

'Obesities': Position statement on a complex disease entity with multifaceted drivers

Abstract

- Academic medicine fosters research that moves from discovery to translation, at the same time as promoting education of the next generation of professionals.
- In the field of obesity, the supposed integration of knowledge, discovery and translation research to clinical care is being particularly hampered.
- The classification of obesity based on the body mass index does not account for several subtypes of obesity.
- The lack of a universally shared definition of "obesities" makes it impossible to establish the real burden of the different obesity phenotypes.
- The individual's genotype, adipotype, enterotype and microbiota interplays with macronutrient intake, appetite, metabolism and thermogenesis.
- Further investigations based on the concept of differently diagnosed "obesities" are required.

1 | INTRODUCTION

Medicine has entered a decade marked by unparalleled advances and inspirational changes in science and technology.¹ The focus of academic medicine has to be on providing care for multiple medical problems, fostering research that moves from discovery to translation, at the same time as promoting education of the next generation of professionals. Whilst an unprecedented amount of information has yielded new insights into disease management and health promotion in some areas these novel scientific developments have not reached clinical practice. The increase in non-communicable diseases (NCDs) together with the ageing of the population is generating a phenomenal rise in health care. However, in the field of obesity, the supposed seamless integration of knowledge,

discovery and translation research to clinical care is being particularly hampered. In what follows we discuss the concept of 'Obesities' which encompasses a complex disease entity with multifaceted drivers.

2 | DEFINITION

According to the World Health Organization (WHO), obesity is defined as an abnormal or excessive fat accumulation that presents a risk to health.² However, the diagnosis of obesity is made with a body mass index (BMI) over 30 kg/m². While the BMI is a very useful, simple, and easy to apply assessment, it is only a surrogate measure of fat mass, with adiposity being the really critical body compartment as regards comorbidity development. Therefore, the BMI-based obesity classification does not account for several subtypes of obesity.³⁻⁷ To overcome the limitation of the classical definition of obesity, a new classification of obesities based on different variables, for instance variables related to cardiometabolic risk, is an essential goal to achieve. The lack of a universally shared definition of 'obesities' makes it impossible to establish the real burden of the different obesity phenotypes.

The coexistence of diverse obesity phenotypes has been reported. From the perspective of the body composition and cardiometabolic risk profile,⁸ the heterogeneous phenotypes expand from metabolically unhealthy obesity to the other extreme part of the spectrum comprising the so-called metabolically healthy obesity (MHO) and even the subgroup of individuals with normal weight but characterized by metabolic complications related to excess dysfunctional adiposity.⁷ Noteworthy, among people with a BMI within the normal range (18.5–24.9 kg/m²), who would be classified as normal weight or thin, in our experience as many as 29% present a body fat percentage within the obesity range.⁹ Others have found that about 60% of men and nearly 45% of women with normal weight actually presented adiposity levels within the obesity range.¹⁰ This is

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known as the 'thin outside, fat inside' or TOFI phenotype. The prevalence of the subgroup of individuals characterized by normal weight but with similar cardiovascular (CV) risk factors to people with obesity can also vary from 7% to 20%, depending on the cut points and number of metabolic alterations considered.^{7,11} These metabolically obese but normal weight individuals are characterized by a higher visceral adiposity, hyperinsulinemia, insulin-resistance, dyslipidemia and elevated circulating pro-inflammatory cytokines. Precisely, the early identification of this type of obesity is extremely relevant due to the underestimation of the CV risk by both patients and physicians because of the normal weight and apparent lack of cardio-metabolic risk.

The MHO phenotype is characterized by the subset of people with obesity according to BMI but with an apparently healthy metabolic profile, with a normal insulin sensitivity, lipid and pro-inflammatory cytokine profile.¹² MHO presents a different body fat distribution with a higher cardiorespiratory fitness as well as a lower visceral adiposity, hepatic steatosis and intima media thickness. Although described as a healthy metabolic profile the MHO phenotype is not a harmless condition, especially when contemplated in longitudinal studies in which the transition to the metabolically altered obesity (MAO) phenotype becomes evident.¹³ Noteworthy, in MHO similarly increased cardiometabolic and inflammatory profiles as regards C reactive protein, fibrinogen, uric acid, leukocyte count, and hepatic enzymes to MAO have been observed.¹⁴ Importantly, over 30% of patients classified as MHO according to fasting plasma glucose exhibited impaired glucose tolerance or type 2 diabetes when challenged with an oral glucose tolerance test. Moreover, the profile of classic (leptin, adiponectin, resistin) and novel (serum amyloid A and matrix metalloproteinase 9) adipokines was almost identical in the MHO and MAO groups. In addition, the expression of genes involved in inflammation and tissue remodelling in visceral AT and liver showed a similar alteration pattern in MHO and MAO individuals.¹⁴ It has been also shown that obesity, even if metabolically healthy, accelerates age-related declines in functional ability and poses a threat to independence in older age.¹⁵

In addition, dynamic molecular endophenotypes focusing on postprandial immunometabolic responses can further characterize a personalized, patient-centric approach aimed at identifying early risk. Extensive anthropometric variables as well as beta cell and glucose-insulin axis phenotypes capturing pivotal metabolic features also provide extremely useful information.¹⁶

Sarcopenic obesity (SO) requires particular attention given the demographic characteristics of an ageing population amidst an obesogenic environment.¹⁷ The so-called dynapenic abdominal obesity, characterized by visceral

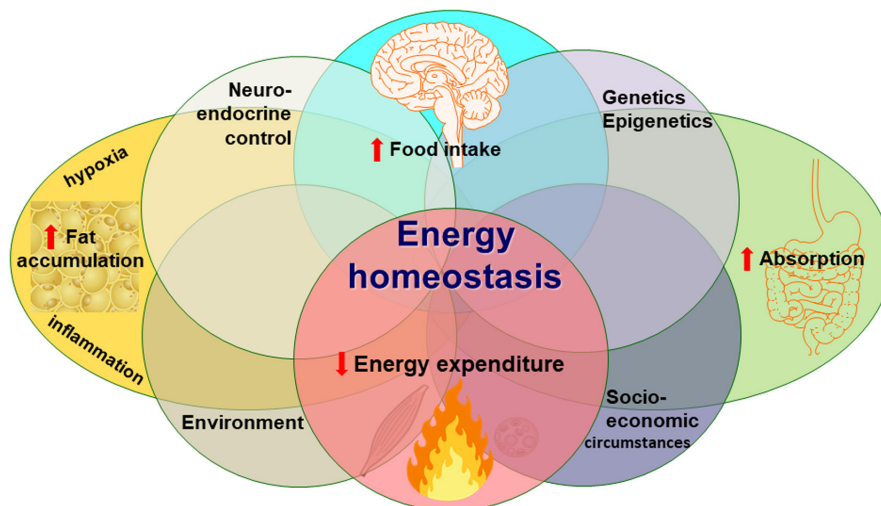
obesity, sarcopenia and muscle weakness is frequently observed in older patients.¹⁸ The combination of low skeletal muscle mass and function together with high fat mass constitutes a particularly relevant phenotype given the aging of the population worldwide.¹⁹ Sarcopenia and obesity partially share the same risk factors including a decline in physical activity, that leads to loss of muscle mass and function as well as to a positive energy balance that causes weight gain. Moreover, the chronic inflammation which characterizes obesity has a catabolic effect on muscle mass, favouring lean mass loss together with an increased risk for development of metabolic alterations, CV diseases (CVD) and for mortality much more than sarcopenia or obesity alone.^{20–22}

3 | CREATING A NEW HOLISTIC DIAGNOSTIC FRAMEWORK

Research has mainly focused on inadequate food intake and reduced physical activity as postulated causes for the increased obesity prevalence rates. However, this simplistic approach does not acknowledge the possibility of potential diverse contributions along the food intake and energy expenditure axes. For instance, in some individuals, an increased food intake may predominate, while in others, a diminished energy expenditure may prevail (Figure 1). The augmented hunger may result from increased orexigenic signals dominating over anorexigenic ones in the hypothalamus, as well as by emotional eating triggered by stress-related events and psychological aspects.^{23,24} In addition to the perceived hunger and stress that influence eating behaviour, at the other end of the energy homeostasis equation, a decreased resting energy expenditure as well as a low adaptive thermogenic response can also determine an obesity phenotype. Likewise, in some people living with obesity an elevated nutrient absorption due to hormonal gastrointestinal secretion and anatomo-histological features may dominate, while in others, an augmented fat accumulation via adipogenesis may preponderate.²⁵ Efficient nutrient digestion and absorption requires sensing by gut enteroendocrine cells, activation of neuroendocrine pathways to regulate gastrointestinal motor, secretory and absorptive functions as well as metabolic control. Furthermore, changes in gut microbiota amount and diversity can perturb the homeostatic humoral and neural pathways controlling energy harvesting.²⁶

Moreover, specific individual adipobiology features like adipose tissue amount, type, distribution and function also need to be contemplated (Figure 1). AT secretes a pleiad of hormones, cytokines, and growth factors, among others, collectively termed adipokines, which play a key role in control of both local and systemic inflammation,

FIGURE 1 Factors influencing energy homeostasis. In the classical Venn diagram, the logical relation between factors shows that energy homeostasis is a balance between fat accumulation, food intake, nutrient absorption, energy expenditure, neuroendocrine control, genetics, epigenetics, environment and socio-economic circumstances. Each factor can also influence single variables



insulin sensitivity and energy homeostasis. Dysfunctional AT synthesizes and secretes an increased number of pro-inflammatory factors, such as tumour necrosis factor- α , IL-6, leptin, and resistin, while the anti-inflammatory molecules adiponectin and omentin are decreased.⁸

Three main AT types can be distinguished, namely white, brown and beige. White AT can be subdivided in subcutaneous and visceral AT. The subcutaneous fat depot is located mainly under the skin all over the body though preferentially in the lower limbs. The increased gluteo-femoral accumulation characteristic of gynoid obesity does not associate with an increased cardiometabolic risk. Visceral AT, on the contrary, is mainly located in the abdomen with its increased deposition being typical of android obesity and associated with an elevated cardiometabolic risk and morbi-mortality.

During periods of energy surplus white AT can enlarge by accumulating triacylglycerols, whereas in response to energy scarcity, it can release glycerol via lipolysis. Adipogenesis and lipolysis contribute to the enormous flexibility and dynamism of AT. In this context, fat accretion underlies the classic balance between β -adrenergic-induced lipolysis as opposed to the insulin-mediated lipogenesis. However, a more complex neurohumoral regulation has to be contemplated. In the last decades adipokines, structural membrane proteins, and protein kinases, among others have been recognized as mediators of lipolysis.²⁷ Leptin, nitric oxide, angiotensin, aquaporins, and Rab18 are good examples of more recently identified further factors participating in the fine-tuning of the lipolytic rate, which may determine individual differences in fat accumulation.^{28–31} Thus, lipolysis needs also to be reconsidered from the wider perspective of the adipobiology phenotype.

When the energy surplus exceeds the hypertrophic and hyperplastic capacity of adipocytes, a spill over of triacylglycerols and free fatty acids to other tissues takes place accumulating as ectopic fat in metabolically noble tissues such as the liver, pancreas, skeletal muscle and heart,

which further adds to the increased cardiometabolic risk profile.

Brown AT is specialized in generating heat and, therefore, exhibits a large amount of mitochondria in line with its thermogenic function. In humans, vestigial depots are located in interscapular, supraclavicular and paravertebral regions being highly vascularized. Noteworthy, obesity and ageing reportedly decrease the amount and function of brown AT.³²

Beige adipocytes exhibit characteristics in between white and brown fat cells. Also called brite AT, resulting from the contraction of 'brown in white',³³ it shows intermediate features as regards gene expression profile resulting from the browning of white adipocytes.

Whilst a pleiad of molecules with quite diverse profiles is involved in energy homeostasis,^{34,35} the existence of additional as yet unidentified factors should not be discarded.^{36,37} Therefore, the individual's genotype, adipotype, enterotype and microbiome interplays with macronutrient intake, appetite, metabolism and thermogenesis. The interactions of the genetic make-up and the other explained personal characteristics condition individualized responses to macronutrients, dietary patterns and lifestyle habits, which represent key factors for the comprehensive and holistic understanding of energy homeostasis and should be considered in the era of precision medicine.³⁸

4 | THE NEED OF A PARADIGM SHIFT

While scientists and policymakers still tend to focus on single initiatives, more should be done to incorporate 'systems thinking' into tackling obesity. More specifically, the independent contribution and recognition of the impact of the socio-economic drivers, and hence much greater acknowledgement of the interactions with the

pathophysiology of the individual were firmly established. The future of our better understanding of obesity needs a personalized model that combines findings in whole-body physiology and genomics (such as endocrinology, nutrition, immunology, genetics, epigenetics, microbiome, and other areas) with a wider reaching integrative and comprehensive approach based on socio-economic circumstances. Without a fundamental paradigm shift in our conceptual models of obesity, the barriers we want to dismantle will be perpetuated.³⁹

To achieve such a paradigm change several steps are required. The opportunity for developing a new model of 'obesities' should not be ignored simply because our views do not fit the prevailing conceptual framework of obesity. Clinicians opened to more nuanced approaches take into account multiple factors and engage varied disciplines — public health, physiology, behavioural science, economics and sociology — to pursue an exciting new path. Thus, embracing complexities and aggregating multiple data sources can be part of the solution. Noteworthy, social determinants of health, constituted by social, psychosocial and economic factors influencing health, exert a relevant role in the pathogenesis of CVD risk and morbi-mortality. Several of the underlying physiological mechanisms linking development of CVD to social determinants of health have been analysed, and encompass inflammation, elevated stress hormones, immune cell activation, and cellular aging.^{40–42}

Transformation is part of the clinical profession, and it is the clinicians' responsibility to look for better ways to care for patients. Although transforming care delivery can feel intimidating, to be successful clinicians need the skills to develop trusting relationships with patients at the same time as sharing evidence-based knowledge with colleagues. In this context, it is important to understand how to enable, lead, and accelerate strategic transformation, while being flexible and nimble in adopting continuous change (Figure 2). Reaching beyond traditional areas to gain expertise that improves the health of patients living with obesity, includes to diversify the clinical approach. Diversity, equity, inclusion, and data analytics also need to be considered in this transformation. A convergence approach tries to overcome a fragmented model of care traditionally organized around silos.

Excess weight is increasingly recognized as a distinct disease entity, due to specific features which apply to gender and comorbidities based on potentially different biological risk factors and clinical behaviour. Moreover, people living with obesity commonly face a pervasive form of social stigmatization, being subject to often discrimination at the workplace and in educational and healthcare settings.⁴³ While weight stigma can reportedly cause physical and psychological harm, affected individuals are less likely to receive adequate care. As recognition of obesities achieves more clearly demarcated entities,



FIGURE 2 Managing process to reach treatment goals. From a strategic point of view, in order to reach treatment goals, we recommend spending time for better understanding the problem, engaging healthcare professionals, identifying resources to sustain the process, defining diagnosis and disease management plan and then targeting the treatment goals

proper assessment, multidisciplinary management for each patient and advocacy will become essential as will new models of collaborative care.

Currently ongoing and planned initiatives, such as making care delivery less episodic, through flexible, nimble, intelligent, continuous, and integrated awareness of when patients need care and what type, are well poised to have a substantial impact on better characterization and enhanced care delivery that will affect people living with obesity, and pave the way to better address the evident gaps in both clinical care and the current understanding of disease biology, as well as their impact on outcomes.⁴⁴ While working towards more comprehensive, accurate, and meaningful pathophysiological-based registries, modelling can be useful for filling gaps of non-existing primary data. Under-reporting or underdiagnosis of excess weight in low-resource settings, underscores the need for optimizing data collection to verify the contribution of specific pathophysiological traits in different socio-economic settings.

Further investigations based on the concept of differently diagnosed 'obesities' are required. A much-needed fresh take on health policies is also necessary to foster progress in combating obesities. Political will can make or break the link between plans and action. However, it takes a collective approach to enact change, with an alignment of minds and policies remaining essential. In resource-restricted settings, financing care is inevitably more challenging than in high-income countries, but with an engaged leadership, progress is also possible. As SARS-CoV-2 continues to overwhelm healthcare systems and the provision of NCD care, prevention, and research worldwide, perhaps the time has never been more ripe for patients, communities and healthcare professionals to truly approach the global burden of obesity.

KEYWORDS

dysfunctional adipose tissue, metabolically healthy obesity, non-communicable diseases (NCDs), Obesity phenotypes, precision medicine, Sarcopenic obesity

ACKNOWLEDGEMENTS

This work was supported by the Spanish Institute of Health ISCIII (Subdirección General de Evaluación and Fondos FEDER project PI19/00785) and CIBEROBN. Funding sources had no role in manuscript writing or the decision to submit it for publication.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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