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Under New Criteria for Clinical Obesity, is Metabolic Obesity with Normal Body Weight Finally a Legitimate Disease Phenotype?

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Abstract

The new definition and diagnostic criteria for clinical obesity brought important advances by recognizing the limitations of body mass index (BMI) in identifying excess body fat. In addition, it has evolved in the characterization of obesity as a standalone disease, including a subclassification based on the clinical repercussions directly induced by excess adiposity. In this context, a phenotype marked by reduced gluteofemoral body fat, accumulation of visceral adiposity, and ectopic fat deposition often occurs in people with normal BMI and obesity-related cardiometabolic disorders. Even without characterizing obesity by the current BMI definition, this high-risk profile is recognized as "metabolic obesity" with normal body weight (MONW). This narrative review addresses the characterization, prognostic implications, and pathophysiology of the MONW phenotype in light of the new diagnostic approach to obesity and discusses the strengths and limitations of these new criteria for clinical obesity, with an emphasis on their implications for improving the health of people living with obesity.

Keywords: obesity; adiposity; body fat distribution; metabolic syndrome

Introduction

"Corpulence (i.e., obesity) is not only a disease itself, but the harbinger of others." This famous quote, attributed to the fifth century Greek physician Hippocrates,[1] recognizes obesity as a standalone disease entity and a risk factor for other illnesses as well. Many centuries later, however, Hippocrates' perspicacity in conceiving obesity as a disease remains a matter of debate. Much of the controversy arises from the current way obesity is defined, based on the body mass index (BMI), a simple anthropometric measure proposed by Adolphe Quetelet, a Belgian astronomer and mathematician, in 1859.[2] BMI is calculated as weight in kilograms divided by height in meters squared, and constitutes a quick, inexpensive, and reproducible measure.[2]

Since 1998, the World Health Organization (WHO) has adopted BMI to identify the presence and severity of excess body weight in adults. The WHO defined overweight as a BMI of 25–29.9 kg/m^2 and obesity as a

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BMI of ≥30 kg/m^2.[3] Obesity was further subdivided into class I (BMI of 30–34.9 kg/m^2), class II (35–39.9 kg/m^2), and class III (≥40 kg/m^2).[3] At the population level, BMI correlates well with type 2 diabetes (T2D)[4,5] and its complications,[5] gestational diabetes risk,[6] osteoarthritis,[7] obstructive sleep apnea,[8] several types of cancer,[9,10] cardiovascular diseases,[11] and all-cause mortality.[12] While useful as a screening tool, BMI is not a direct measure of adiposity nor does it assess the distribution of body fat. Therefore, at the individual level, BMI lacks accuracy and reliability as an index reflecting adipose tissue (AT) mass and, consequently, it does not provide an indication of the impact of excess adiposity on health.[2]

BMI overestimates adiposity in athletes with high muscle mass and in patients with edema but underestimates adiposity in sarcopenic individuals and in people with unfavorable fat distribution despite normal weight.[2,13] In this case, a phenotype marked by reduced gluteofemoral body fat, accumulation of visceral adiposity, and ectopic fat deposition often occurs in people with normal BMI and obesity-related cardiometabolic disorders. Even without characterizing obesity by the BMI definition, this high-risk profile is recognized as "metabolic obesity" with normal body weight (MONW).[13]

In summary, the current BMI-based definition of obesity: (i) can both underestimate and overestimate adiposity; (ii) provides valuable information about obesity-related disorders at the population level but may lead to inappropriate conclusions about health status at the individual level; and (iii) compromises the recognition of obesity as a disease itself. As BMI does not directly reflect fat mass, clinical assessment of obesity should ideally include additional measures of adiposity (other anthropometric measures or direct measurement of AT mass) to avoid misclassification.[14] Therefore, a more accurate definition of obesity, consistent with evidence that the risk for other diseases and ongoing illness can both be associated with excess adiposity, is necessary to explain the full effect of obesity on health.[14]

The New Definition and Diagnostic Criteria of Obesity

Despite evidence that excess adiposity alone can affect the functioning of multiple organs and tissues, the illness caused by obesity itself had not yet been characterized.[14] In a collaborative effort to provide a more accurate and clinically relevant approach, a Commission of leading global experts has established a new definition and diagnostic criteria for obesity.[14]

Obesity is characterized by excessive adiposity, with or without abnormal distribution or function of the AT. Abnormalities of body fat distribution, function, or both, can characterize subtypes of obesity and play major roles in identifying the effect of obesity on health, particularly due to their association with metabolic dysfunction. In the absence of excess adiposity, however, abnormal AT distribution or function is not sufficient to meet the definition of obesity.[14]

Given the limitations of BMI, the Commission proposed a new diagnostic approach to obesity that includes other measures of body size (i.e., waist circumference [WC], waist-to-hip ratio [WHR], or waist-to-height ratio [WHtR]) and objective signs and symptoms of ill health.[14] The first step to diagnosis obesity is confirming excess body fat via one of the following three criteria: (i) ≥1 measurement of body size and BMI; (ii) ≥2 measurements of body size regardless of BMI; and (iii) direct body fat measurement, such as dual-energy X-ray absorptiometry or bioimpedance. Pragmatically, however, it is reasonable to assume the presence of excess adiposity in people with BMI >40 kg/m^2.[15] If excessive adiposity is confirmed, the second step in the diagnostic approach should be the assessment of objective signs and symptoms of ill health, by evaluation of the person's medical history, physical examination, standard laboratory tests, and additional diagnostic tests as needed.[14]

Following these steps, the Commission defined two new categories of obesity: "preclinical obesity" and "clinical obesity." "Preclinical obesity" is a condition of excess adiposity without current organ dysfunction or limitations in daily activities, but with increased future health risk. "Clinical obesity" is a chronic, systemic illness characterized by alterations in the function of tissues, organs, or the whole organism, directly induced by excessive and/or abnormal adiposity.[14] It is worth noting that although the term clinical obesity identifies an illness and can be considered as a disease state, preclinical obesity is not equivalent to a predisease state, in the same way as, for example, prediabetes.[15] Furthermore, the meaning of preclinical obesity does not coincide with the terms overweight or preobesity (BMI of 25–29.9 kg/m^2). Preclinical obesity implies confirmation of excess adiposity (not merely an overweight level of BMI) plus a clinical assessment of preserved organ function. However, as BMI can underestimate excess adiposity, some individuals

traditionally classified as having overweight or preobesity might have either preclinical or clinical obesity.[14]

In addition, the Commission differentiated the terms "complications," "comorbidities," and "obesity-related diseases," which are often inappropriately considered synonymous when used in relation to obesity. "Complications" of clinical obesity should refer to the worsening of organ dysfunction or end-organ damage (e.g., acute myocardial infarction).[14] The term "comorbidities" should only be used to diseases and conditions that incidentally coexist with obesity, and can therefore complicate patient management, without cause-effect relationship or pathophysiologic overlap (e.g., erysipelas). "Obesity-related diseases/disorders" refers to conditions that typically co-occur with obesity, for which there is a plausible cause-effect relationship or, at least, a clear overlapping etiology and/or pathophysiology (e.g., T2D). They can co-occur with both clinical and preclinical obesity and should be considered in decision-making about indications to treatment and type of treatment.[14]

Because health or illness is not solely defined by metabolic abnormalities, it is noteworthy that preclinical and clinical obesity do not coincide with the previously proposed distinctions of metabolically healthy or metabolically unhealthy obesity. Clinical obesity can exist even in the absence of metabolic dysfunction.[14]

Is MONW Finally a Legitimate Obesity Subtype?

The concept of MONW was first established by Ruderman et al. in the 1980s.[16] These authors argued that the definition of obesity current at the time required revision, due to cases of people with normal weight and classical obesity-related metabolic disorders, such as hyperinsulinism, hyperglycemia, hypertriglyceridemia, and hypertension. In 1989, Ruderman et al.[15] also proposed the first diagnostic criteria to identify people with MONW, based on a score system that assessed 22 features, each with its own number of points. Obtaining at least 7 points was equivalent to the diagnosis of MONW.[16] This system had its drawbacks, and the search for much simpler and more accessible diagnostic criteria was started (reviewed by Tyrka et al.[17] and Pluta et al.[18])

Although there is no consensus on its definition, it appears that, in clinical practice, MONW should be diagnosed in individuals with a BMI of 18.5–24.9 kg/m^2 and metabolic syndrome, as defined by International Diabetes Federation.[19] The criteria includes a high WC (ethnic-specific cutoffs points) and at least two of the following: blood glucose >100 mg/dL (5.6 mmol/L) or diagnosed T2D; high-density lipoprotein (HDL) cholesterol <40 mg/dL (1.0 mmol/L) in men, <50 mg/dL (1.3 mmol/L) in women or specific drug treatment; plasma triglycerides >150 mg/dL (1.7 mmol/L) or specific drug treatment; blood pressure >130/85 mmHg or specific drug treatment.[19]

Because unfavorable fat distribution despite normal weight is a hallmark of MONW, a phenotype characterized by increased amount of visceral and subcutaneous fat in the abdominal area[18,20] and reduced subcutaneous fat in gluteofemoral depot, it is reasonable to assume that WHR and WHtR will be particularly useful for evaluating people with MONW. Confirmation of excess body fat in people with MONW can also be achieved via direct body fat measurement. At least in the Japanese population, subjects with BMI <25 kg/m^2 and visceral fat area (measured using a computed tomography scan) >100 cm^2 fulfill the criteria for MONW diagnosis.[20] In a Korean population-based study, using bioimpedance, MONW was defined as BMI <25 kg/m^2 and high body-fat percentage of ≥25% in men and ≥30% in women.[21]

Considering the new definition and diagnostic criteria for obesity,[14] which include different measures of body size or direct measures of body fat that can be used to confirm excess adiposity, disregarding the BMI, MONW could be classified as obesity, whether in its clinical or preclinical form. In the spectrum of obesity, MONW also constitutes a subtype essentially prone to cardiometabolic disorders[22] and obesity-related complications, such as T2D,[23,24] major adverse cardiac events, and mortality.[24,25]

MONW: The Most Dangerous Obesity Phenotype?

The incorporation of a combination of other measures of body size (WC, WHR, or WHtR) as an option for determining excess adiposity in the new recommendations for diagnosing obesity was a very wise decision. Despite the importance of BMI in characterizing health risk at the population level, as it correlates well with obesity related disorders,[4–11] the association between adiposity and mortality is complex and may depend more on fat distribution than on the amount of body adiposity,[26] which is significant from both an individual perspective and clinical practice. This is especially true for patients with MONW, where the combination of body size measurements is essential

for diagnosis; while WC reflects abdominal AT (it cannot distinguish between visceral and subcutaneous fat depots), WHR is a specific measure of fat distribution ("apple shape" vs. "pear shape"), which could not be inferred from measuring WC alone.

Classically, the association curve between BMI and mortality is U-shaped, with the nadir generally among overweight or obesity categories, and underweight and normal-weight categories having the highest risk.[27,28] Although factors such as low lean mass and unintentional weight loss secondary to occult disease or serious illness could increase the risk of death in the underweight category, influencing the shape of the BMI versus mortality curve,[27,28] they do not explain the high mortality risk generally found in the normal weight category nor the lower risk in the overweight/obesity categories. As discussed below, however, the MONW phenotype certainly influences this so-called "obesity paradox."

In a meta-analysis of 40 studies in people with coronary artery disease (CAD), individuals with a BMI of 25–29.9 kg/m^2 had lower mortality compared with those with a BMI of 20–24.9 kg/m^2, and individuals with a BMI of 30–34.9 kg/m^2 had no increase in mortality. These findings cannot be explained by adjustment for confounding factors.[29] In another study including data of 15,923 subjects with CAD, central obesity (defined as abnormal WC and/or WHR) but not BMI was directly associated with mortality.[26] Central obesity was associated with higher mortality even in individuals with normal BMI, and it remained an independent predictor of higher mortality in people with a BMI ≥30 kg/m^2. Moreover, the combination of abnormal WC and WHR, present in over 20% of subjects, was associated with the highest mortality risk in the whole cohort and in people with normal BMI.[26] All of these findings, consistent with the "obesity paradox," turned out to be the "BMI paradox" when WC and WHR were incorporated into the assessment.

In this context, to assess the prognostic value of the MONW phenotype relative to other patterns of body adiposity, based on a combination of BMI and either WC or WHR, Coutinho et al.[30] created a large database through a systematic review of the literature and collaborative effort, comprising 15,547 subjects with CAD. Because there is no controversy surrounding the increased mortality observed in individuals with BMI <18.5 kg/m^2, they were excluded from analysis. The crude death risk based on different combinations of BMI and WC or WHR evidenced that subjects who have a normal BMI (18.5–24.9 kg/m^2) but are in the highest quintiles of central adiposity (the typically MONW pattern) have higher 5-year mortality risk than any other combination of BMI and central adiposity.[30] Conversely, subjects who had a BMI in the overweight (25–29.9 kg/m^2) or obesity (≥30 kg/m^2) categories, but were in the lowest quintiles of central adiposity, had the lowest mortality. Similar findings were observed when using WC or WHR as the measure of central adiposity.[30]

In addition, to compare the mortality risk of subjects with normal weight central adiposity (MONW phenotype) and other adiposity patterns, a multivariate stratified Cox model was created. For these comparisons, the authors chose a BMI of 22 kg/m^2 to represent "normal BMI," 26 kg/m^2 to represent "overweight BMI," and 30 kg/m^2 to represent "obesity BMI." For WC and WHR, they chose values that represented the 25th and 75th percentiles of the sample, which corresponded to a WC of 85 and 101 cm, respectively, and a WHR of 0.89 and 0.98, respectively. Based on the results from this model, subjects with MONW phenotype have higher mortality than those with any other combination of BMI and WC or WHR.[30] Specifically, a person with MONW had 10%–17% higher mortality risk than a person with similar BMI but no central adiposity; 20%–31% higher risk of mortality than a person with overweight BMI without central adiposity; 57%–61% greater mortality than a person with obesity BMI without central adiposity; and 27%–44% higher risk of dying than a subject with obesity and similar WC (Fig. 1) or WHR (Fig. 2). Taken together, these results confirm that among individuals with CAD, those with MONW have the worst prognosis compared with those with other adiposity patterns.[30]

There are some possible explanations for the worst prognosis of the MONW phenotype compared with those with other adiposity patterns, such as the occurrence of sarcopenia, low fitness level, and medical neglect (normal weight patients may be less likely to receive recommendations for a healthy diet, exercise, or other interventions).[30] However, what really seemed to differentiate the lower risk phenotypes from the higher risk ones was the amount of fat located in the hips and legs (i.e., subcutaneous gluteofemoral fat), which are likely reflected in BMI estimates and have been linked to healthy metabolic profiles.[31]

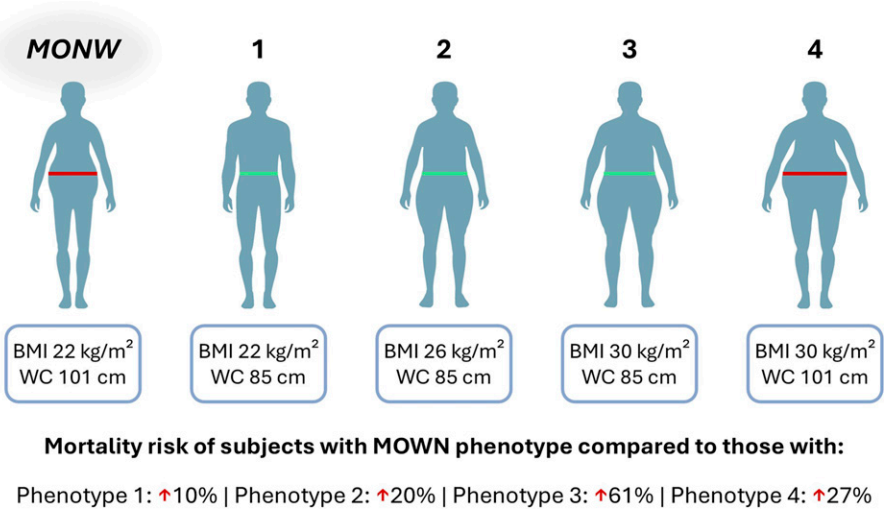

FIG. 1. Mortality risk of metabolic obesity with normal body weight compared with other body adiposity patterns, using waist circumference as a measure of central adiposity. Results based on a multivariate stratified Cox model. Mortality risk (HR [95% CI]) between the MONW phenotype and phenotypes 1 to 4, consecutively: HR 1.10 (1.05–1.17), $P < 0.0001$; HR 1.20 (1.09–1.31), $P < 0.0001$; HR 1.61 (1.39–1.86), $P < 0.0001$; and HR 1.27 (1.18–1.39), $P < 0.0001$. BMI, body mass index; CI, confidence interval; HR, hazard ratio; MONW, metabolic obesity with normal body weight; WC, waist circumference. Adapted from Coutinho et al.[30]

MONW: When Lack of Regional Adiposity Leads to Obesity-Related Disorders

White AT is composed of subcutaneous AT (SAT) and visceral AT (VAT). SAT is the most appropriate local for fat storage due to its expandability and plasticity,[32] while VAT is more associated with metabolic disorders. Although most studies emphasize increased VAT as an essential factor for the high cardiometabolic risk associated with MONW,[13,15–18] the true origin of metabolic alterations and obesity-related disorders in this phenotype appear to be the impairment of SAT, especially in the gluteofemoral region.

Some evidence corroborates that VAT may be a bystander and peripheral SAT may be of utmost importance for metabolic health.[33–35] Based on this premise, Virtue & Vital-Puig[36] put forward the "AT expandability hypothesis," by which the capacity for stock lipids by expanding AT is limited in an individualized fashion. Therefore, when the expansion capacity is reached, lipids can no longer be stored in AT and instead accumulate in ectopic tissues, such as muscle and liver. This ectopic lipid deposition promotes insulin resistance (IR), through lipotoxic mechanisms (Fig. 3).

Impairment of peripheral fat storage capacity is etiological and genetically associated with IR and metabolic diseases.[34] In addition to MONW, other conditions that result in gluteofemoral fat loss, such as Cushing's syndrome and familial partial lipodystrophy type 2 (Dunnigan's syndrome), lead to ectopic fat deposition and metabolic abnormalities.[31,37] Furthermore, pioglitazone, a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist, is able to stimulate adipogenesis, with subsequent increase in SAT and concomitant decrease in VAT. This fat redistribution is explained by PPAR-γ agonist-induced remodeling of abdominal AT, characterized by the differentiation of preadipocytes into small adipocytes in SAT and apoptosis of large differentiated fat cells (hypertrophic adipocytes) in VAT and/or SAT.[38] Despite the stimulation of adipogenesis, pioglitazone effectively improves glucose homeostasis and insulin sensitivity,[38] leading to positive effects on many components of metabolic syndrome, metabolic dysfunction-associated steatotic liver disease, and atherosclerotic cardiovascular disease (ASCVD).[39,40] Overall, the evidence supports the AT expandability hypothesis and highlights the protective properties of

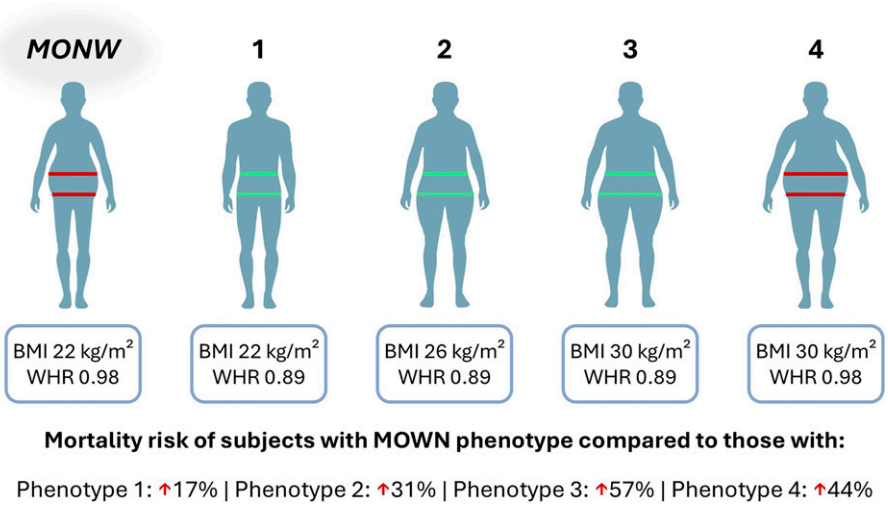

FIG. 2. Mortality risk of metabolic obesity with normal body weight compared with other body adiposity patterns, using waist-to-hip ratio as a measure of central adiposity. Mortality risk (HR [95% CI]) between the MONW phenotype and phenotypes 1 to 4, consecutively: HR 1.17 (1.12–1.23), $P < 0.0001$; HR 1.31 (1.21–1.41), $P < 0.0001$; HR 1.57 (1.34–1.80), $P < 0.0001$; HR 1.44 (1.30–1.59), $P < 0.0001$. WHR, waist-to-hip ratio. Adapted from Coutinho et al.[30]

the gluteofemoral SAT as a determinant of metabolic health.[31]

Final Considerations and Future Perspectives

The new definition and diagnostic criteria for obesity brought important advances by recognizing the limitations of BMI and incorporating other measurements of body size to characterize excess adiposity. In addition, it advanced in the characterization of obesity as a standalone disease, including a subclassification based on the clinical repercussions directly induced by excess adiposity.[14] This reframing of how we conceptualize and approach obesity could have important implications for clinical practice, public health policy, and societal views of obesity, potentially reducing stigma.[41] However, despite the evident importance of gluteofemoral SAT paucity in the development of MONW-related disorders, it is worth noting that the new diagnostic criteria for obesity incorporated other body size measurements only to characterize the presence of excess adiposity, not considering body fat distribution or abnormal AT function to define clinical obesity.[14] Although MONW represents a condition with greater cardiometabolic risk, clinical obesity defines an ongoing illness, not a grading of risk.[14]

The new model recognizes that obesity can cause illness by altering the function of various organs systems, not only those involved in metabolic regulation.[14] A person with musculoskeletal signs and symptoms of excess adiposity would have clinical obesity even in the presence of normal metabolic function, whereas another person with a single metabolic alteration (e.g., dyslipidemia) would be classified as having preclinical obesity. In addition, an individual with clinical obesity due to knee pain, with joint stiffness and reduced range of motion, is placed on the same level as one with established ASCVD, even though it represents the leading cause of death in this population. Is this new model really the best approach to improving the lives of people living with obesity?

As defined, clinical and preclinical obesity are very heterogeneous conditions. There is substantial scope for stratification of clinical obesity into different subtypes, potentially based on their clinical presentation or pathophysiology, which should enable better management and understanding.[41] Future research is therefore needed to better characterize obesity and develop scoring systems to aid prognostic assessment, guiding interventions according to the level of individual health risk, particularly benefiting individuals at high risk of mortality, such as those with MONW.

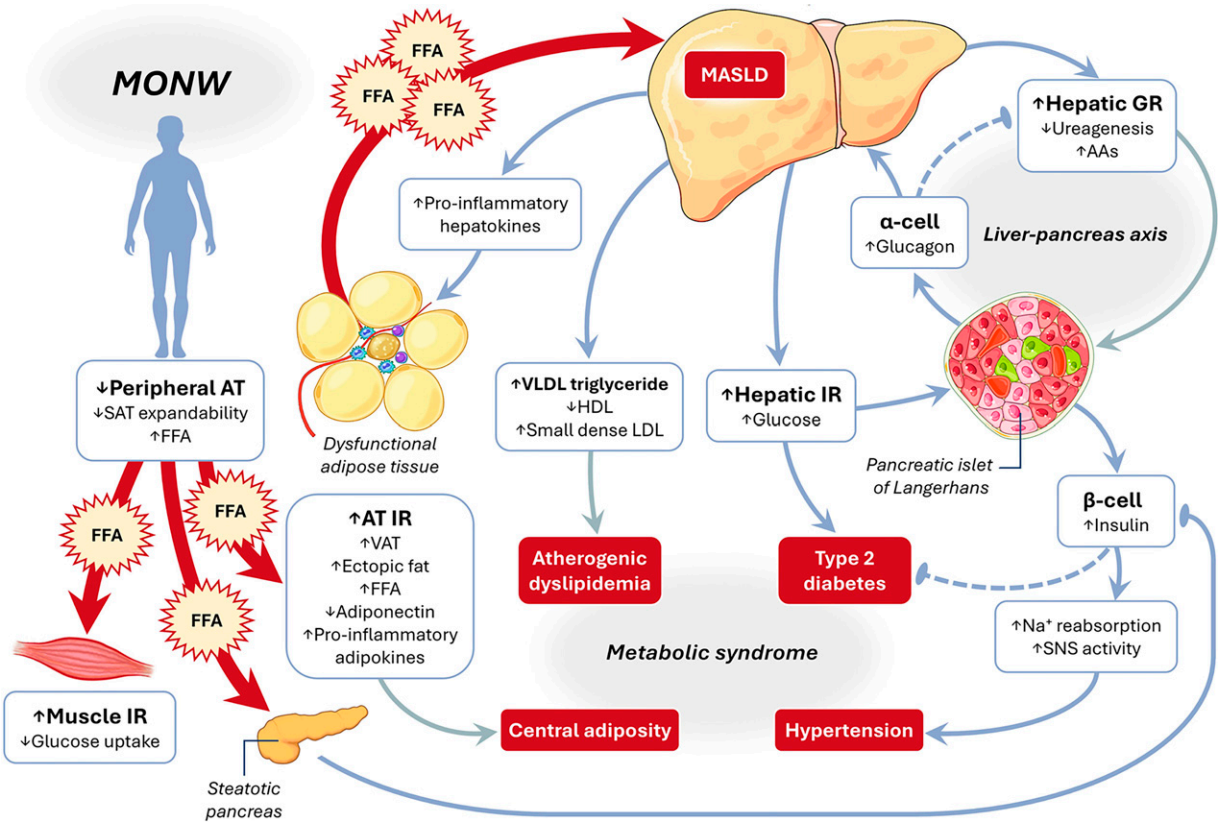

FIG. 3. Pathophysiology of adiposity-related disorders in people with MONW. Individuals predisposed to developing MONW have impaired expansion of SAT, which compromises their ability to store fat. If an unfavorable caloric balance is maintained, leading to weight gain, when the capacity to expand SAT is reached, increased FFAs deposition occurs in visceral and ectopic sites. One ectopic site is the muscle, where increased FFAs deposition promote IR, inhibiting insulin-mediated glucose uptake. On the contrary, AT IR facilitates lipolysis and increases the flux of FFAs to the liver, inducing MASLD, hepatic IR, enhanced glucose production, de novo hepatic lipogenesis, and VLDL biosynthesis. VLDL release translates into hypertriglyceridemia, and through the action of lipoprotein lipase, CETP, and hepatic lipase, LDL particles of high atherogenic potential are formed from VLDL particles. In addition, CETP-mediated multiplied lipid transport generates HDL particles of larger sizes, which are more prone to be degraded, composing the atherogenic dyslipidemia. FFAs spill over into the pancreas, facilitating β-cell dysfunction through lipotoxicity, hyperglycemia, and diabetes. MASLD also promotes hepatic glucagon resistance through amino acid metabolism, reducing ureagenesis and resulting in hyperaminoacidemia. Increased amino acids stimulate glucagon production to compensate for hepatic glucagon resistance, and a vicious cycle occurs (the liver–pancreas axis). This hyperglucagonemia also leads to increased hepatic glucose release. A global IR state results in hyperinsulinemia, which may enhance sodium reabsorption and increase sympathetic nervous system activity, contributing to hypertension. Inflamed dysfunctional AT leads to increased IR, the release of proinflammatory adipokines, and decreased levels of the anti-inflammatory adipocyte-derived hormone adiponectin. In the liver, triglycerides and toxic metabolites induce lipotoxicity, mitochondrial dysfunction and endoplasmic reticulum stress, leading to hepatocyte damage, apoptosis, and fibrosis. These dysfunctional hepatocytes synthesize and secret hepatokines, which promote inflammation in AT macrophages and increased IR. AT, adipose tissue; CETP, cholesterol ester transfer protein; FFAs, free fatty acids; HDL, high-density lipoprotein; IR, insulin resistance; LDL, low-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease; SAT, subcutaneous adipose tissue; SNS, sympathetic nervous system; VAT, visceral adipose tissue; VLDL, very low-density lipoprotein. Pointed arrows indicate stimulation or enhancement, while blunt ends indicate inhibition or repression. Dashed arrows indicate progressive reductions in a pathway. Adapted from Godoy-Matos et al.[35]

Importantly, the advances in the categorization of clinical obesity will allow the selection of therapeutic interventions for obesity that aim to promote benefits beyond simply reducing adiposity. Taking T2D as a model: recent guidelines[42,43] recommend specific interventions for people with T2D considering the presence or absence of cardiorenal complications, such as ASCVD, heart failure, or chronic kidney disease, based on the actions of antidiabetic agents beyond glycemic control. Similarly, there is already antiobesity medication with proven ability to reduce cardiovascular outcomes,[44] and several antiobesity drugs are in clinical development, constituting combinations of entero-pancreatic hormones with different mechanisms of action that will possibly allow personalized treatment plans.[45,46] Thus, if future studies confirm the hypothesis that some of these new antiobesity agents may better serve specific patients subtypes, it could open the door for precision medicine in the treatment of people living with obesity, including those with MONW.

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Authors' Contributions

W.S.S.J.: Conceptualization, Resources, Writing—review and editing, Visualization.

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Abbreviations Used

ASCVD = atherosclerotic cardiovascular disease
AT = adipose tissue
BF% = body-fat percentage
BMI = body mass index
CAD = coronary artery disease
CETP = cholesterol ester transfer protein
CI = confidence interval
DXA = dual-energy X-ray absorptiometry
FFAs = free fatty acids
HDL = high-density lipoprotein
HR = hazard ratio
IR = insulin resistance
LDL = low-density lipoprotein
MASLD = metabolic dysfunction-associated steatotic liver disease
MONW = metabolic obesity with normal body weight
PPAR-γ = peroxisome proliferator-activated receptor-γ
SAT = subcutaneous adipose tissue
SNS = sympathetic nervous system
T2D = type 2 diabetes
VAT = visceral adipose tissue
VLDL = very low-density lipoprotein
WC = waist circumference
WHO = World Health Organization
WHR = waist-to-hip ratio
WHtR = waist-to-height ratio