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Editorial

Metabolic health and weight: Understanding metabolically unhealthy normal weight or metabolically healthy obese patients

Obesity is most commonly defined as a BMI of over 30 kg/m^2. Typical classification is into categories of Class I (BMI >30 kg/m^2), Class II (BMI equal to or over 35 kg/m^2) and Class III (equal to or over 40 kg/m^2), with the latter also known as severe obesity. While this method is most frequently utilized by clinicians, it has limitations — such as in those individuals with high muscle to fat ratios or those of Asian descent. Alternate methods for obesity definition and classification include data such as waist circumference, hip to waist ratio, or body fat percentage.

Using the BMI criteria for obesity, over 600 million people worldwide, including one third of adults in the United States meet criteria for obesity [1]. In the United States, this translates to mounting healthcare costs (estimated close to 128 billion dollars in 2008) and increased mortality compared to normal weight individuals [2]. Cardiovascular disease and secondarily malignancies have long been identified as the primary reason for these increases in mortality and costs. This in turn has been attributed to a worse metabolic profile which includes various combinations of impaired glucose tolerance/type 2 diabetes, dyslipidemia, hypertension and systemic inflammation.

However, hidden among traditional obesity related concerns, there lies a subset of patients without the expected sequelae of their weight. These patients circumvented the classic models of metabolic and cardiovascular risk, and are known as the "metabolically healthy obese" (MHO). Simultaneously, there are individuals who despite having "normal" weights, shoulder an increased burden of these risks. Accurate classifications and mechanistic understandings for individuals with these conditions would be required to ensure the best healthcare and appropriate treatments as well as to decrease healthcare costs due to improper treatments and requisite subsequent medical interventions. Here we discuss the current knowledge surrounding these two groups, and highlight important features for provider management.

Historically, the primary concern regarding obesity was due to the concurrent metabolic and cardiovascular risk. Yet, in recent years increased notice has been made of those individuals who do not fit into this traditional phenotype. Instead, metabolically healthy obese (MHO) and metabolically unhealthy normal weight (MUHNW) patients are generating important discussions regarding the classification of metabolic, and thus cardiovascular risk in patients. These cohorts have been previously highlighted in Metabolism, with discussions in recent years ranging from the association with diabetes, liver enzymes and vitamin D to the role of weight status and inflammation [3–9]. Here we discuss these two phenotypes, and highlight current knowledge regarding their classification, development and management features for healthcare providers.

Presently, beyond cutoffs for surgical intervention, obesity guidelines do not distinguish between management of the various subclasses of obesity despite the fact that there has not been evidence for increased mortality in simple Class II obesity [10]. In fact, while studies have shown that individuals with Grade II-III have greater mortality, there is evidence that Class I obesity patients may have lower all-cause mortality than normal weight patients [11]. Furthermore, existing guidelines also fail to individualize the management of MHO or metabolically unhealthy/abnormal obese (MUHO/MAO) patients. This is further complicated by a gap in the recognition and appropriate management of those normal weight individuals, who demonstrate high risk metabolic risk profiles.

Here we highlight these subtypes of obesity and metabolic profiles for providers, as well as ongoing research in the field.

1. Metabolically Healthy Obese (MHO)

Since 1982, there has been recognition of a group of patients who, despite meeting traditional BMI criteria for obesity, do not demonstrate high risk metabolic profiles. These individuals have been deemed as the "metabolically healthy obese" (MHO) [12–14]. Broadly, this categorization is described as an absence of metabolic disorders such as insulin resistance, type 2 diabetes, dyslipidemia and hypertension in those patients with BMIs greater than 30 kg/m^2[15]. More specific classification schemes vary by study/research group, with variable cutoffs for blood pressure, and cholesterol (HDL, LDL, TC, TG or TG/HDL ratios) [16–18]. Further conflict is introduced by variable definitions for insulin resistance, which can

include fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), and/or homeostasis model assessment (HOMA). For instance, one study showed that over 30% of patients were not correctly diagnosed with impaired glucose tolerance/T2DM when fasting plasma glucose was used as the primary criteria [19]. Thus, clearer and more consistent criteria are needed to determine whether an individual is MHO.

2. Metabolically Unhealthy Normal Weight (MUHNW)/Metabolically Obese Normal Weight (MONW)

In contrast to those metabolically healthy obese, there are also of subsets of patients who are considered "normal/healthy" weight, but demonstrate increased metabolic/cardiovascular risk. However, these patients have been even harder to define or characterize than the aforementioned group. First suggested by Ruderman in the 1980s, these individuals were described as hyperinsulinemic, insulin resistant, hypertriglyceremic and predisposed to subsequent development of type 2 diabetes mellitus and coronary artery disease [20,21]. Broadly, these patients have been categorized by body mass indices of less than 25 kg/m^2, but have metabolic abnormalities more commonly associated with their obese counterparts, including abdominal fat distribution and elevated blood pressure. Most studies set the cutoff as three or more metabolic derangements to fulfill "metabolic unhealthy" definition. More recently, Lee et al. [22] proposed utilizing the TyG index — a product of the fasting blood glucose and triglyceride levels to identify patients who are MONW.

Classification is further complicated by the limitations associated with utilizing BMI in definitions. The metabolically abnormal phenotype has been associated with increased waist circumference and body fat percentage in normal weight individuals, which may not be picked up with standard BMI measurements [23].

In coming years, it will be increasingly important to identify consistent criteria for these metabolic states/body phenotypes. With the ability to accurately and precisely classify these patients, healthcare providers will be better able to assess prevalence and study the predisposing factors for metabolic disease — and target therapies accordingly.

3. Prevalence

Given the inconsistency of MHO definitions, there is high degree of variability surrounding the estimated prevalence of this phenotype. In 2010, one analysis found that the prevalence of MHO varied from 3.3–32.1% in men and 12.2% to 57.5% in women, largely depending on which criteria for MHO patients were applied [18]. Another study found a prevalence of 53.7% for MHO among overweight adults when classified by visceral-to-subcutaneous fat ratio and this further related to lipoprotein subfraction analyses particularly for small dense LDL particles [7]. A study coming out of Korea found that the prevalence was 14.9% in the entire or 47.7% among obese individuals [4]. More recently, a systematic review by Rey-Lopez et al. [24] evaluated 27 prospective studies and found that prevalence ranged from six to 75%, depending on classification scheme used. The prevalence of MHO varies widely depending on how it has been defined, yet again underscoring the importance of establishing a clear definition and criteria.

Without one standardized definition, however, the true prevalence of the MUHNW phenotype is difficult to quantify. Using criteria of two or more metabolic abnormalities, Wildman et al. [25] reviewed NHANES data from 1999–2004 to find that 23.5% of normal weight adults were metabolically abnormal. Similarly, a Korean study, using data from the third national Korean National Health and Nutrition survey, found a prevalence of 8.7% for the MUHNW phenotype [26]. There is some evidence that race may contribute to MUHNW, as for certain races, central adiposity is high despite low overall BMI. One study has shown that Asian Americans have a 5× prevalence of being lean as compared to obese with diabetes mellitus, suggesting that they are more likely to be MUHNW than typically obese [27]. African and Latino Americans had the highest overall prevalence of lean body weight with diabetes in the same study, suggesting higher overall levels of MUHNW, although they showed similar rates with obesity and diabetes, suggesting higher levels of metabolic dysfunction regardless of body weight [27]. These differences are likely due to differences in central adiposity. For instance, lean (defined by BMI) Asian Indians show lower insulin sensitivity than other races of Asian descent but also higher body fat percentage and waist circumference [28]. Similarly, lean Chinese participants have NAFLD which also correlates with higher waist circumference and poorer metabolic outcomes such as blood glucose, blood pressure, and insulin levels [29]. One should keep in mind that for a given BMI, Chinese subjects tend to accumulate fat intra-abdominally and thus even lean subjects may have ectopic fat deposition and intra-abdominal obesity. With varying prevalence, it becomes more difficult to identify at risk populations and subsequently dedicate research into the genetic and lifestyle factors that contribute to their presentations.

4. Genetic Factors

Obesity as a whole has and continues to undergo extensive study into the underlying genetic mechanisms contributing toward its development. Notable findings have been monogenic obesity presentations secondary to disruptions of the POMC, leptin and MCR4 loci [30] in addition to minor contributions by several other genes [31]. In general, overall obesity is a polygenic disorder and gene–environment interactions play a very important role. The genetic and pathophysiologic development of metabolically healthy obesity remains an area of continued study. As suggested before, MHO patients are noted to have less central and visceral obesity. These studies have also alluded to reduced adipocyte hypertrophy, fibrosis and stress as potential contributors to this presentation.

Implicated genes include those involved in transcription related to adipogenesis [32]. With the knowledge that white adipose tissue plays a role both lipid and glucose regulation,