, may be an alternative to anticipate overt cardiovascular disease. Overall, further studies are needed to better understand the pathophysiology of MHO as well as to identify high-risk individuals who deserve more intensive management.

Keywords: Obesity, metabolically healthy obesity, cardiovascular risk, hormones, cytokines, microcirculation

Introduction

According to the World Health Organization (WHO), the global prevalence of obesity has almost tripled in the last 40 years. Currently, 40% of the world's population is overweight and about 13% obese [1]. In 2030, the WHO estimates that 45% of the entire United States, 48% of the United Kingdom and 20% of the world's population will be considered obese, making it a major health problem and a public health concern worldwide [2-5].

Obesity is a major risk factor for noncommunicable diseases (NCDs), including cardiovascular diseases (CVD), cancer and diabetes mellitus, responsible for more than 70% of early deaths in the world [6]. Although considered a chronic disease, and not only a risk factor for other diseases, in 1980 some researchers launched the term "benign obesity phenotype" for describing obesity developed without hypertension, CVD, insulin resistance, diabetes, dyslipidemia or metabolic syndrome (MeTS) [7]. According to them, this obesity phenotype was not associated to increased morbidity and mortality risk and, for that reason, the concept of metabolically healthy obesity (MHO) emerged [8].

Derived from the International Diabetes Federation (IDF), a major definition of MHO is the presence of body mass index (BMI) ≥30 Kg/m^2 without any of the listed criteria: (1) high blood pressure, defined as blood pressure ≥130/85 mmHg or drug treatment; (2) high fasting blood-glucose level, defined as glucose ≥100 mg/dL or drug treatment for type 2 diabetes mellitus (T2DM); (3) high serum triglycerides, defined as triglycerides ≥150 mg/dL or drug treatment; (4) low high-density lipoprotein cholesterol (HDL-C) level, defined as HDL-C <40 mg/dL in men and <50 mg/dL in women or drug treatment for dyslipidemia [9].

However, one of the major challenges in studying MHO is its inconsistent and contradictory definition [8]. While WHO defines obesity as

excessive fat accumulation, diagnosed by BMI ≥30 kg/m^2, that might impair health, how could a healthy obesity phenotype exist? Furthermore, considering the absence of a consensual definition, MHO remains surrounded by several criteria making even more difficult the comprehension about its real meaning: is MHO a really healthy phenotype or just a transitory period in the progression from health to disease? **Table 1** describes the criteria used to define MHO in several studies in the literature [10-26].

Therefore, cardiovascular risk may be a key point for understanding obesity and MHO [27-29]. Recently, a cohort study demonstrated that, although stable patients with MHO may be at lower cardiovascular and mortality risk, the transition of this phenotype to MetS is significantly associated with increased incidence of CVD [30]. Consequently, as there is no consensus on cardiovascular risk for MHO and its definition stirs confusion, it is necessary to discuss about MHO, the potential increase of cardiovascular risk and its possible associated mechanisms.

Cardiovascular risk and MHO

The scores applyed to evaluate cardiovascular risk are usually based on information such as age, gender, total cholesterol, HDL-C, systolic blood pressure, smoking and physical activity habits [31, 32]. MHO individuals have a favorable metabolic profile characterized by normal blood pressure, normal lipid values, normal fasting glucose concentrations and do not present other major cardiovascular risk factors. Therefore, the use of traditional scores to evaluate risk in MHO seems to not be appropriate [21].

There is still no consensus in the literature about cardiovascular risk in MHO individuals. Some studies demonstrate a higher risk of CVD, cancer and mortality in MHO when compared to metabolically healthy normal weight (MHNW) individuals [33-38]. However, other studies support the idea that MHO phenotype presents no increased risk of CVD and mortality [39-42]. An observational study with 22,203 individuals, conducted by Hamer & Stamatakis, examined the association between MHO and risk of CVD and all-cause mortality, and concluded that MHO participants were not at increased risk of CVD and all-cause mortality over 7 years compared with MHNW [42].

In contradiction, a systematic review and meta-analysis, conducted by Kramer and cols, included eight studies with 61,386 participants and demonstrated that MHO individuals are at increased risk for death and CVD events over the long-term compared with MHNW. Thus, obese people are at increased risk even in the absence of metabolic abnormalities [36]. In addition, Fan and cols included 14 studies about MHO and CVD risk, CVD mortality and all-cause mortality in a meta-analysis. They showed that despite the fact that metabolically unhealthy obese (MUO) group had the greatest CVD risk and mortality, the MHO individuals had a higher risk for CVD during the longer-term follow-up (more than 15 years) when compared to MHNW group [37].

The lack of a universal classification to determine MHO could overcast the CVD risk profile on this population. Eckel and cols conducted a systematic review and meta-analysis of prospective studies to evaluate whether there is a suitable approach that identifies obese participants who are not at an increased risk of cardiovascular events. They concluded that, independently of the criteria used to define MHO (absence of insulin resistance, hypertension, diabetes, hyperlipidemia or simultaneous absence of metabolic factors) all obese subgroups considered metabolically healthy presented increased risk of cardiovascular events when compared with MHNW [38].

Furthermore, although a well accepted independent risk factor for CVD, obesity has still a paradoxical correlation with CVD prognosis [43, 44]. Some patients with heart failure (HF), coronary heart disease and other CVD, demonstrate a more favorable prognosis than underweight or eutrophic people. It occurs mainly in overweight (BMI 25-29.9 Kg.m^2) and class I obese (BMI 30-34.9 Kg.m^2) people. This "obesity paradox" is still unclear, but could be explained in part by the increased lean mass (LM) and increased cardiorespiratory fitness (CRF). The increased LM might improve clinical outcomes in a progressive and chronic catabolic state, associated with HF and other CVD. In addition, a greater CRF is

Table 1. Characteristics of different criteria used to define metabolically healthy obesity

Study, Year (Reference)	Sample size and Type of study	BP (mmHg)	FPG (mg/dL)	TG (mg/dL)	HDL (mg/dL)	WC (cm)	Others	Criteria MHO
Karelis et al., 2004 [10]	19 MHO of 154 obese postmenopausal women; cross-sectional study	-	-	<150	≥50	-	TC <200 mg/dL; LDL <100 mg/dL HOMA-IR <1.95 score	≥4 of the criteria and BMI ≥30 kg/m²
Meigs et al., 2006 [11]	236 MHO of 2902 participants; prospective cohort study (1989-1992 to 2001-2004; mean follow-up of 11 years)	≥130/85 or treatment	100-126	≥150	<40 (M) <50 (W)	≥102 (M) ≥ 88 (W)	HOMA-IR >75th percentile	<3 of the criteria and BMI ≥30 kg/m²
Aguilar-Salinas et al., 2008 [12]	171 MHO of 716 participants; cross-sectional study	<140/90 and no treatment	<126 and no treatment	-	≥40	-	Random glucose <200 mg/dl; 2 h-PG post challenge <200 mg/dl	All of the criteria and BMI ≥30 kg/m²
Stefan et al., 2008 [13]	31 MHO of 314 participants; cross-sectional study	-	-	-	-	-	WBISI <75th percentile	All of the criteria and BMI ≥30 kg/m²
Wildman et al., 2008 [14]	527 MHO of 5440 participants; cross-sectional study	≥ 130/85 or treatment	≥100 or treatment	≥150	<40 (M) <50 (W) or treatment	-	hsCRP >0.1 mg/L (90th percentile) HOMA-IR >5.13 (90th percentile)	<2 of the criteria and BMI ≥30 kg/m²
Hankinson et al., 2013 [15]	149 MHO of 775 obese participants; cross-sectional study	≤120/80, no treatment or special diet for hypertension	-	-	-	-	No physician diagnosis, medication, or special diet for other metabolic risk factors (i.e., diabetes and dyslipidemia); no prevalent cardiovascular disease	All of the criteria and BMI ≥30 kg/m²
Ortega et al., 2013 [16]	1738 MHO (BMI-based obesity) of 43265 participants; prospective cohort study (1979-2003; mean follow-up of 14.3 years)	≥130/85 or history of physician-diagnosed hypertension	≥100 or history of physician-diagnosed diabetes	≥150	<40 (M) <50 (W)	-	-	≤1 of the criteria and BMI ≥30 kg/m²
Cao et al., 2015 [17]	204 MHO of 6852 participants; prospective cohort study (2007-2012; mean follow-up of 5 years)	≥130/85 or treatment	≥100 or treatment	≥150 or treatment	<40 (M) <50 (W)	≥90 (M) ≥80 (W)	-	≤2 of the criteria and BMI ≥28 kg/m² (Chinese standard)
Hashimoto et al., 2015 [18]	302 MHO of 3136 participants; retrospective cohort study (2001-2009; mean follow-up of 8 years)	≥130/85 or treatment	≥100 or treatment	≥150 or treatment	<40 (M) <50 (W)	-	-	≤1 of the criteria and BMI ≥25 kg/m² (Asia-Pacific cutoff)
Rondanelli et al., 2015 [19]	103 MHO subjects; intervention study	-	-	≤150 or treatment	≥50 or treatment	-	TC ≤200 mg/dL; LDL ≤100 mg/dL or treatment HOMA-IR ≤1.95 score	≥4 of the criteria and BMI ≥30 kg/m²
Jung et al., 2015 [20]	8587 MHO of 41194 participants; prospective cohort study (2007-2013; mean follow-up of 3.2 years)	≥130/85 or treatment	≥100 or treatment	≥150	<40 (M) <50 (W)	-	-	≤1 of the criteria and BMI ≥25 kg/m² (Asia-Pacific cutoff)
Jamar et al., 2016 [21]	64 MHO of 142 obese participants; cross-sectional study	≥130/85 or a history of hypertension treatment	≥100	≥150 or a history of hyperlipidemia treatment	<40 (M) <50 (W)	-	Physician diagnosis, medication, or special diet for other metabolic risk factors (i.e., diabetes and dyslipidemia); prevalent cardiovascular disease	None of the criteria and BMI ≥30 kg/m²

Chang et al., 2016 [22]	8149 MHO of 62249 participants; prospective cohort study (2009-2013; mean follow-up of 5 years)	≥130/85 or treatment	≥100 or treatment	≥150 or treatment	<40 (M) <50 (W)	-	HOMA-IR ≤2.5 score	None of the criteria and BMI ≥25 kg/m² (Asia-Pacific cutoff)
Mottaghi et al., 2016 [23]	500 MHO of 5672 participants; prospective cohort (1999-2009; mean follow-up of 9.4 years)	≥135/85 or treatment	≥100 or treatment	≥150 or treatment	<40 (M) <50 (W) or treatment	≥95 (Iranian cutoff)	Have diabetes (FPG ≥126 mg/dl or 2 h-PG ≥200 mg/dl or current use of glucose-lowering drugs)	Don't have diabetes, ≤2 of other criteria and BMI ≥30 kg/m²
Lin et al., 2017 [24]	441 MHO of 2491 participants; prospective cohort (2009-2013; mean follow-up of 3.9 years)	≥130/85 or treatment	≥100 or treatment	≥150 or treatment	<40 (M) <50 (W)	-	-	≤2 of the criteria and BMI ≥25 kg/m² (Asia-Pacific cutoff)
Nam et al., 2018 [25]	1697 MHO of 8589 participants; prospective cohort (2001-2014; mean follow-up of 9.3 years)	≥130/85 or treatment	≥100 or treatment	≥150 or treatment	<40 (M) <50 (W)	-	-	≤1 of the criteria and BMI ≥25 kg/m² (Asia-Pacific cutoff)
Echouffo-Tcheugui et al., 2019 [26]	187 MHO of 4291 participants; prospective cohort study (1998-2001 to 2014; mean follow-up of 14 years)	≥130/85 or treatment	≥100 or treatment	≥150 or treatment	<40 (M) <50 (W)	-	-	<2 of the criteria and BMI ≥30 kg/m²

Abbreviations: BMI: body mass index; BP: blood pressure; FPG: fasting plasma glucose; HDL: high-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance index; hsPCR: high-sensitivity C-reactive protein; LDL: low-density lipoprotein cholesterol; M: men; MHO: metabolically healthy obesity; TC: total cholesterol; TG: triglycerides; WBISI: whole-body insulin sensitivity index; WC: waist circumference; 2 h-PG: 2-hour plasma glucose; W: women.

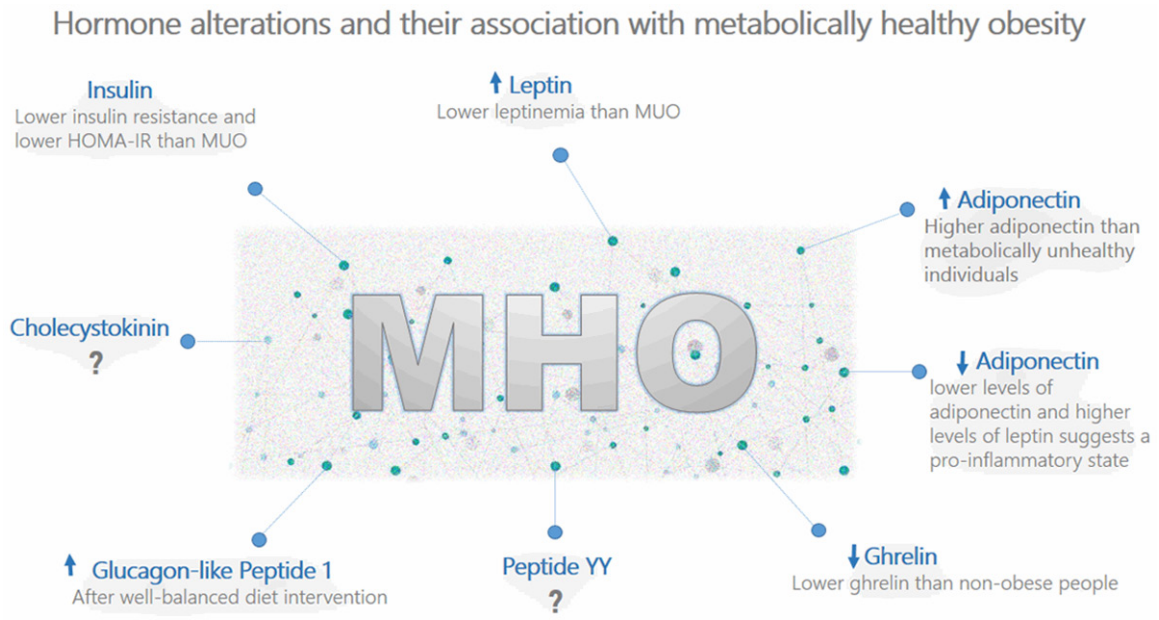

Figure 1. Major hormones associated with obesity pathogenesis and their association with metabolically healthy obesity. Abbreviations: HOMA-IR: homeostasis model assessment of insulin resistance index; MHO: metabolically healthy obesity; MUO: metabolically unhealthy obesity.

associated with lower CVD risk regardless of BMI. It shows how BMI is a limited measurement for adiposity and emphasizes that individuals with similar BMI may differ in metabolic profile and body composition [44-46].

Similarly to the "obesity paradox", MHO also presents paradoxically. A benign obese phenotype might be characterized by strict definitions, but few studies exist to support this hypothesis [38]. Moreover, there is still no consensual definition for MHO and some studies suggested that increased BMI is not a benign condition even in the absence of metabolic abnormalities [36]. In this setting, the recognition of high cardiovascular risk individuals is highly recommended to promote preventive strategies and a profound discussion about the mechanisms associated with the increased CVD risk in the MHO phenotype is warranted [47].

Keypoints on cardiovascular risk and MHO phenotype

Obesity is a major risk factor for the development of cardiometabolic complications [21]. Currently, it is known that obesity is associated not only with excess energy intake and poor physical activity but with dysregulation on hormonal production, inflammatory cytokines [43] and microcirculatory function [48].

Some alterations in hormone and cytokine production and microcirculation are already known in obesity and are part of the pathophysiology related to the adipose tissue accumulation [21]. However, little is known about these alterations in MHO [7, 49, 50]. Thus, evaluating these factors (hormones, cytokines and microcirculation) in MHO could be the key to identifying possible changes related to an increased CVD risk and could help to disentangle whether this phenotype can really be considered healthy or not.

Hormones

The most important hormones associated with obesity pathogenesis are leptin, insulin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY), ghrelin and adiponectin [43, 51]. **Figure 1** shows several hormone alterations and their association with MHO.

Leptin: Leptin is a 16-kDa protein produced mainly by white adipose tissue (WAT) [43]. This hormone crosses the blood-brain barrier, binds to brain receptors down-regulating appe-

tite stimulators and up-regulating anorexigenic alpha-melanocyte-stimulating hormone [52]. Although leptin is an anti-obesity hormone, its concentration may be elevated in obese people due to a hormone resistance. Thus, individuals become resistant to its effects such as satiety and weight-loss. Moreover, some forms of obesity may be characterized by a "selective leptin resistance", limited to its favorable metabolic effects, i.e., satiety and weight loss, while its sympathoexcitatory effects on the cardiovascular system are maintained, thus leading to arterial hypertension [53-55]. The deficiency of leptin or leptin receptor also results in obesity, due to an impairment of its signaling, regulation of food intake, energy expenditure and others functions [43, 52].

Jamar and cols demonstrated that MHO showed lower leptinemia than MUO, but the values presented by the groups still indicated a hyperleptinemia state [21]. Similar results have been reported previously [50]. Leptin has a crucial role as a biomarker for cardiometabolic diseases and also affects the vascular structure, leading to hypertension, angiogenesis, and atherosclerosis [21]. It is even suggested that leptin can predict myocardial infarction [56] and elevated leptin levels could be related to increased cardiovascular risk [21].

Adiponectin: Adiponectin is a 247-aminoacid adipokine produced by WAT. It is secreted mostly by visceral than subcutaneous adipose tissue. The decreased production of adiponectin in obesity is responsible for improvemets on gluconeogenesis and reducings on glucose uptake, generating hyperglycemia and contributing to insulin resistance and T2DM. Low levels of adiponectin can also cause hyperlypidemia, which colaborates to CVD [51].

It has already been shown that metabolically healthy individuals have higher plasma adiponectin than metabolically unhealthy individuals, among both nonobese and obese group [57]. Another study observed that adiponectin concentrations were reduced in the MHO and slightly further reduced in the MUO group [58], similarly to results showed by Jamar and cols. In this benign phenotype, the altered adipokine profile with higher levels of leptin and lower levels of adiponectin suggests a pro-inflammatory state [21].

Insulin: Insulin is an endocrine peptide hormone that regulates the level of blood glucose [43]. It is produced and secreted by the beta pancreatic cells (β-cell) and exerts its physiological effects by binding to the insulin receptor (INSR) in the target cells plasma membrane. Insulin is responsible for glucose uptake mediated by the translocation of glucose transporter type 4 (GLUT4), and responsible for decreased food intake by binding to the hypothalamus receptor [59].

One of the major mechanisms for the T2DM development is the increased workload of the endocrine pancreas, which can generate a β-cell decompensation [59]. The obesity-associated insulin resistance may occur as a consequence of complex mechanisms (decreased surface INSR content and impaired insulin signal transduction) generating a hyperglycemia state and causing micro and macrovascular damages [43, 59].

A recent study demonstrated that insulin resistance index (HOMA-IR) and insulin values were lower in metabolically healthy morbidly obese when compared to unhealthy morbidly obese [9]. Further, insulin resistance increased gradually from MHO to obese with low HDL-C (LHO) and to MUO [60]. This suggests that insulin e HOMA-IR could be predictors of MeTS development in these individuals [9].

Ghrelin: Ghrelin is a gastric peptide hormone produced by a subset of stomach cells, by the hypothalamus, hypophysis and other tissues. This 28-amino acid peptide promoves growth hormone (GH) secretion, appetite and food intake stimulation, modulation of pancreatic secretions, gastric motility and gastric acid secretion [61]. It has been demonstrated that ghrelin secretion is reduced in obesity, generating a GH hyposecretion [62].

A recent study evaluated the levels of ghrelin in MHO, MUO, LHO and non-obese groups. In that study, the MHO, MUO and LHO groups had a lower level of ghrelin when compared to non-obese people. However, despite the results suggesting a small reduction in ghrelin in the MUO group when compared to MHO, there was no statistically significant difference [60].

PYY: The PYY is a 36-amino acid peptide that is synthesized and released from distal gastro-

intestinal tract cells called L-cells. It has two circulating forms, the PYY1-36 and PYY3-36 (predominant), and belongs to the same family as neuropeptide Y (NPY) and pancreatic polypeptide (PP) [63]. This peptide acts on the hypothalamus to reduce intestinal motility, gastric emptying and gall bladder secretion, decreasing the appetite and increasing satiety [43].

Despite some contradictory results, it was shown that in humans, there is a negative association between circulating PYY and markers of adiposity. It was also reported that attenuated postprandial PYY release observed in obese subjects was associated with impaired satiety, which reinforce the association of this hormone to appetite regulation and obesity [63]. In contrast, there is no study with PYY in MHO individuals, demonstrating an area that still needs to be explored.

GLP-1: Another gut peptide is the GLP-1 released by the gut in response to food intake [64], just like the PYY. It acts stimulating insulin secretion, β-cell growth and survival, preventing glucagon release and reducing appetite [43]. It has been shown that functional deficits in GLP-1 signalling caused by weight gain may maintenance the obesity phenotype. Further, it has been suggested that an altered GLP-1 signalling could be considered as a risk factor for obesity development [65]. There are also results that suggest that GLP-1 inhibits thrombosis, prevents atherogenesis, protects against oxidative stress and vascular damage, acting as a cardiovascular protector [43]. So, GLP-1 impairment in obese people has several implications in these individuals [64].

An intervention study evaluated the efficacy of body weight reduction induced by a low-energy mixed diet in 103 MHO indiviuals. They observed a significant GLP-1 increase after 2-months of well-balanced diet. Therefore, the intervention improved the metabolic indices in MHO and reinforced the hypothesis that these subjects would benefit from a lifestyle weight reduction program [19].

CCK: The CCK also is a gut peptide hormone [43], mainly produced by the small intestinal endocrine I-cells and cerebral neurons [66]. CCK was the first hormone associated with appetite reduction. It affects exocrine pancreatic enzyme secretion, gastrointestinal motility and secretory function of the gall bladder, promoting satiety [67]. There are some forms of CCK, like CCK-5, CCK-8 (potent neurotransmitters) and CCK-22, CCK-58, CCK-33 (the most prevalente form found in plasma and intestines) [67].

Obese people have reduced CCK levels. The CCK interaction with leptine (that promote more inhibition of food intake) also is disrupted in obesity [2]. The use of CCK has been considered as a therapeutic strategy to treat obesity by regulating appetite [68, 69]. In addition, it has been shown that reduced CCK sensitivity is associated with low HDL-C concentrations in obese people [70], which could be associated with increased cardiovascular risk. However, there is no available study evaluating CCK in MHO individuals, demonstrating a research gap.

Cytokines

Cytokines are low-molecular-weight proteins secreted mainly by leukocytes and by a wide variety of cells in response to infection or cellular damage. Compared to hormones, they are usually produced and secreted by different types of cells and have a more local action, allowing the communication between immune system and host tissue cells, and modulating immune and inflammatory responses [71].

The level of inflammation is a hallmark for many diseases and can be measured using cytokines. Obesity is associated with chronic, low-grade and noninfectious inflammation, which has been suggested to be a cause of insulin resistance [72]. Recently, waist circunference has been showed as an important clinical risk parameter used to predict the presence of obesity and fatty liver [73]. It occurs mainly due to the visceral adipose tissue, a dysfunctional tissue that have many macrophages in its composition [74]. Studies show that macrophages are the most abundant immune cell in adipose tissue [72], which produce proinflammatory cytokines that contribute to the state of subclinical inflammation and promote insulin resistance, T2DM and MeTS [74].

The subcutaneous adipose tissue have a lower infiltration of macrophages and, therefore a lower production of proinflammatory cytokines

when compared to the visceral adipose tissue [74]. This difference might be the reason why MHO people do not present other comorbidities. Several studies evaluate the cytokines profile in different phenotypes of obesity, with different results [9, 73, 75, 76]. A cross-sectional study demonstrated that MHO and metabolically healthy nonobese individuals have lower concentrations of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) when compared to their metabolically unhealthy groups [75]. Another study realized with morbid obesity people before submission to bariatric surgery showed a similar level of TNF-α comparing metabolically healthy morbidly obese to metabolically unhealthy morbidly obese [9].

A recent study measured the levels of TNF-α and IL-6 in obese and non-obese individuals with MeTS. There was no statistically difference in the cytokine levels in these groups, but they found a significant proportion of individuals categorized as normal-weight with an increased waist circumference (which is correlated with BMI, acanthosis nigricans and fatty liver) and should serve as a warning of bias in future researches [73].

A more complete study of the cytokine profile evaluated interleukin-5 (IL-5), interleukin-10 (IL-10), interleukin-12 (IL-12), interleukin-13 (IL-13) and interferon (IFN-γ) and found elevated levels in both general and central obesity. Furthermore, physical activity modulated cytokine production in obese group, demonstrating a beneficial effect in prevention of comorbidities in these subjects. Another important finding was the IL-5 concentrations, which showed the strongest correlation with adipometrics indices and could be a promising new target for obesity treatment study [76].

Microcirculation

Obesity is associated with systemic vascular endothelial dysfunction and development of atherosclerosis [48]. In addition to atherosclerosis in the larger arteries, functional changes in microvascular reactivity in obesity may increase the risk of developing cardiovascular complications in these patients [77, 78].

Expanded and/or dysfunctional adipose tissue increases the release of inflammatory mediators resulting in reduced nitric oxide and increased endothelin-1 production [79, 80]. Moreover, there is a shift in the adipokine profile characterized by reduced adiponectin and increase of leptin, resistin, and angiotensinogen production [79]. The main sources of this endocrine signaling to the microcirculation appear to be the visceral adipose tissue and the paracrine signaling from perivascular adipose tissue [81]. In obesity, there is also a shift in factors secreted by perivascular fat, that either directly, or via an increase in oxidative stress, alters the normal vasomotor tone to a state of vasoconstriction and insulin resistance [82].

Impaired microvascular function observed in obese individuals appears to be mediated, at least in part, by elevated free fatty acids (FFAs) levels and the intracellular accumulation of substances derived from FFAs [83]. These intracellular lipids have also been suggested to play a role in FFA-induced insulin resistance since intracellular lipids are associated with impaired insulin-induced glucose uptake [79, 84].

In addition to functional alterations, obesity is also associated with structural arteriolar and capillary rarefaction [85, 86]. Obesity and insulin resistance are also associated with a loss of insulin-mediated endothelial-dependent capillary recruitment [87, 88]. In this context, we have previously shown that obese individuals have structural and functional alterations in the systemic microcirculation that are related to the increase in the degree of global and central obesity. Furthermore, in obese subjects with MeTS, the cutaneous capillaries at rest are already maximally recruited, indicating an absence of functional capillary reserve, which may be related to the insulin resistance observed in these individuals [89].

Obesity is an important risk factor for insulin resistance and hypertension and plays a central role in the MeTS. Outstandingly, microvascular dysfunction associated with obesity is considered to be a linking factor between insulin resistance, hypertension (increased peripheral resistance) and T2DM [80, 90-93]. It is important to note the existence of a decreased sensitivity of resistance vessels [94] and the systemic microcirculation [95] to insulin-

induced endothelium-dependent vasodilation in obese individuals. Experimental studies demonstrated that obesity is associated with microvascular rarefaction [96, 97] and structural remodeling [98] in the smooth muscle circulation; microvascular rarefaction in the human skeletal muscle have also been demonstrated [99]. Moreover, a causal role for obesity in the pathophysiology of vascular endothelial dysfunction has been suggested by the fact that weight loss improves endothelial function [100].

We also demonstrated that, in non-diabetic hypertensive patients, capillary density is negatively and independently influenced by overweight [101]. Interestingly, it has been shown that subjects with the MeTS already have systemic microvascular dysfunction, even among individuals presenting with normal plasma glucose levels [102] or in patients without T2DM [103]; moreover, microcirculatory dysfunction appeared to be associated with BMI [102].

Considering that microvascular dysfunction in obesity is related to systemic metabolic alterations, then the question arises whether MHO individuals present altered endothelial-dependent microvascular reactivity. In this context, a recent cohort study reported that obese individuals without metabolic abnormalities have altered systemic microvascular function, when compared to normal-weight individuals. Additionally, MUO individuals have more severely impaired microvascular function than MHO individuals. In that study, individuals were classified as normal-weight, overweight, or obese according to BMI and were stratified into healthy or unhealthy metabolic status based on the presence of the MeTS using the ATP-III criteria. The study included three community-based cohorts of geographically diverse background: The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), The Framingham Heart Study, a largely white American cohort, and the Gutenberg Study (GHS), a German-European cohort, with a total number of 16,830 individuals. Systemic microvascular function was evaluated using peripheral arterial tonometry (PAT), which is a non-invasive technique that uses fingertip plethysmography to measure pulse volume amplitude (PVA). The PVA changes induced by reactive hyperemia, compared to baseline values, have been shown to be related to nitric oxide bioavailability, suggesting that PAT is a measure of endothelial function [104]. Overall, this meta-analysis emphasizes the existence of an association between excess weight and impaired microvascular function, suggesting that obesity induces endothelial-dependent vascular dysfunction irrespective of the metabolic status, calling into question the concept of a healthy pattern of obesity [105].

Conclusion

Despite some recent studies have been demonstrating that MHO may present impairments on several mechanisms that could increase CVD risk such as alterations in hormones and cytokines production, and vascular microcirculatory damages, this phenotype is still characterized as a benign obesity status. Therefore, the discussion about the exact pathogenic mechanism or about the transition status to unhealthy obesity remains unclear and controversial. MHO is still a challenge that needs to be more investigated and that needs a standard definition to generate more conclusive findings.

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Disclosure of conflict of interest

None.

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