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METABOLICALLY HEALTHY OBESITY

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ABSTRACT

Obesity is a disease whose incidence is increasing day by day and is accepted as the pandemic of the 21st century. In addition to genetic factors that cause obesity, the main causes are a diet containing high-energy foods, rich in saturated fat and simple sugar, and a sedentary lifestyle. Obesity does not only affect the individual physically, but also brings along many metabolic problems. However, metabolic health problems may not be seen in every obese individual. Although there are many factors underlying this concept, which is defined as "metabolically healthy obesity", not all of them have been fully elucidated. Although the lack of general diagnostic criteria prevents definitive information on the prevalence of metabolically healthy obesity, it is known that individuals with this phenotype are more advantageous in terms of cardiometabolic risk. Metabolic and cardiovascular abnormalities should be considered to reduce the risk of early death, cardiovascular diseases, type 2 diabetes and cancer in all individuals with obesity. Researches in this article should enlighten determinants and modifiable risk factors for better prevention of metabolic healthy obese to metabolic unhealthy obese conversions and manifestations.

KEYWORDS: Obesity, metabolically benign, metabolic syndrome, overweight

METABOLİK OLARAK SAĞLIKLI OBEZİTE

ÖZET

Obezite, gün geçtikçe insidansı artan ve 21. yüzyılın pandemisi olarak kabul edilen bir hastalıktır. Obeziteye neden olan genetik faktörlerin yanı sıra esas nedenler yüksek enerjili besinleri içeren, doymuş yağ ve basit şekerden zengin beslenme tipi ve hareketsiz yaşam tarzıdır. Obezite, bireyi sadece fiziksel olarak etkilemez, birçok metabolik sorunu beraberinde getirir. Ancak, her obez bireyde metabolik sağlık sorunları görülmeyebilir. "Metabolik olarak sağlıklı obezite" olarak tanımlanan bu kavramın altında birçok faktör yatmakla birlikte hepsi tam olarak aydınlatılamamıştır. Genel geçer tanı kriterlerinin olmaması, metabolik olarak sağlıklı obezite prevalansı hakkında kesin bilgiye ulaşılmasını engellese de bu fenotipe sahip bireylerin kardiyometabolik risk açısından daha avantajlı olduğu bilinmektedir. Obezitesi olan tüm bireylerde erken ölüm, kardiyovasküler hastalıklar, tip 2 diyabet ve kanser riskini azaltmak için metabolik ve kardiyovasküler anormallikler göz önünde bulundurulmalıdır. Bu makalenin ele aldığı araştırmalar, metabolik sağlıklı obezlerden metabolik sağlıksız obezlere dönüşüm ve tezahürlerin daha iyi önlenmesi için belirleyicileri ve değiştirilebilir risk faktörlerini aydınlatmalıdır.

ANAHTAR SÖZCÜKLER: Obezite, metabolik olarak iyi huylu, metabolik sendrom, fazla kilolu

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INTRODUCTION

Obesity is a worldwide epidemiological disease characterized by an increase in fat mass, particularly visceral fat. Obesity can cause health problems such as hypertension, cardiovascular diseases, diabetes, cancer, sleep apnea, and osteoarthritis through various mechanisms (1). However, there are also individuals who have a high degree of obesity and can be considered metabolically healthy (2). In this review, individuals defined as metabolically healthy obese and the different criteria used to diagnose metabolically healthy obesity (MHO) were examined. In addition, the mechanisms underlying the metabolically healthy obesity phenotype were examined while the health status of individuals with the MHO phenotype and other individuals were compared.

METABOLICALLY HEALTHY OBESITY

From the data of the World Health Organization (WHO) in 2016 related to obesity increase, it is seen that 39% of adults worldwide are classified as overweight and 13% as obese (1). Obesity is a problem that occurs with a positive energy imbalance because of the body getting more energy than the energy expended. This excess energy is stored in the host's fat storage, causing cell growth and disruption of its functions (3). Growing fat cells reveal the physical effects of obesity. Its metabolic effects are revealed by the cytokines released from these fat cells. Enlarged fat cells produce biologically active substances called adipokines, which have anti-inflammatory and pro-inflammatory effects. The proinflammatory adipokine family includes factors such as leptin, resistin, visfatin, lipocalin 2, and interleukin-18 (IL-18). An increase in these factors leads to the development of chronic inflammation, deterioration of glucose metabolism, and insulin sensitivity mechanisms (4).

Obesity can cause health problems such as hypertension, cardiovascular diseases, diabetes, cancer, sleep apnea, and osteoarthritis through various mechanisms (1). However, the "fatter, more metabolic disease" paradigm does not always hold. Despite a high degree of obesity, there are obese and morbidly obese individuals who can be considered healthy, and these individuals are called "metabolically healthy obese (MHO)" (2). Depending on the difference in the criteria used, the prevalence of this phenotype is thought to be between 10% and 34%. Although it is more common in women than men, its incidence decreases with age in both genders (5). Overall, the metabolic and cardiovascular risks associated with obesity are concerning. However, in recent years, it has been observed that fat storage is not the only determinant of obesity in individuals who do not fit the general phenotype. Consequently the term "adiposopathy" began to be used (2).

CRITERIA FOR METABOLICALLY HEALTHY OBESITY

Obesity is characterized by a body mass index (BMI) greater than 30 kg/m^2 and an increased proportion of fat. In addition, waist circumference, which varies by gender and ethnicity, is used to define abdominal obesity, and body fat percentage is used to define general obesity, but there are some limitations. Waist circumference is associated with visceral adipose tissue but does not reflect the whole body fat distribution. BMI cannot distinguish between lean and fat body mass, and people with short or muscular stature may then be misclassified (6).

MHO is characterized in most studies as obesity with a BMI ≥ 30 kg/m^2 but in the absence of metabolic diseases. However, there are no accepted criteria to define MHO individuals. (7). The absence of a standard diagnostic criterion makes it difficult to identify patients with MHO. Various approaches have been used to identify and define the MHO phenotype. These approaches are reviewed in Table 1.

Another marker that is becoming increasingly important in the MHO phenotype is fatty liver. Comparing MHO patients with metabolically unhealthy obese (MUO) patients, nonalcoholic fatty liver disease is lower in the MHO phenotype (8). Based on current knowledge, the MHO classification is associated only with metabolic or cardiovascular complications. The current literature does not associate obesity with orthopedic problems, pulmonary complications, or other physiological conditions (2).

MECHANISMS EXPLAINING THE PRESENCE OF METABOLICALLY HEALTHY OBESITY

a. Subclinical Inflammation

Inflammation increases insulin resistance (IR). Increased adipose tissue inflammation is associated with an increased risk of type 2 diabetes mellitus (T2DM), cardiovascular disease, and fatty liver. However, metabolic risk is reduced in obese individuals without adipose tissue inflammation. It is believed that subclinical

inflammation may be one of the underlying mechanisms in determining whether a person is MHO or not (2).

Subclinical inflammation is associated with IR. C-reactive protein (CRP) is one of the best markers of vascular inflammation and metabolic syndrome (9). There is a notable relationship between CRP levels and body composition. Accordingly, CRP has been suggested as a screening tool to evaluate the risk of metabolic syndrome in young people (10).

In adulthood, the MHO phenotype has been associated with low levels of the three complementary components, CRP, tumor necrosis factor-α (TNF-α), IL-6, a lower number of white blood cells, and a more favorable inflammatory state than in non-MHO individuals (16). Other inflammatory markers include free fatty acids and peripheral leukocytes. Therefore, IL-6, free fatty acids, absolute peripheral leukocyte count, and glycerol levels are higher in the blood of obese patients with T2DM than in those of obese patients without T2DM (17).

b. Expansion Capacity of Adipose Tissue

Studies have proposed the "adipose tissue extensibility hypothesis" to explain the transition from normal adipose tissue to adipose tissue, which leads to metabolic abnormalities. This hypothesis postulates that when adipocytes reach the threshold level for storage, they begin to increase IR by lipotoxicity and adipokine release. This hypothesis has been supported by studies such as models of lipodystrophy and, changes in adipokine secretion following saturation of adipose tissue. In addition, while investigating this hypothesis, genetic factors contributing to the pathways of adipogenesis, apoptosis, and angiogenesis were better defined (2).

Another theory attributes the differences between individuals with MHO and MUO to the differential capacity of adipose tissue to adapt to excess energy (18). In cases of increased fat storage, the storage capacity of adipose tissue must increase, which may increase the size or number of adipocytes. In addition, this increase fat should be accompanied by increased vascularization.

Table 1. MHO Diagnostic Criteria (6)

	Aguilar-Salinas (11)	Karelis (12)	Meigs (13)	Wildman (14)	NCEP ATP III (15)
Blood pressure (mm/Hg)	SBP<140 and DBP<90 or no treatment	-	SBP≥130 and DBP≥85 or treatment	SBP≥130 and DBP≥85 or treatment	SBP≥130 and/or DBP≥85
TG (mg/dl)	-	≤65	≥65	≥65	≥65
LDL-c (mg/dl)	-	≤100 and no treatment	-	-	-
HDL-c (mg/dl)	≥40	≥50 and no treatment	<40 (Male)	<40 (Male)	<40 (Male)
			<50 (Female)	<50 (Female) or treatment	<50 (Female)
Total-c (mg/dl)	-	≥200	-	-	
FPG (mg/dl)	<126	-	≥100 or treatment	≥100 or treatment	≥100
HOMA	-	≤1.95	-	>90. percentile	
Other	-	-	Waist circumference for men >102 cm	CRP>3.0 mg/L	Waist circumference for men>102 cm
			Waist circumference for women >88 cm		Waist circumference for women>88 cm
MH criteria	All	At least 4 of them	At above 2 of them	At above 1 of them	At above 3 of them

(ATP III: Adult Treatment Panel III, CRP: C-reactive protein, DBP: Diastolic blood pressure, FPG: Fasting plasma glucose, HDL-c: High density lipoprotein cholesterol, HOMA: Homeostatic model assessment, LDL-c: Low density lipoprotein cholesterol, MH: Metabolically healthyı, NCEP: National Cholesterol Education Program, SBP: Systolic blood pressure, TG: Triglyceride, Total-c: Total cholesterol)

Metabolic diseases occur in people who have difficulty expanding the adipose tissue in the most healthy way. This is observed in people with MUO who are unable to maintain appropriate storage capacity (19). However, loss of expansion capacity can occur even in normal-weight individuals. This theory explains the existence of metabolically unhealthy lean individuals. In addition, the lack of expansion capacity of adipose tissue has been associated with loss of primary lipogenic function and formation of lipotoxic products (20).

Contrary to what was previously thought, fat tissue can hyperplasia throughout life, with stem cells. Protoadipocytes in stem cells are progenitor cells that differentiate into mature adipocytes through a complex gene expression program (21). Another variable directly related to the total number of fat cells is cell death, which can occur in various ways (22). In summary, factors directly related to the expansion and functionality of adipose tissue are lipogenesis, adipogenesis through stem cells, apoptotic and anti-apoptotic pathways, and angiogenesis (2).

Adipose tissue has several compartments, and these have different links with metabolic diseases. Visceral and intrahepatic fat are directly related to obesity, whereas subcutaneous fat is not directly related to metabolic disease. Another hypothesis is that the salutiferous way to accumulate fat is through the expansion of subcutaneous fat. According to this hypothesis, when this capacity decreases or disappears, fat accumulation must shift to other compartments. This situation leads to metabolic diseases (23).

c. Other Possible Mechanisms

A new potential factor to explain the differences between MHO and MUO might be circulating microRNA. IR in peripheral organs such as the liver may develop because of toxic stimuli. It induces IR in these tissues by initiating the secretion of IR-associated microRNAs in muscle and fat cells (24).

Adiponectin secreted from adipose tissue is a protein that has protective properties against obesity-related diseases, particularly T2DM and cardiovascular diseases (25). In a study, it was found that 20% of individuals with BMI over 40 kg/m^2 had adiponectin levels above the average of individuals with normal BMI. This result shows that adiponectin plays a vital role in the pathogenesis of obesity-associated metabolic complications. Individuals with the MHO phenotype have similar adiponectin levels as normal weight individuals (11). In addition, individuals with the MHO have lower visceral fat, fatty liver, and muscle fat content than obese individuals without MHO or obese individuals with IR. This suggests that MHO is related to an increased ability to seize free fatty acids in adipose tissue. These differences in body composition between individuals with and without MHO are also consistent across sexes (8).

Lifestyle factors such as physical activity level or cardiorespiratory status also seem to play an important role in determining whether an individual has MHO or not. Individuals with the MHO have a higher level of physical activity than individuals with the MUO phenotype. Similarly, occupational physical activity or leisure physical activity is important because the two exercise regimens are differently related to obesity and IR (26).

METABOLICALLY HEALTHY OBESITY AND METABOLICALLY UNHEALTHY OBESITY

Obesity is a long-lasting, relapsing, and progressive disease (1). Individuals in long-term obesity treatment programs may undergo cycles of weight loss and weight gain as their phenotype changes from MUO to MHO and back to MUO. In general, subcutaneous fat distribution is observed in the MHO phenotype, whereas visceral and intrahepatic adiposity is observed in the MUO phenotype. In the MHO phenotype, adiposity is observed in the leg region, and abdominal obesity is observed in the MUO phenotype. Hyperplasia is seen in the MHO phenotype, and the fat cells are small. However, hypertrophy is more common in the MUO phenotype.

The MUO phenotype has a low degree of chronic inflammation and is usually IR (27).

In the Multi-Ethnic Study of Atherosclerosis (MESA), almost 50% of participants initially identified as having MHO developed metabolic abnormalities during the approximately 12-year follow-up period (28). Supporting this finding is a meta-analysis of 12 studies involving more than 5900 individuals over a follow-up period of 3 to 10 years, showing that almost half of the participants classified as MHO developed at least 1 metabolic abnormality (29). The MHO phenotype can be seen in any age group, but the prevalence of MHO has been found to be lower in increasing age groups (30). The decreased prevalence of MHO in postmenopausal women compared with premenopausal women suggests that changes in

sex hormones may play a role in the transition from MHO to MUO (31).

The northwest Adelaide Health Study included males and females over 18 years of age, 51% of whom were female (n=3743). When the participants were re-examined 10 years later, it was reported that 16% changed from MHO to MUO, regardless of gender. The persistence of MHO was associated with younger age, lower waist circumference, greater peripheral fat distribution in women, and positively associated with diabetes and cardiovascular disease (32). Finally, 30-year follow-up data from 90257 participants in the Nursing Health Study confirm the frequent shift from the MHO phenotype to the MUO phenotype, and this study demonstrates a decline in metabolic health with age across all BMI ranges (33).

When all these data are considered, longitudinal studies show that metabolic health is not a stable state; it is not only dependent on obesity but, can also deteriorate with aging. On the other hand, MUO can also be considered as a temporary feature that can be converted to MHO with targeted interventions (27).

DISEASE RISK IN METABOLICALLY HEALTHY OBESITY

Obesity significantly increases the risk of developing T2DM and cardiovascular disease (13). Because the augmented cardiometabolic risk in obese individuals may be accompanied by metabolic and cardiovascular abnormalities, it has been hypothesized that people with MHO are protected against T2DM, atherosclerotic cardiovascular disease, and even death from all causes (34). Meta-analyses of prospective studies have steadily shown that MHO is associated with a significantly lower incidence of T2DM and cardiovascular diseases (33).

Individuals with MHO were not at risk of developing cardiovascular disease compared with metabolically healthy normal weight (MHNW) individuals (13). However, studies with longer follow-up periods (>15 years) have reported that individuals with the MHO phenotype are at increased risk for major cardiovascular disease events compared with individuals with the MHNW phenotype (35). Recently, researchers who systematically examined the relationships between BMI and metabolic status and total mortality and cardiovascular events reported that individuals with the MHO phenotype are at higher risk for cardiovascular diseases compared with individuals with the MHNW phenotype. It was also concluded that obese individuals are at a higher risk for adverse long-term outcomes, even in the absence of metabolic abnormalities, compared with individuals with the MHNW phenotype (36). In a study evaluating the prevalence of elevated plasma high-sensitivity C-reactive protein (hs-CRP) levels and hepatic steatosis in MHO, MHNW, and metabolically unhealthy normal-weight (MUNW) individuals, both high plasma hs-CRP levels and hepatic steatosis were found to be higher in MHO and MUNW individuals. However, it was most frequently observed in individuals with the MHO phenotype. This suggests that obesity is not completely good in the absence of metabolic risk factors, but is associated with subclinical vascular inflammation (37).

In summary, evidence has accumulated in recent years to support the notion that obesity has harmful long-term consequences on cardiometabolic health, even in individuals with MHO. Although MHO is associated with a significantly lower risk than MUO, it does not protect against cardiometabolic disease (27).

CONCLUSION

MHO is a concept derived from clinical observations that a subset of people with obesity does not exhibit overt cardiometabolic abnormalities. People with MHO have a lower risk of developing cardiometabolic disease than those with MUO. However, metabolic and cardiovascular abnormalities should be considered to reduce the risk of early death, cardiovascular diseases, T2DM, and cancer in all obese individuals. Prospective research should identify determinants and modifiable risk factors for better prevention of MHO to MUO conversions and manifestations. In addition, the possible effects of fat distribution, body composition, subcutaneous adipose tissue extensibility, and genetic factors potentially contributing to MHO should be investigated.

Ethical Approval

Ethics committee approval is not required for review articles.

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