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Review

Metabolically healthy obese individuals: Key protective factors

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ABSTRACT

Objectives: Obesity is a significant quality of life-impairing health problem affecting industrialized nations. However, despite carrying a large fat mass, some very obese individuals exhibit normal metabolic profiles (metabolically healthy obesity). The physiological factors underlying their protective and favorable metabolic profiles remain poorly defined.
Methods: A search of the National Library of Medicine PubMed database was performed using the following keywords: Metabolically healthy obese, metabolically normal obese, insulin resistance, metabolically unhealthy normal weight, and uncomplicated obesity.
Results: This article reviewed factors associated with severe obesity that lacks complications, and suggests putative activities by which these obese individuals avoid developing the clinical features of metabolic syndrome, or the metabolic complications associated with severe obesity.
Conclusions: Despite the knowledge that visceral fat deposition is the seminal factor that ultimately causes insulin resistance (IR) and the detrimental inflammatory and hormonal profile that contributes to increase risk for cardiovascular disease, it remains unknown whether metabolically healthy obesity (MHO) has genetic predisposing factors, and whether MHO ultimately succumbs to IR and the metabolic syndrome, indicating a need for prophylatic bariatric surgery.

Introduction

Obesity (BMI > 30) remains highly prevalent in the US, with approximately 35% of the adult population estimated to be obese [1]. Obesity has become a national health care priority imposing significant cumulative medical complications and costs due to the comorbidities that frequently accompany excessive adiposity. However, a number of obese men and women have been identified who exhibit less visceral adiposity and fewer adverse metabolic disturbances and cardiovascular risk factors than would be expected on the basis of their body mass index (BMI), a condition that has been termed metabolically healthy obesity (MHO) or uncomplicated obesity [2].

Limited data exist concerning the key protective factors accountable for the healthy metabolic profile that is characteristic of MHO. Identifying the characteristics that distinguish individuals with MHO from those obese men and women with metabolic syndrome will contribute to greater understanding of those protective metabolic, genetic, and etiologic factors and may serve to redirect the focus of global approaches to the management of the obese 'at risk' individual. In the preparation of this discussion, a search of the National Library of Medicine PubMed database was performed using the following keywords: Metabolically healthy obese, metabolically normal obese, insulin resistance, metabolically unhealthy normal weight, and uncomplicated obesity.

Obesity and the metabolic syndrome

Extensive central or visceral adiposity is accompanied by a set of comorbidities (the metabolic syndrome) that includes insulin resistance (IR), type 2 diabetes mellitus (T2 DM), hypertension, dyslipidemia, a systemic proinflammatory condition, and cardiovascular disease [3–7]. A cornerstone of the metabolic syndrome, IR is typically accompanied by an increased presence of more atherogenic low-density lipoprotein (LDL) particles, including: lower circulating concentrations of high-density

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lipoprotein-associated cholesterol (HDL cholesterol), elevated circulating concentrations of triacylglycerol (TG), endothelial dysfunction, microalbuminuria, and impaired fasting plasma glucose clearance with elevated fasting plasma glucose concentrations [8,9]. Men are more prone to develop visceral adiposity as a by-product of excessive caloric intake combined with sedentary lifestyles [10], increased activity of the hypothalamic-pituitary-adrenal axis [11], and decreased sympathetic nervous system activity [12,13].

Both the deposition of visceral adipose tissue and the development of IR are associated with an overabundance of portal vein free fatty acids (FFA) [14,15]. Increased influx of FFA to the liver stimulates hepatic production of apolipoprotein B-containing, TG-rich very low-density lipoprotein (VLDL) particles, while hepatic insulin resistance releases VLDL secretion from inhibition by insulin; together, increased FFA supply and VLDL secretion produce hypertriglyceridemia, a predominance of small, dense, cholesterol-depleted LDL particles, and low circulating concentrations of large cholesterol-enriched HDL particles [16,17]. In addition to dyslipidemia, IR results in fasting hyperglycemia (T2 DM) accelerated pancreatic insulin secretion with fasting hyperinsulinemia, and increased sympathetic nervous system activity that contributes to the development of hypertension. Furthermore, visceral adipose tissue is a source of the proinflammatory cytokine, C-reactive protein (CRP), and circulating CRP concentrations are directly correlated with the amount of visceral adipose tissue present as well as with the risks for hypertension, obesity, insulin resistance, and coronary vascular disease [18,19]. Consequently, the metabolic syndrome is the result of several factors acting in concert to produce an unfavorable metabolic profile that promotes the development of chronic degenerative diseases, particularly among the obese.

Metabolically healthy obesity (MHO)

Metabolically healthy obese individuals represent between 10%–45% of the adult obese population, with higher prevalence among younger obese individuals and obese women (differences in diagnostic criteria account, in part, for the discrepancies in prevalence estimates) [20–26]. The absence of insulin resistance or of criteria indicative of the metabolic syndrome, among others, has been proposed as criteria diagnostic for the MHO phenotype [25]. Several studies have identified MHO based on insulin sensitivity using the hyperinsulinemic-euglycemic clamp technique [27–29]; however, this technique is invasive, expensive, and time consuming. The identification of individuals with MHO is hampered by the absence of a standardized definition of the condition.

Despite this ambiguity, MHO is characterized by the absence of at least some of the increased risks for degenerative diseases that accompany typical adult obesity. For example, the relative risks for developing cardiovascular disease in individuals with MHO are not significantly greater than those observed in metabolically healthy non-obese individuals [30,31]. Consistent with these reports, a recent Finnish study that included 61,299 participants that were monitored up to twelve years found that MHO did not increase the risk for myocardial infarction, although the risk for heart failure was greater in men and women with MHO than in metabolically healthy non-obese participants [32]. More importantly, Ortega et al. [33] reported 62% and 57% lower risks for cardiovascular and all-cause mortalities, respectively, in subjects with MHO compared to the risks for subjects exhibiting 'metabolically unhealthy obesity (MUO).' These findings suggest that metabolic health confers a measure of protection against cardiovascular disease in the obese.

Metabolically healthy obesity can be produced by genetic predisposition, lifestyle factors, or a combination of both. Visceral adiposity is a fundamental obstacle to the metabolic health of the obese and causes chronic systemic inflammation, linking obesity with metabolic disease [3–7]. It also appears that variations in inate endocrine functions and responses to nutriture, physical activity (PA), and cardiorespiratory fitness (CRF) interact to facilitate the healthy metabolic profile of MHO. Consistent with the inconsistent descriptions of MHO, the elucidation of the factors or mechanisms underlying this protective profile is far from complete.

Body fat distribution: A clue to the MHO phenotype?

Central obesity, clinically defined by the ratio of waist circumference to hip circumference ($\geq$0.95 in men or $\geq$0.80 in women) or by waist circumference alone and ($\geq$102 cm in men and $\geq$88 cm in women [34]), is associated with metabolic and cardiovascular changes related to the metabolic syndrome [35]. A genetic correlation exists between IR and visceral fat, suggesting that central fat distribution is not only a predictor of IR, but it also shares considerable genetic influence with IR [36]. Janssen [37] recently suggested that waist circumference is a more important determinant of obesity-related health risk than BMI. According to this interpretation, overweight, obese and normal weight persons (according to BMI) with the same waist circumference share comparable risks for developing the components of the metabolic syndrome. In contrast, individuals with normal BMI (and therefore considered to be of normal weight) with excessive waist circumference exhibit metabolic characteristics associated with the metabolic syndrome [38,39]. Could it be that body fat distribution is a cardinal feature determining metabolic fate?

Individuals with MHO have lower visceral adipose tissue content compared with metabolically unhealthy obese individuals [27]. A clue to the etiology of MHO is provided by the results of a morphologic study of women with the

Table 1
Protective factors identified in metabolically healthy obesity versus metabolically unhealthy obesity

Risk factors	Obesity types	
	Metabolically healthy	Metabolically unhealthy
Body fat [41,44]	Peripheral>visceral	Visceral>peripheral
Inflammatory markers profile [45,57]	Decreased circulating concentrations of CRP and α1-antitrypsin	Elevated circulating concentration of CRP, TNF-α, C3, IL-6, and IL-8
Metabolic profile [19,20,30]	Insulin Sensitive, low fasting plasma glucose and insulin, low plasma triacylglycerol, higher high density lipoprotein cholesterol [30]	Insulin Resistance, elevated portal vein free fatty acids, hypertriglyceridemia, elevated small dense low density lipoprotein cholesterol [19,20]
Hormonal profile [85]	Adiponectin is possibly elevated (decreased visceral fat)	Decreased adiponectin levels

CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; IL-8, interleukin 8