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REVIEW ARTICLE

Metabolically Healthy Obesity and Bariatric Surgery

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Abstract
A peculiar category of persons with obesity lacking common metabolic disturbances has been depicted and termed as metabolically healthy obesity (MHO). Yet, although MHO patients are free of obesity-associated complications, they might not be entirely precluded from developing cardio-metabolic disorders. Among patients with morbid obesity (MO) who are referred to bariatric surgery, a subset of metabolically healthy MO (MHMO) has been identified and the question arises if these patients would benefit from surgery in terms of mitigating the peril of cardio-metabolic complications. We revisited the pathophysiological mechanisms that define MHO, the currently available data on the cardio-metabolic risk of these patients and finally we reviewed the benefits of bariatric surgery and the urge to better characterize MHMO before submission to surgery.

Keywords Metabolically healthy obesity · Morbid obesity · Bariatric surgery

Introduction

It is widely accepted that obesity is a rising issue and a challenge for public healthcare systems [1]. Commonly, obesity is associated with a cluster of disorders such as type 2 diabetes (T2DM), dyslipidaemia and hypertension, which all together define the metabolic syndrome (MS) [2]. However, emerging data show that metabolic and cardiovascular disturbances are distributed unevenly among individuals with obesity [3–5]. Interestingly, a subset of patients with obesity, deemed as metabolically healthy obesity (MHO), remain free of the aforementioned abnormalities despite an excess of adipose tissue, underlining that the overall amount of adiposity may not be the linking factor between obesity and metabolic derangements [3–6]. MHO seems to carry higher insulin sensitivity, lower chronic inflammation, better lipid profile and no hypertension [4, 5]. Yet, currently available evidence indicates that the lack of comorbidities is not synonymous with the absence of the mortality risk [7, 8]. MHO seems to be more a transient state towards the onset of overt metabolic disturbances rather than a stable condition. Therefore, whether these individuals are really more resistant to cardio-metabolic risk, and what could be the pathways that lead to such a favourable stage are still to be elucidated [3].

To date, there are few studies to address the prevalence of MHO according to the degree of body mass index (BMI) and more specifically, the data on the prevalence of the metabolically healthy morbid obesity (MHMO) are scant. For patients with morbid obesity (MO) who have failed to obtain and sustain a lower weight, bariatric surgery has been proven to be the only efficient treatment [9]. Robust data have indicated that besides weight loss, bariatric surgery is followed by significant remission of comorbidities in a weight-dependant and independent manner [10]. However, to what extent in terms of metabolic and cardiovascular endpoints surgery is a solid option for MHMO is still under discussion.

Obesity and Metabolic Syndrome

A constellation of diseases such as T2DM, hypertension and dyslipidaemia accompany abdominal obesity and define the MS [2]. Along the way, various diagnostic criteria have been proposed to characterize this condition. The first definition launched in 1998 by World Health Organization (WHO) considered insulin resistance (IR) the cornerstone of the MS and

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required the evidence of this criterion for the diagnosis plus two additional risk factors, including obesity, hypertension, high triglycerides level, reduced high-density lipoprotein cholesterol level (HDL-C) or microalbuminuria [11]. However, in 2001, The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) established that no single factor is compulsory and that demonstration of IR per se was not needed for the diagnosis. Therefore, they proposed the definition of MS as the presence of three of the following five factors: abdominal obesity, elevated triglycerides, reduced HDL-C, elevated blood pressure and elevated fasting glucose (impaired fasting glucose or T2DM) [12]. Criteria were revisited in 2004 by the American Heart Association (AHA) and the National Heart Lung and Blood Institute (NHLBI), with the adjustment of the blood glucose threshold form 110 to 100 mg/dl and the inclusion of previous treatment for dyslipidaemia, hypertension and hyperglycaemia among the criteria for MS [13]. Later, in 2005, the International Diabetes Federation (IDF) made central obesity as assessed by waist circumference (WC) mandatory as one of the five conditions nominated by ATP III together with the presence of any two of the remaining four criteria in order to establish the diagnostic of MS. It should be noted that the WC threshold used by IDF for Caucasians was lower as compared with the one used by NCEP [14]. Finally, in 2009, in an attempt to harmonize the definitions of the MS, the IDF, NHLBI, American Heart Association, World Heart Federation, International Atherosclerosis Society and International Association for the Study of Obesity considered any three out of five criteria of ATP III in order to set out the diagnostic of MS. Also, the joint interim statement recommended that the WC thresholds for abdominal obesity should be considered with regard to country-specific and population-specific definitions. Finally, individuals with T2DM as well as anyone on medication for any condition of MS, irrespective of the value, are to be considered as having MS [15]. A scheme reporting these different definitions of the MS is reported in Table 1.

Although low-grade systemic inflammation expressed by the elevated pro-inflammatory markers such as C-reactive protein (CRP), tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and reduced levels of anti-inflammatory molecules like adiponectin has been reported to be associated with MS features, currently, it is not included among the diagnostic criteria [16, 17].

Definition and Prevalence of MHO

The MHO concept has its origins in the 1980s when it was first described by Brochu et al. [18] and Sims [19]. Broadly, this category is deemed to be the absence of T2DM, dyslipidaemia and hypertension in subjects with excess fat mass [20]. However, there are still no unanimously accepted criteria to define metabolic health and therefore a general consensus is warranted [8]. Several definitions have been proposed so far, most of them based on the ATP III definition of MS but not all included fasting glucose, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), blood pressure or markers of chronic inflammation [18, 20–23]. In addition, another question to be discussed refers to the cut-off points of the metabolic parameters [24]. Finally, in an elegant proposal of harmonizing the definition criteria, Ortega et al. [25] consider as having MHO a person who has a BMI ≥ 30 kg/m^2 and meets zero of the MS criteria (excluding WC).

Hence, due to the inconsistency in defining this subset of individuals with obesity, the prevalence of MHO ranges widely from 3 to 57% [21, 26]. In Europe, The Healthy Obese Project, the largest study so far, analysed a 10 population-based cohort from different seven European countries using none of the MS criteria endorsed by the NCEP ATP III. Across all cohorts, the prevalence of MHO was ~ 17% with a range from 11.6 to 26.3% [4, 27]. With regard to MHMO patients, data from the literature reported ranges between 7 and 28.3% [22, 28–31].

Metabolically Healthy Versus Unhealthy Obesity

Adipose tissue holds the role to accommodate fat and, although it is generally accepted that excess adiposity is harmful, studies have demonstrated that the deficiency (lipodystrophy) or incapacity of adipose tissue to store lipids is deleterious too in leading to fat spilling over into other tissues and therefore to ectopic fat [32, 33]. In other words, in conditions of overfeeding, the ability of the adipose tissue to harbour fat prevents ectopic fat installation and mitigates the peril of metabolic syndrome onset [32, 33]. What are then the factors that grant the adipose tissue the capacity to prevent the installation of the obesity-associated metabolic disturbances? Although, currently, the precise mechanisms involved in MHO versus metabolically unhealthy obesity (MUO) are not entirely understood, several factors like the capacity of fat storage, fat distribution, adipocyte turnover, biology of adipocytes (adipocyte dysfunction), levels of physical activity and cardiorespiratory fitness rather than overall obesity have been described [4, 18, 25, 32–35]. Above all, Blüher and Schwarz [34] concluded that the most important contributors to the MHO phenotype are lower amount of visceral adipose tissue and inflammatory markers as well as preserved insulin sensitivity.

Hyperplastic and Hypertrophic Obesity

One factor that might influence the cardio-metabolic risk is the type of adipose tissue expansion upon stimulation by

Table 1 Criteria for clinical diagnosis of metabolic syndrome

	Risk factors		Obesity	Dyslipidaemia	Hypertension	Hyperglycaemia	Other
	Mandatory	Plus					
WHO 1998	IR (IFG, IGT T2DM, or lower insulin sensitivity[a])	Any two or more of the following components	Waist to hip ratio Men > 0.90 Women > 0.85 and/or BMI ≥ 30 kg/m2	Triglycerides ≥ 150 mg/dl and/or HDL cholesterol < 35 mg/dl in men < 39 mg/dl in women	≥ 140/90 mmHg	T2DM IFG ≥ 110 mg/dl IGT ≥ 140 mg/dl	Microalbuminuria (urinary albumin excretion rate ≥ 20 μg/min or albumin/creatinine ≥ 20 mg/g)
NCEP/ATP III 2001	None	Any three or more of the following components	Waist circumference Men ≥ 102 cm Women ≥ 88 cm	Triglycerides ≥ 150 mg/dl HDL cholesterol < 40 mg/dl in men < 50 mg/dl in women	≥ 130/85 mmHg	≥ 110 mg/dl (includes diabetes)	–
AHA/NHLBI Modified NCEP/ATP III 2004	None	Any three or more of the following components	Waist circumference Men ≥ 102 cm Women ≥ 88 cm	≥ 150 mg/dl or on drug treatment for elevated triglycerides HDL cholesterol < 40 mg/dl in men < 50 mg/dl in women or on drug treatment for reduced HDL-C	≥ 130 mmHg systolic blood pressure or ≥ 85 mmHg diastolic blood pressure or on antihypertensive drug treatment in a patient with a history of hypertension	≥ 100 mg/dl or on drug treatment for elevated glucose	–
IDF 2005	Central obesity (waist circumference population specific)	Any two or more of the following components	Waist circumference Men ≥ 94 cm Women ≥ 80 cm	≥ 150 mg/dl or on drug treatment for elevated triglycerides HDL cholesterol < 40 mg/dl in men < 50 mg/dl in women or on drug treatment for reduced HDL-C	≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or on antihypertensive drug treatment	≥ 100 mg/dl (includes diabetes)	–
Harmonised Definition 2009	None	Any three or more of the following components	Elevated waist circumference (population- and country-specific definitions)	≥ 150 mg/dl (drug treatment for elevated triglycerides is an alternate indicator HDL cholesterol < 40 mg/dl in men < 50 mg/dl in women (drug treatment for reduced HDL-C is an alternate indicator)	≥ 130 and/or diastolic ≥ 85 mmHg (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	100 mg/dl (drug treatment of elevated glucose is an alternate indicator)	–

[a] Insulin sensitivity measured under hyperinsulinaemic euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation

excessive food intake [35]. Under conditions of caloric overload, excess fat is stored in adipose tissue and this takes place by increasing in both number (hyperplasia) and size (hypertrophy) of adipocytes, with either hyperplastic or hypertrophic pattern of obesity as a dominator [33]. Current evidence has shown that hyperplastic response of adipose tissue can be found mainly in subcutaneous adipose tissue (SAT) and that this pattern of increase leads to a 'healthy' adipose tissue due to greater potential of storage [33, 36, 37]. In other words, the SAT ability to recruit new cells and to differentiate precursor cells into adipose cells plays an important role in protecting against development of dysfunctional SAT and against intra-abdominal and ectopic fat deposition, making the subcutaneous site a safe place of storage [38–40].

Taken together, these data suggest that MHO is a phenotype that is based on preserved adipose tissue function and predominantly subcutaneous fat distribution [41]. In fact, it appears that the MHO phenotype displays smaller adipocytes and greater adipogenesis than MUO [42, 43]. In particular, McLaughlin et al. [44] showed that MHO individuals exhibit a two- to threefold increase of gene expression related to adipocyte differentiation as compared with MUO individuals. Another factor that sets the difference between the SAT of obesity with and without IR lays in the expression of important proteins involved in lipid droplet organization [35, 38, 45]. Finally, along with hyperplastic expansion of adipose tissue, the plasticity of the extracellular matrix and the angiogenetic capacity determine a benign phenotype despite increased fat mass [35]. The adipogenesis capacity in SAT is under genetic regulation, and large inter-individual differences have been reported explaining the development of 'healthy' or 'unhealthy' adipose tissue [40, 46].

Opposite to the increase of the adipocyte number, hypertrophic obesity with enlarged adipocytes is rather 'unhealthy' as it is associated with hypoxia, impaired angiogenesis, adipocyte dysfunction, cell necrosis, chronic inflammation and ultimately with the inability of adipose tissue to store efficiently the excess energy [35, 47–49]. Therefore, patients with hypertrophic obesity are prone to develop metabolic disturbances including T2DM, dyslipidaemia and chronic inflammation [38]. Hoffstedt et al. [50] demonstrated in 80 women with MO that large visceral fat cells are more strongly linked to dyslipidaemia, whereas large subcutaneous fat cells correlate with impaired glucose metabolism, hyperinsulinaemia and IR. Moreover, MO women with many, but smaller, adipocytes in visceral or subcutaneous tissue may be protected from metabolic complications [50]. On the other hand, some studies have shown that insulin-resistant individuals display an excess of small 'immature' adipocytes that very likely fail to transform into mature cells explaining the limitation of fat storage capacity and redistribution of fat excess towards ectopic sites [33, 44, 51]. This information highlights the concept of MS being associated with an impaired healthy adipose tissue expansion [33].

Subcutaneous Versus Visceral Adipose Tissue and Ectopic Fat

As aforementioned, the ability of SAT to safely store excess fat is the main hallmark of metabolic health, notwithstanding the positive energy balance [40, 52]. Several studies have discussed the 'adipose tissue expandability hypothesis' which states that in the face of continuous caloric overload the SAT reaches a point at which it can no longer expand appropriately and subsequently harbour energy. Hence, the excess of visceral adipose tissue (VAT) and ectopic fat in non-adipose tissues such as liver, skeletal muscle, pancreatic beta cells and heart is a result of exceeded/inability of SAT storage capacity under conditions of positive energy balance [38, 53–56] (Fig. 1). More precisely, in terms of cardio-metabolic complications, data from the literature show that it is not overall obesity but rather fat distribution, i.e. mainly visceral (omental, epiploic and mesenteric) and ectopic fat rather than subcutaneous that is correlated with such a risk [57, 58]. In this context, it is interesting to outline the lipodystrophy, a condition whose feature is the impaired capacity of SAT fat storage leading to accumulation of lipids in visceral and ectopic tissues and subsequently to IR even in the face of modest weight gain, as opposed to some patients with extreme obesity yet remaining insulin sensitive as they are able to accumulate high subcutaneous fat and lower levels of visceral and ectopic fat [59]. In fact, Pardina et al. [60] showed that MHMO display 17.5% more subcutaneous fat compared with the diabetic and dyslipidemic individuals with MO.

Several studies have demonstrated that MHO exhibit low VAT while MUO display increased amounts of visceral adiposity that is linked to IR, T2DM, dyslipidaemia and hypertension [17, 33, 38, 53, 56, 61–63]. Moreover, some authors claim that despite the presence of overall excess adiposity, it is smaller amount of VAT (identified in MHO individuals matched for percentage body fat with MUO individuals) that holds a paramount importance in the maintenance of the favourable metabolic profile of MHO [1, 61, 64]. In this respect, Brochu et al. [18] revealed 49.6% less VAT and higher levels of insulin sensitivity in MHO postmenopausal women when compared with MUO, both groups holding comparable total body fatness [18]. Also, higher superficial SAT and peripheral fat mass as well as less VAT were reported by Meissner et al. [64] in MHO sedentary postmenopausal women than in at-risk subjects. On the other hand, Stefan et al. [52] when looking at insulin sensitive and insulin-resistant individuals with obesity observed no statistically significant difference between the two groups in terms of amount of visceral fat. They explained that it may well be that other factors than excess of visceral fat could be involved in regulating insulin

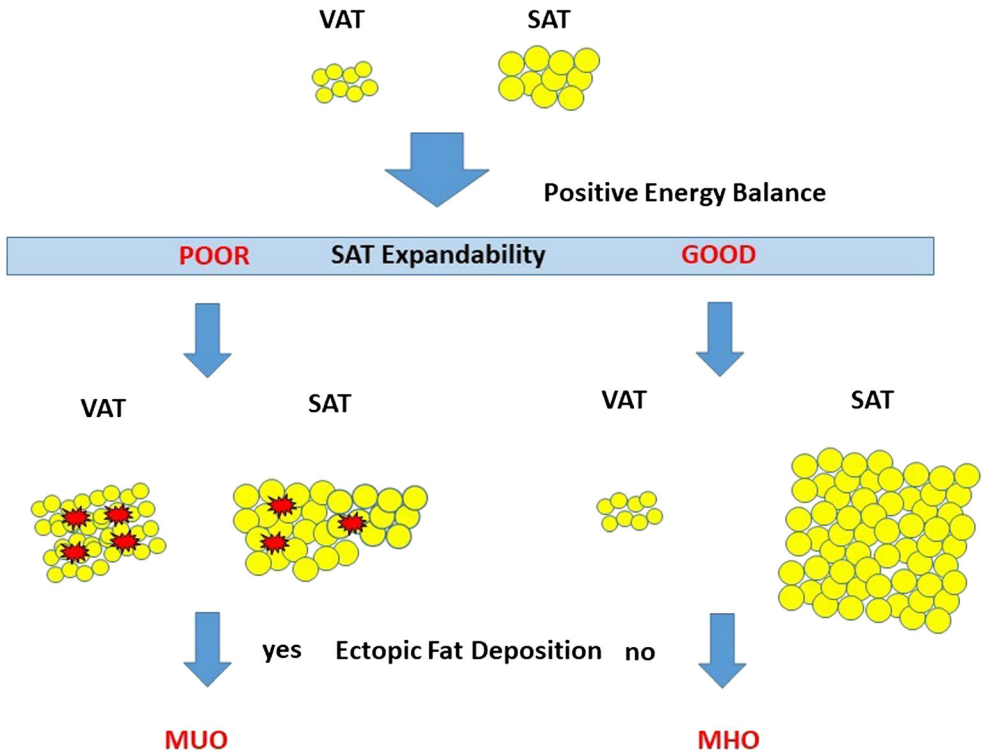

Fig. 1 A simplified description of the theory of adipose tissue expandability. In case of positive energy balance, adipose tissue needs to expand in order to store excessive fats. If subcutaneous adipose tissue (SAT) expandability is poor, SAT expands poorly and macrophages infiltration occurs (red stars). Excessive fats then tend to accumulate in the visceral adipose tissue (VAT) that expands with much more inflammation. Ectopic fat accumulation also occurs and metabolic complication arises. In case of good SAT expandability, SAT is able to store all the excessive fats without inflammation, VAT accumulation and ectopic fat deposition

sensitivity [52]. In addition, when referring to MO some authors showed that WC and waist-to-hip ratio (WHR) are similar in MHMO and metabolically unhealthy MO (MUMO) and therefore cast a doubt on the body fat distribution as a disparity between the two phenotypes, claiming that the difference lies mostly in the total amount of body fat instead [29, 65]. In a proteomic analysis of the VAT isolated from patients with MHMO and MUMO, Alfadda et al. [66] found that MHMO expresses proteins that improve the adipose tissue expansion capacity as compared with the MUMO group which showed an increase in proteins that reflected a greater alteration in the mitochondrial and lipid droplet metabolic activity.

The currently available data have shown that visceral adipocytes are dysfunctional as they are lipolitically active and release an increased amount of free fatty acids that are delivered to the liver through the portal vein, creating a 'hepatic-visceral adipose tissue axis' leading to hepatic IR and lipid metabolism disturbances such as higher plasma levels of very low-density lipoprotein (VLDL) and other components of atherogenic dyslipidaemia [1, 16, 48, 67–69]. Furthermore, IR brings about fasting hyperinsulinaemia, T2DM and increased sympathetic nervous system activity that induces the onset of hypertension [1]. The fact that VAT has a greater lipolytic activity than SAT has been reinforced by the finding that VAT from MO patients shows a significant increase in the expression of genes involved in lipolysis (hormone-sensitive lipase, and perilipin). On the other hand, in the same patients, SAT shows a decrease in the expression of genes involved in de novo lipid synthesis and energy generation [70].

Hepatic fat has been demonstrated by Stefan et al. [52] to be lower in MHO as compared with MUO [59]. However, while Messier et al. [71] showed that MHO has lower concentrations of hepatic enzymes compared with at-risk subjects which may reflect lower liver fat content, Ogorodnikova et al. [72] reported an intermediate liver fat content between metabolically benign normal weight and at-risk overweight/obesity, suggesting that the metabolically benign phenotype may not be free from liver fat infiltration. Higher liver fat infiltration and more VAT were demonstrated also in MO patients with metabolic disease as compared with MO without MS [73]. More precisely, Haskins et al. [31] found that 35.6% of MHMO free form hypertension, dyslipidaemia or IR had some degree of fatty liver disease and nearly one quarter of these patients had nonalcoholic steatohepatitis (NASH). Other liver alterations in MO were revealed by Pardina et al. [60] who showed that the mRNA of the adipose triglyceride lipase (the enzyme is also present in the liver) level is decreased by 30% in the MHMO compared with the control group, and it is reduced by 23 and 18%, respectively, in the MO with

comorbidities. Also, the de novo cholesterol synthesis regulatory enzyme HMG-CoA reductase displays significantly decreased expression in the MHMO as compared with controls (50% decrease) but this reduction was not as notable in the obese with metabolic derangements [60].

At present, little is known about the factors that are involved in the determination of fat distribution, hyperplasia/hypertrophy and associated metabolic disturbances, hence leading to a healthy or non-healthy obese phenotype [38]. Studies have shown that fat mass and distribution as well as adipocyte number are heritable traits, with genetics accounting for 25–70% of the variability [41, 74]. Some genetic studies have been performed showing that there are several developmental genes which display differences in their expression and play an important role in the pattern of fat distribution [41, 75]. Using data from publicly available GWAS (genome-wide association studies), Yaghootkar et al. [76] reported that subtle genetically influenced higher visceral-to-subcutaneous adipose tissue ratio, fasting insulin and dyslipidaemia in combination can increase the risk of hypertension, coronary artery disease and T2DM in the absence of increased BMI. Moreover, other authors have shown that out of the 19 common genetic variants identified by GWAS to be associated with indices of IR, only one was in the fat mass and obesity-associated (FTO) gene, underlining that other pathways are involved in the onset of IR [77, 78]. Finally, a more recent study conducted by Lotta et al. [79] identified 53 genomic regions associated with IR phenotypes and showed that the 53 loci were associated with lower body fat percentage, BMI and hip circumference, suggesting that impaired expansion of subcutaneous fat mass mainly of lower body fat mass might prone individuals to a metabolically unhealthy obesity phenotype.

MHO and Low-Grade Chronic Inflammation

Obesity is known to be a chronic, low-grade inflammatory state which is one of the links between excess adiposity (mainly intra-abdominal), IR, T2DM and MS [1, 16]. As a consequence of adipocyte hypertrophy, the culprit that sets off the onset of adipose tissue inflammation is hypoxia due to the disturbances in diffusion of oxygen as well as to dysregulation of adipose tissue blood flow [48, 80, 81]. Subsequently to hypoxia, cell necrosis is installed and hence macrophages congregate near necrotic adipocytes [82]. Once infiltrated, macrophages become activated, start to produce pro-inflammatory cytokines (TNF-α, IL-6, interleukin 1 (IL-1)) and are correlated with both adipocyte size and BMI [48, 82]. Moreover, macrophage infiltration appears to be greater in omental fat as compared with SAT, leading to the conclusion that the inflammatory state appears to be greater in VAT relative to SAT [83–85]. Another consequence of the hypoxic adipocytes is their upregulation of hypoxia-inducible factor-1α which activates specific pro-inflammatory signalling pathways such as nuclear factor κB (NF-κB) leading to the overproduction of pro-inflammatory factors such as TNF-α, IL-6, interleukin 8 (IL-8) and plasminogen activator inhibitor 1 (PAI-1) accompanied by a reduction of anti-inflammatory substances such as adiponectin [48, 55]. Finally, hypoxia also induces oxidative stress, a process that is also linked to activation of inflammation [86].

Low-grade chronic inflammation has been investigated in MHO by several studies but conflicting results have been revealed. Karelis et al. [61] showed that besides displaying 49% less VAT than at-risk obese postmenopausal women, MHO have significantly lower levels of high sensitivity (hs) CRP, α-1 antitrypsin, fasting insulin and HOMA-IR as compared with their at-risk counterparts. The authors highlighted that lower amounts of CRP levels, despite high levels of body fat, could contribute to the favourable metabolic profile observed in MHO individuals. Moreover, after controlling for visceral fat, the significant differences between the two groups in terms of CRP values were abolished, suggesting that lower CRP levels in MHO individuals appear to be a marker of lower visceral fat content [61]. Even when using five different criteria to define MHO, Phillips and Perry [87] reported a lower inflammatory state, i.e. reduced concentrations of complement component 3, CRP, IL-6, TNF-α and white blood cell count and higher adiponectin levels relative to their metabolically unhealthy counterparts. The increased circulating levels of adiponectin imply a protective role against developing an unhealthy metabolic state [65]. Finally, similar reduced circulating values of CRP, IL-6 and TNF-α have been found by other authors as well [88–90].

However, opposite to the aforementioned results, Gomez-Ambrosi et al. [91] claim that the cardio-metabolic and inflammatory profiles (CRP, fibrinogen, uric acid, leukocyte count and hepatic enzymes) are similarly increased in MHO and MUO, even over 30% of the individuals classified as MHO exhibited IGT or T2D. They also reported that the expression of genes involved in inflammation and tissue remodelling in VAT and liver showed a similar alteration pattern in MHO and MUO individuals [91]. In agreement with these results, similar chronic inflammation assessed by hsCRP levels in MHO and obese individuals with MS was reported also by Iglesias Molli et al. [92], while MHO seem to be less insulin-resistant. Although the link between abdominal obesity, chronic inflammation and IR has been much discussed [48, 93], interestingly, Jiménez et al. [94] revealed that among insulin-sensitive women with MO (IS-MO), 100 and 92% displayed a WC > 88 cm and hsCRP > 3 mg/l, respectively, and reported the presence of MS in 51.9% of the IS-MO individuals. Moreover, Soverini et al. [95] showed that among MO with MS, not all cases were identified as having IR. Our latest results on MO patients referred to bariatric surgery showed less IR in MHMO as compared with MUMO and both similarities and differences between the two groups in terms of chronic

inflammation in accordance with the evaluated parameter. Namely, we observed no differences with regard to circulating hsCRP and TNF-α between the two groups, but disparities were identified with respect to chemerin and nitric oxide metabolites (NOx) [96]. It may be well understood that the association between inflammatory biomarkers and MHO depends on the definition used [91, 97]. Nevertheless, chronic inflammation seems to be the most common derangement when looking at MHMO [29]. Also, Wildman et al. [90] showed that despite no clustering of cardio-metabolic risk, women with obesity still exhibit abnormal levels of inflammatory markers, suggesting that MHO could change into MUO [29, 91]. Obesity per se, independently of insulin sensitivity, may hold its own inflammatory pathways that lead to an increased cardio-metabolic risk [98], or tissue level inflammation could be a better explanation for the association with IR as revealed by Barbarroja et al. [99]. The authors observed high levels of TNF-α mRNA expression in VAT of MO regardless of the degree of IR whereas non-insulin-resistant (NIR) MO patients expressed low levels of both IL-1β and IL-6 mRNA as compared with IR-MO patients and argued that NIR-MO individuals lack the inflammatory response that characterizes the IR-MO patient. Moreover, they showed higher macrophage infiltration and activation of NF-κB in IR-MO which may account for the increased IR state. Also, it seems that NIR-MO patients have an increased insulin receptor substrate-1 (IRS-1) mRNA expression in VAT compared with IR-MO that may contribute to the paradox of healthy carbohydrate metabolism in these individuals [99]. Finally, when divided by the absence/presence of T2DM, van Beek et al. [100] showed that MO carrying T2DM seem to have higher circulating levels of IL-6 but no differences with regard to CRP and TNF-α between the two groups. Interestingly, the authors found that MO women with normal glucose tolerance hold lower subcutaneous crown-like structures and macrophages as compared with the obese with T2DM but no changes in VAT [100].

Altogether, these data show conflicting results that might be explained by the difference in the number and ethnicity of the subjects, as well as the pro-inflammatory markers and definition criteria used to define metabolic health, and outline that further investigations are needed for a better understanding of this peculiar category of individuals. Yet, the underlying molecular mechanisms remain largely unknown. Hence, in an attempt to investigate the mechanisms that are involved in the MHO phenotype, Doumatey et al. [101] approached the proteomics analysis. The authors confirmed that inflammation is a key hallmark of metabolic health in individuals with obesity but also identified a network of acute phase reactant proteins involved in the inflammatory processes associated with MHO, out of which some could account as good candidates to follow-up in further studies in order to determine their ability to predict which MHO individuals convert to metabolically abnormal obesity [101].

MHO and Cardio-metabolic Risk

Individuals with MHO remain an intruding subset of patients not only due to the unknown underlying mechanisms, but also with regard to their clinical relevance [8]. Several studies have been set up in order to establish whether these patients remain in this stable state or if they are on their way to harvest the abnormalities commonly associated with obesity [102–108]. Initially, it seemed that MHO subjects would carry a prognosis similar to those of normal weight, but, as longer follow-up studies came up, this presumption has become debated and in doubt [109, 110]. In fact, in an elegant paper, Xavier Garcia-Moll [110] states that it is high 'Time to forget about metabolically healthy obesity' citing the European Society of Cardiology Guidelines on Cardiovascular Prevention where this type of obesity is only regarded as a transient phase towards MUO [110, 111]. In accordance with this statement, several authors challenge the MHO as a stable condition [102–104, 112]. The currently available data show that MHO rise to MUO within a range of 33.1 to 84% in accordance with the follow-up duration [105–108, 113, 114]. Interesting results came out form the Clinical Practice Research Datalink (CPRD) from UK who analysed 180.560 patients with a BMI over 35 kg/m^2 and reported that the prevalence of MHO was 71%, of which 55.8% remained healthy on long-term follow-up, leaving the other half on progress towards an unhealthy status [113]. In addition, the longest study conducted so far, the Nurses' Health Study (NHS) who followed up 90.257 women along 30 years, reported a conversion of 84% of the MHO women into a metabolically unhealthy phenotype during the follow-up [114].

Several studies have examined the cardiovascular and all-cause mortality risk of MHO [102, 112, 114–118]. A systematic review and meta-analysis by Kramer et al. [115] concluded that as compared with metabolically healthy normal-weight, individuals with obesity in the absence of metabolic disturbances at baseline hold an increased risk for adverse long-term events but this was revealed only when studies with 10 or more years of follow-up were considered [115]. However, in a more recent cohort study, with a mean follow-up of 5.4 years, looking at 3.5 million men and women, the prospectively collected data from The Health Improvement Network (THIN) database showed that individuals with obesity and no metabolic abnormalities had a higher risk of coronary heart disease, cerebrovascular disease and heart failure compared with normal-weight healthy individuals [116]. Finally, a systematic review and meta-analysis of 22 prospective studies that considered the full range of possible definitions for MHO pointed out that none of the approaches did identify an obese subgroup with no increased risk of cardiovascular events relative to normal-weight healthy participants [117]. Hence, in line with these findings, the pan-European cohort study (EPIC-CVD) outline that the results of the study do not support the concept of MHO [112].

Another important finding showed that when compared with MUO subjects, the MHO hold a lower risk for becoming diabetic [102] but this risk remained, however, significant [106]. Moreover, Soriguer et al. [106] reported that after losing weight, the association between MHO phenotype and T2DM incidence disappeared, even after adjusting for HOMA-IR. On the other hand, almost one half of the Multi-Ethnic Study of Atherosclerosis (MESA) participants developed MS during the 12.2 years of follow-up and then had significantly higher odds of CVD, although lower than for those with MUO from baseline [118]. Finally, important conclusions were unveiled from a multicentre study by Bradshaw et al. [119], namely that there is a consistent increase in the rate of installation of MS components among MHO free from any component of MS as compared with metabolically healthy normal weight and that the onset of glucose dysregulation occurs the most rapidly [119].

Given the aforementioned data which demonstrate that MHO are not precluded from developing cardio-metabolic derangements and hence they are the harbingers of the future MUO, the questions with regard to which factors hold responsible for the rise of MUO and which are in charge of delaying this state have yet to be answered. Among them, two factors have been demonstrated to be involved in the increasing odds of incidence of MS, namely both duration and severity of obesity, pointing out once again that MHO pave the way towards the onset to cardio-metabolic disease [104]. On the other hand, fat distribution, precisely peripheral adiposity, seems to be in favour of maintaining MHO [105]. Another factor that has been depicted as a culprit of a significantly higher risk for T2DM incident as compared with the metabolically healthy nonobese is the degree of systemic inflammation [120]. In addition, increased triglycerides, low HDL cholesterol and IR are significant predictors of the shift from MHO to MUO [108, 121]. Finally, data from CPRD, a large-scale primary care database, pointed out that the predictors to progression towards an unhealthy state were male gender, age category, higher baseline BMI category, a higher index of multiple deprivation (IMD) which is a score of the socio-economic background and smoking. Being female, aged between 30 and 40 years at baseline, with a lower initial BMI, a lower IMD and non-smokers decrease the relative risk of transitioning into an unhealthy state [113].

MHMO and Lessons Learned from Bariatric Surgery

Given the currently available data, we could argue that MHO individuals would hold an important cardio-metabolic benefit from weight loss. With regard to MO, a large body of work has shown the benefits of bariatric surgery on weight and obesity-associated disturbances such as T2DM [122], IR [123], dyslipidaemia [124] and hypertension [125]. Nevertheless, the question arises if this subset of patients with MO termed as metabolically healthy would gain any cardio-metabolic benefit after bariatric surgery. Surely, there are some important non-metabolically benefits on morbidity and mortality, such as improved sleep apnoea and arthropathy, reduced incidence of cancer and improved quality of life [9], but data on the metabolic profile after bariatric surgery in this particular subset of MO are still scarce.

To our knowledge, so far, there are few studies that have assessed the outcomes of bariatric surgery in MHMO patients as compared with their MUMO counterparts [28, 29, 126]. Sesti et al. [126] investigated the 6-month effects of laparoscopic adjustable gastric banding (LAGB) on anthropometric and cardio-metabolic risk factors among MO who were stratified based on their insulin sensitivity index (ISI), estimated from an oral glucose tolerance test, into MHO (ISI index in the upper quartile) and IR obese (IRO) (ISI in the three lower quartiles). Body weight, BMI, waist circumference, fasting glucose, insulin levels and triglycerides were significantly reduced and HDL cholesterol significantly increased after surgery with no difference in percent changes from baseline between the two groups. Altogether, MHO individuals had a significant improvement in cardio-metabolic risk factors 6 months after surgery [126]. On the other hand, Jimenez et al. [94] showed that changes in fasting plasma glucose, glycated haemoglobin, HDL cholesterol and triglycerides that accompanied bariatric surgery were larger in the IR-MO group relative to the IS-MO group.

Goday et al. [28] conducted a non-randomized, prospective cohort study on 222 patients with severe obesity (BMI > 40 kg/m2) who were assigned to either laparoscopic Roux-en-Y gastric bypass (LRYGB) or laparoscopic sleeve gastrectomy (LSG) and who were classified as MHMO at baseline if only one or no cardio-metabolic factors among the MS criteria as well as HOMA-IR > 3.29 were present. MHMO displayed a similar weight loss to MUMO. MHMO subjects showed a significant decrease in blood pressure, plasma glucose, HOMA-IR, total cholesterol, LDL-C and triglycerides and an increase in HDL-C 1 year after bariatric surgery. However, MUMO patients showed a more marked response to bariatric surgery than MHMO subjects in terms of reduction of glucose, glycated haemoglobin, HOMA-IR and triglycerides and increase of HDL cholesterol. Out of the 34 MHMO patients carrying one metabolic abnormality at baseline, 17 still exhibited a cardiovascular risk factor after surgery [28]. Finally, although cardiovascular risk factors in these patients were within normal range, an improvement in all these factors was observed 1 year after bariatric surgery, reinforcing the benefit of the surgical treatment in these subjects [28]. The lack of significant effect of obesity phenotype on BMI and absolute weight loss over time was reported also by the group of Pelascini et al. [29]. The authors studied 102 patients with

MO who were submitted to RYGB, completed the 2-year follow-up and were divided into MHMO and MUMO based on more strict criteria proposed by Wildman et al. [21] which besides the components of MS encompass CRP and HOMA-IR. MHMO phenotype was significantly associated with a greater percentage of excess BMI loss independent of gender and age, and the authors discussed the hypothesis of limited weight loss in MUMO as a consequence of a structurally different adipose tissue from MHMO [29]. Moreover, Moreno Castellanos N et al. [127] showed that it is the initial metabolic status that influences the final outcomes of bariatric surgery in terms of adipose tissue molecular remodelling. Another important finding of Pelascini et al. [29] was that although an important improvement of the metabolic parameters in both MUMO and MHMO patients was observed over the study, patients with preoperative MHMO phenotype still had a better metabolic profile 24 months after surgery relative to the MUMO individuals. Therefore, the authors highlighted that notwithstanding the important weight loss, MHMO and MUMO patients are hardly the same after bariatric surgery and that both phenotypes are, in fact, different stages in the course of obesity evolution [29].

An important aspect to be marked is the insulin sensitivity of MO and whether these patients may benefit from surgical weight loss. Sesti et al. [126] showed that 2-h glucose and insulin levels were significantly reduced only in the IRO group, and the percent change of insulin sensitivity was significantly greater in the IRO group relative to the MHO group. Moreover, the importance of the baseline fasting insulin has been revealed also by the Swedish Obese Subjects (SOS) study, although this study did not specifically approach the MHMO category [128]. The authors reported that higher insulin at baseline predicted favourable effects of bariatric surgery in terms of reduced mortality and incidence of T2DM as compared with lower baseline levels. Therefore, stratification based on fasting insulin levels and insulin sensitivity should be proposed before undergoing bariatric surgery in order to select those patients who would most likely benefit from surgery at least from this point of view [128].

In conclusion, as Ferrer et al. [129] concluded, 'morbidly 'healthy' obese are not metabolically healthy but less metabolically imbalanced than those with type 2 diabetes or dyslipidaemia' [129]. As underlined by Haskins et al. [30], even if clinically speaking these patients with obesity are metabolically healthy, they may not carry a similar phenotype at the cellular level. Moreover, although within a normal metabolic range, MHO display an elevated lipid profile and IR as compared with normal-weight subjects [129]. Finally, altogether, these findings fit with the concept that MHO is not entirely a benign and stable state, but rather a changing condition whose natural course is to progress to unhealthy obesity as years go by [111]. In terms of T2DM, the available evidence argues the use of bariatric surgery in obese patients with prediabetes or high diabetic risk [130]. Therefore, from a metabolic point of view, all these data endorse bariatric surgery as an appropriate and beneficial approach for all MO patients, including those who are termed as MHMO [105, 117] due to its ability to prevent or delay the onset of metabolic disorders.

Compliance with Ethical Standards

Ethical Approval Statement This article does not contain any studies with human participants or animals performed by any of the authors.

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