The Paradox of Healthy Obesity

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Abstract

Obesity is typically associated with metabolic dysfunction and increased inflammation, which underlie the increased risk for cardiovascular disease, Type 2 diabetes and other metabolic changes seen in obese human subjects. However, not all obese subjects are at increased cardiometabolic risk. Approximately one-quarter of obese adults are considered metabolically healthy, the so-called "healthy obese" or "obese metabolically normal." In these individuals, the obese phenotype may exist in the absence of metabolic abnormalities such as dyslipidemia, insulin resistance, hypertension, and an unfavorable inflammatory profile. Preserved insulin sensitivity appears to be a key mechanism in healthy obesity. Obesity subgroups are likely to provide a useful tool to further study the mechanisms linking obesity to its associated metabolic diseases. More complete metabolic characterization of obese dogs and cats may reveal a similar healthy obese phenotype to that recognized in human subjects. If metabolic subgroups of obese dogs and cats were to be established, veterinarians may be able to better select patients likely to benefit from weight-management programs.

Glossary of Abbreviations
AGEs: Advanced Glycation Endproducts
BCS: Body Condition Score
BF: Body Fat
BMI: Body Mass Index
CI: Confidence Interval
CVD: Cardiovascular Disease
DM: Diabetes Mellitus
ELSA: English Longitudinal Study of Ageing
HOMA: Homoeostasis Model Assessment
HR: Hazard Ratio
MONW: Metabolically Obese Normal Weight
MS: Metabolic Syndrome
RR: Relative Risk

Synonyms for 'Healthy Obese'
Obese Metabolically Normal (OBMN)
Obese Metabolically Healthy (OBMH)
Metabolically Healthy Obesity (MHO)
Metabolically Benign Obesity
Uncomplicated Obesity

Introduction

Obesity represents a major human public health concern as it promotes insulin resistance and is associated with increased risk of developing comorbidities including metabolic syndrome (MS), Type 2 diabetes mellitus (DM), and cardiovascular disease (CVD), leading to an increased risk of premature death and higher all-cause mortality. A range of metabolically healthy and unhealthy obese and nonobese phenotypes has been recognized since the 1980s. Unhealthy obesity is commonly defined as obese individuals who exhibit at least three risk factors for MS, whereas "healthy obese" individuals do not. Recent obesity research has focused on this subset of obese individuals who are metabolically healthy, the so-called obese metabolically normal (OBMN) or metabolically healthy obese (MHO). Normal weight individuals may also have insulin resistance and MS disorders.[1] Such individuals are designated metabolically obese normal weight (MONW). Although the MHO phenotype is now well recognized in human patients, it remains unclear whether metabolic phenotype modifies the morbidity and mortality associated with higher body mass index (BMI).

Early Suggestions of a Metabolically Normal Subtype of Obesity

As summarized by Sims, Vague recognized in 1947 that android obesity, with upper body predominance and pronounced muscle development, was associated with metabolic and cardiovascular disturbances.[2] In contrast, gynecoid obesity, with predominance of lower body fat and less muscular development, mainly presented mechanical and aesthetic problems. In 1954, Albrink reported that upper body obesity, based on measurements of skinfold thickness, was associated with disorders of blood lipids. In 1973, Keyes analyzed the seven available epidemiologic studies of the relationship between overweight and heart attacks.[2] He concluded that "gross obesity is bad," but that much of the propaganda about overweight went beyond scientific justification and resulted in inappropriate therapeutic programs. Shortly after this, Andres reviewed the major population studies of obesity in relation to mortality and suggested that "there are some poorly understood or entirely unknown benefits of mild or moderate obesity" and that "we have to be very cautious in our weight loss goals."[3,4]

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Definition of Healthy Obese

In general, healthy obesity describes the absence of any metabolic disorder including Type 2 DM, dyslipidemia and hypertension in an obese individual. People characterized as MHO have favorable metabolic profiles, characterized by remarkably high insulin sensitivity, no sign of hypertension, and normal lipid, inflammation and hormonal profiles (low triglycerides and C-reactive protein concentrations and high HDL cholesterol and adiponectin concentrations).[5] Beyond these general statements, however, there are no standardized criteria to categorize MHO individuals except for the presence of obesity (BMI ≥30 kg/m^2). Blüher documented a continuous relationship between BMI and insulin sensitivity as determined by glucose infusion rate during the steady state of an euglycemic-hyperinsulinemic clamp in healthy individuals.[6] Accordingly, this author opines that a more precise definition of healthy obesity using specific parameters would imply the existence of a biologically distinct subgroup and disregard the fact that healthy obesity most likely represents the extremes of continuous relationships between increased BMI and different metabolic deteriorations. Regardless, after excluding intermediate phenotypes, the distinction between healthy and unhealthy obesity represents a useful model to study the mechanisms linking obesity to its associated metabolic diseases.

Despite the above argument, the following methods have been used in published studies to identify MHO individuals:[7,8]

1. The euglycemic-hyperinsulinemic clamp (infusion of glucose >8 mg min^{-1} kg^{-1} of lean body mass, upper quartile of glucose disposal rates)
2. The upper quartile of an insulin-sensitivity index derived from oral glucose-tolerance tests
3. Fewer than two cardiometabolic abnormalities (systolic/diastolic ≥130/85 mm Hg, triglycerides ≥1.7 mmol/L, glucose ≥5.6 mmol/L, homoeostasis model assessment [HOMA] >5.13, high-sensitivity C-reactive protein >0.1 mg/L, HDL <1.3 mmol/L)
4. Meeting four of five metabolic factors (HOMA ≤2.7, triglycerides ≤1.7 mmol/L, HDL ≥1.3 mmol/L, LDL ≤2.6 mmol/L, high-sensitivity C-reactive protein ≤3.0 mg/L)

Klöting hypothesized that healthy individuals with insulin-resistant obesity are already metabolically "unhealthy obese" even without the diagnoses of overt Type 2 DM, hypertension and dyslipidemia. They studied differences in a variety of metabolic parameters between 30 insulin-resistant and 30 insulin-sensitive healthy obese individuals, based on glucose-infusion rate during euglycemic-hyperinsulinemic clamps, and strictly matched 1:1 for age, sex, BMI, and total body-fat mass.[9] In the absence of overt DM and dyslipidemia, increased fasting plasma glucose and glycated hemoglobin (HbA_{1c}), as well as higher triglyceride and lower HDL-cholesterol serum concentrations, were associated with insulin-resistant obesity, suggesting that insulin-resistant healthy obese individuals are, indeed, on their way to becoming "unhealthy" obese. On the basis of such data, only individuals with insulin-sensitive obesity are considered to be "healthy obese" by many investigators.

Prevalence of the Healthy Obese Phenotype in Humans

The prevalence of healthy obesity ranges from 10 to 30% in different studies.[2,10,11] The prevalence of insulin-sensitive obesity is not significantly different between age groups in the range of 30 and 75 years.[6] In a study of over 5,000 Korean adults, the MHO phenotype was found in 47.9% of obese subjects and in 15.2% of total subjects.[12] The odds ratio for the MHO phenotype was significantly lower for those at older ages, men, those with less education, and former/current smokers. This study also identified that 12.7% of normal weight subjects were "metabolically obese." The odds ratio for this MONW phenotype was significantly higher for those at older ages, those with less education, those who had moderate alcohol consumption, and those who spent less time participating in moderate-intensity exercise. The investigators concluded that, regardless of metabolic status, health behaviors should be modified to help prevent metabolic syndrome.

Epidemiological Evidence for a Protective Effect of the Overweight Phenotype

Epidemiologic support for a protective effect of the overweight phenotype recently was provided by a very large systematic review that reported all-cause mortality for overweight and obesity relative to normal weight subjects.[5] PubMed searches by the authors yielded 7,034 articles, of which 141 (2.0%) were considered eligible. An EMBASE search yielded two additional articles. After eliminating overlap, 97 studies were retained for analysis, providing a combined sample size of more than 2.88 million individuals and more than 270,000 deaths.

Predefined standard BMI groupings were:
Normal weight (BMI of 18.5-<25)
Overweight (BMI of 25-<30)
Obese (BMI of ≥30)
Grade 1 obesity (BMI of 30-<35)
Grades 2 and 3 obesity (BMI of ≥35)

Random-effects summary of all-cause mortality hazard ratios (HRs) were calculated for overweight and each obese group relative to normal weight individuals in the general population. The summary HRs were 0.94 (95% confidence interval [CI], 0.91-0.96) for overweight, 1.18 (95% CI, 1.12-1.25) for obesity (all grades combined), 0.95 (95% CI, 0.88-1.01) for grade 1 obesity, and 1.29 (95% CI, 1.18-1.41) for grades 2 and 3 obesity. Relative to normal weight, both obesity (all grades) and grades 2 and 3 obesity were associated with significantly higher all-cause mortality. Grade 1 obesity, however, was

not associated with higher mortality, and overweight was associated with significantly lower all-cause mortality, indicating a protective effect for individuals with BMI of 25-<30. Considering that the median BMI in the U.S. population is currently 27.8 for men and 27.3 for women,[13] this powerful study may have broad implications.

A second-meta-analysis evaluating all-cause mortality or CVD, or both, and clinical characteristics of over 61,000 patients was published the same year.[14] The results differed from the conclusions of the Flegel study. Criteria for six patient groups were normal weight (BMI≥18 and <25), overweight (BMI≥25 and <30) and obese (BMI≥30) and metabolic status (healthy/unhealthy, as defined by presence or absence of various criteria of the MS). In this study, MHO individuals had increased risk of mortality and/or CVD compared to metabolically healthy normal-weight subjects *when studies with 10 years or more of follow-up were considered* (RR 1.24, CI 1.02-1.55). Unlike Flegel's study, this study did not stratify obesity into grades, so it is not possible to determine if Grade 1 obese subjects may have differed from the more obese subjects in their MHO cohort.

Why Is the Healthy Obese Phenotype Protective?

Recent studies suggest that inflammation of visceral adipose tissue, ectopic fat deposition (e.g., liver) and adipose tissue dysfunction mediate insulin resistance in human obesity independent of total body fat mass.[7] Mechanisms beyond a positive caloric balance, such as inflammation and adipokine release, likely determine the pathological metabolic consequences in obese patients. Conversely, obese individuals classified as MHO are most likely metabolically healthy due to preserved insulin sensitivity. Data from the European Group for the Study of Insulin Resistance, which included 1,146 men and women ages 18 to 85 years, demonstrate that in nondiabetic, normotensive obese individuals, the prevalence of insulin resistance is relatively low,[11] supporting that preserved insulin sensitivity is a key mechanism in healthy obesity. Despite the differences in the methods used to distinguish between MHO and at-risk obese people in the literature, other recurrent characteristics are observed (in addition to insulin sensitivity), including a favorable lipid profile and lower visceral fat content.

Factors that may contribute to development of healthy and unhealthy obesity are being actively investigated. Recently, an interesting dietary component was described.[15] Advanced glycation endproducts (AGEs), or glycotoxins, are a group of pro-oxidant, cytotoxic compounds that contribute to chronic inflammation and diabetic complications and correlate with factors involved in MS including inflammation and insulin resistance. Although hyperglycemia is traditionally thought to be the major source of AGEs, they also can be diet-derived. AGEs are present in many animal food products, particularly those processed under high heat, as is often the case with Western diets.

A recent study evaluated 130 subjects with MS and 139 subjects without MS to determine if AGEs are a risk factor for MS.[15] Participants were of both sexes and >50 years old. The MS cohort included participants with two or more features of MS. Compared to non-MS individuals, subjects with MS had higher body weight, waist circumference, BMI, percentage BF, diastolic blood pressure, fasting blood glucose, HOMA, and triglycerides but lower HDL-cholesterol. Serum AGEs were markedly elevated in obese people with >1 other MS criteria but not in obese subjects without MS criteria. Serum AGEs directly correlated with markers of insulin resistance (HOMA) and inflammation (including leptin and TNFα) and inversely with adiponectin and other innate defenses. Serum AGEs correlated with dietary AGEs but not with calorie or nutrient consumption or fat mass measures. Consumption of dietary AGEs, but not of calories, was markedly higher in MS than in non-MS. The authors concluded that high serum AGEs, a modifiable risk factor for insulin resistance, may indicate people at-risk for cardiometabolic complications. High dietary AGE consumption and serum AGE levels may link healthy obesity to at-risk obesity.

What Is the Natural Course of Healthy Obesity in Humans?

There are a number of open questions related to the natural course of individuals exhibiting the MHO phenotype. It is not clear whether MHO individuals can maintain insulin sensitivity over their entire lifetime or whether healthy obesity simply represents the delayed onset of obesity-related insulin resistance. Interestingly, it has been shown that longer duration of obesity is associated with better insulin sensitivity independently of BMI.[16] However, Bell, et al., concluded that prospective evidence does not indicate that healthy obesity is a harmless condition.[17] These authors used published prospective studies of Type 2 DM incidence and subjects from the English Longitudinal Study of Ageing (ELSA) to investigate the risk of Type 2 DM among obese adults aged ≥18 years at baseline who were metabolically healthy (defined by BMI and normal cardiometabolic clustering, insulin profile, or risk score). Subjects had a mean follow-up of 5.9 years. Estimates from seven published studies and ELSA were pooled (1,770 healthy obese participants, 98 Type 2 diabetes cases). The pooled adjusted relative risk (RR) for incident type DM was 4.03 (95% CI = 2.66–6.09) in healthy obese adults and 8.93 (6.86–11.62) in unhealthy obese compared with healthy normal weight adults. Although there was between-study heterogeneity in the size of effects, RR for healthy obesity exceeded one in every study, indicating a consistently increased risk across study populations. The authors concluded that MHO adults show a substantially

increased risk of developing Type 2 DM compared with metabolically healthy normal weight adults. Such studies are leading to acceptance that diagnosis of MHO at one time point does not (always) translate into a lifelong reduced cardiometabolic risk though maintained MHO is clearly beneficial for reduced cardiovascular risk.

The causal factors leading to transitions between the healthy and the unhealthy obese phenotype are poorly understood. Noteworthy, bariatric surgery in morbidly obese patients results in long-term weight loss and improvement and/or remission of metabolic diseases and comorbidities, suggesting that the unhealthy obese phenotype can be reversed, at least in selected patients. Recently, there has been consensus that normalization of adipose tissue function and improved "adiposopathy" may explain the beneficial effects of bariatric surgery on obesity-related disorders.

Why Might Recognition of the Healthy Obese Phenotype Be Important?

The prevalence of obesity is increasing worldwide, with the condition predicted to affect more than 1 billion people by 2030.[18] With the MHO phenotype representing approximately one-quarter of all obese individuals, it is clear that a "one size fits all" approach to obesity management ignores the large degree of heterogeneity among obese subjects. A better understanding of metabolically benign obesity has important implications for medical education and clinical research. Education of health-care professionals about the different approaches to subsets of obese individuals is important. In clinical research, data from cohorts mixing at-risk individuals with those with metabolically benign obesity might be difficult to interpret. In addition, novel anti-obesity treatment strategies targeting adipose tissue dysfunction are needed.

Recommendations for obesity treatment should distinguish the metabolically "healthy" from "unhealthy" obese phenotype to permit early identification of the obese person who will benefit the most from weight loss. "Healthy obese" individuals may not significantly improve their cardiometabolic risk by weight loss and, therefore, may not benefit to the same extent as obese patients with metabolic comorbidities from early lifestyle, bariatric surgery or pharmacological interventions. In one study, at-risk obese and MHO women were placed on a six-month restricted caloric diet.[19] Insulin sensitivity improved by about 26% in at-risk obese subjects but deteriorated by about 13% in MHO individuals. Future studies need to investigate the effect of exercise training on the metabolic profile of MHO subjects.

The Obesity Paradox

The "obesity paradox" is well recognized in human medicine. Patients with chronic kidney disease, end-stage renal disease, chronic obstructive pulmonary disease, rheumatoid arthritis, acute heart failure, chronic heart failure, and acute myocardial infarction who are overweight or obese have improved survival when compared to those who are normal weight or underweight.[20] The paradox arises as many studies have shown obesity to be one of the factors contributing to the development of these disorders in the general population. The key question is whether the better prognosis is caused by the higher BMI or by other factors that are noncausally associated with the BMI. Several theories have been advanced to try to explain the mechanism by which overweight and obesity exert a protective effect in these diseases. It is known that overweight/obese patients are younger, receive more aggressive pharmacological intervention, and differ in other characteristics. Altered adipokine profiles and neurohormonal alterations may play a role. One important explanation for the obesity paradox is that obesity reflects higher muscle mass, or lack of cachexia, because obese people not only have more adipose tissue compared to lean people but also more lean-body mass. Muscle loss has a detrimental effect in a variety of diseases. Therefore, the extra lean-body mass associated with obesity may provide a greater reserve in catabolic diseases.

Most studies on the obesity paradox have evaluated short-term (e.g., 30 day), all-cause mortality during follow-up. A recent study focused on both short-term mortality (30 day) and long-term mortality (follow-up for at least two years [median 32.1 months, range 0 - 77.5 months]) after acute heart failure.[21] The obesity paradox held up even with long-term follow-up.

Despite recognition of the obesity paradox, weight reduction may be recommended in the management of some chronic conditions, such as chronic heart failure. Due to the lack of evidence-based medicine about the benefit of weight reduction in such circumstances, the obesity paradox remains an important topic of clinical research.

The obesity paradox has been investigated to a limited extent in dogs and cats. In cats with heart failure, low body weight was associated with shorter survival times compared to cats with moderate or high body weight.[22] In this study, cats with the highest body weights also had reduced survival times, suggesting a U-shaped relationship between body weight and survival. Dogs with heart failure that gained body weight had longer survival times compared to those that lost or maintained weight, but there was no association between body condition score (BCS) and survival.[23] Higher BCS at the time of diagnosis was associated with improved survival in dogs with acquired chronic kidney disease.[24] Dogs classified as underweight at the time of diagnosis (BCS = 1–3 of 9, median survival = 25 days) had a shorter survival time compared to that in both moderate (BCS = 4–6, median survival = 190 days) and overweight dogs (BCS = 7–9, median survival

= 365 days). There was no difference in survival between moderate and overweight dogs.

Does the Healthy Obese Phenotype Exist in Companion Animals?

Obese pets develop some, but not all, of the metabolic complications seen in obese human subjects. For example, obese cats are at increased risk for developing DM,[25] and obesity is associated with insulin resistance in dogs and cats.[26-28] Life span is shortened in obese dogs compared to their lean counterparts.[27] Such similarities in disease relationships in obese individuals across species suggests that the MHO phenotype may be identified in companion animals. At this time, however, lack of a clinically applicable method to assess insulin sensitivity limits the ability of investigators to establish metabolic subgroups of obese dogs and cats. This may prove a fruitful area of future investigation.

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