Mini Review article

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Metabolically healthy obesity: Is it really benign?

Nikolaos Kourris, Konstantinos Tziomalos

First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece

ABSTRACT

Recently, a subgroup of patients with obesity but without cardiometabolic abnormalities has attracted considerable attention and has been characterized as metabolically healthy obese (MHO) patients. MHO is quite prevalent among patients with obesity. Even though these subjects have less pronounced metabolic abnormalities compared with patients with metabolically unhealthy obesity (MUO), they are at increased risk for progressing to MUO and for developing cardiovascular disease. Accordingly, diet, exercise and appropriate pharmacotherapy should be recommended to patients with MHO as strongly as in those with MUO.

KEY WORDS: *Obesity, metabolically healthy obesity, cardiovascular risk, metabolic syndrome*

Undoubtedly, obesity represents one of the most important public health problems[1]. In the last decades, a steady increase of its prevalence has been observed and it is expected that by 2030 over a billion people are going to suffer from its consequences[1]. Indeed, obesity is a major risk factor for type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD) and various types of cancer[2]. However, over the past years, a subgroup of patients with obesity that has been coined metabolically healthy obese (MHO) has attracted the attention of the medical community[3]. Despite the interest on this subset of patients with obesity, there is still no clear, uniform definition of MHO[3]. A frequently used definition of MHO is obesity without any of the diagnostic criteria of the metabolic syndrome (MetS), i.e. high blood pressure, high levels of triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C) and high levels of glucose[3]. The absence of insulin resistance and normal high-sensitivity C-reactive protein (hsCRP) levels has also been used to distinguish between MHO and metabolically unhealthy obese (MUO) individuals[3]. The exact prevalence of MHO is also unclear and varies between studies, ranging between 10 and 40% of the patients with obesity[4].

Subjects with MHO display a more favourable metabolic profile than patients with MUO[5]. Indeed, the former are more insulin sensitive and have lower glucose and insulin levels[5]. Furthermore, some studies reported lower HbA_{1c} levels in MHO subjects[5]. Regarding the lipid profile, patients with MHO have lower triglyceride, oxidized low-density lipoprotein cholesterol (LDL-C) and free fatty acid levels than patients with MUO, whereas the concentration of HDL-C is higher in the former[5]. Waist circumference is also smaller in MHO individuals[5]. Transaminase and gamma-

Corresponding author:

Konstantinos Tziomalos, MD, PhD,
Associate Professor of Internal Medicine
First Propedeutic Department of Internal Medicine,
AHEPA Hospital
1 Stilponos Kyriakidi Street, Thessaloniki, 54636, Greece
Tel.: +30 2310 994621
E-mail: ktziomalos@yahoo.com

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glutamyltransferase levels, i.e. markers of NAFLD, are also lower in these patients than in subjects with MUO[5]. Levels of several markers of subclinical inflammation, including hsCRP, interleukin-6, tumor necrosis factor α and white blood cell count are also lower in patients with MHO[5,6]. In addition, levels of adiponectin, an insulin-sensitizing adipokine, are elevated in these patients whereas leptin levels are lower[5,7].

Several factors appear to protect against the development of adverse metabolic characteristics in patients with obesity, giving rise to the MHO phenotype. Increased birth weight and early weight gain appear to predispose to the MHO profile[8]. Early onset of obesity also appears to be related to MHO, particularly in women[8]. Female gender also appears to confer protection against development of MUO[4,8]. Younger age, African ancestry and a healthier lifestyle, including more vigorous physical activity, no smoking, lower consumption of red meat and higher ratio of monounsaturated to saturated fatty acids in the diet also appear to be associated with MHO in patients with obesity[3]. In contrast, greater mass of visceral and ectopic fat as well as hypertrophy, dysfunction and inflammation of the adipose tissue contribute to the development of MUO, by affecting the balance between insulin-sensitizing adipokines and adipokines promoting insulin resistance[3]. It has also been suggested that MHO subjects have greater ability to expand the subcutaneous adipose tissue, which is insulin-sensitive[3]. Finally, genetic factors also appear to be implicated in the favourable metabolic profile of MHO, including the fatty mass and obesity (FTO) gene and loci near the insulin receptor substrate 1 and the sprouty homolog 2 genes[9].

A critical question pertaining to MHO is whether these patients are at risk for developing MUO. In a meta-analysis of 12 cohort studies (n = 32,117), 49% of subjects with MHO developed at least 1 metabolic disorder within 10 years. Moreover, subjects with MHO had 80% greater risk for developing a metabolic disorder than metabolically healthy subjects with a normal body mass index (BMI)[4]. In another meta-analysis of 14 cohort studies (n = 140,845), patients with MHO had 4.1 times greater risk for developing T2DM than metabolically healthy subjects with normal BMI[10].

Even though some patients with MHO will not develop metabolic disorders, MHO per se appears to be associated with increased cardiovascular risk. In a systematic review of 6 studies, patients with MHO (without MetS or insulin resistance) had greater carotid intima-media thickness and more severe coronary artery calcification than metabolically healthy subjects with normal BMI[11]. In a meta-analysis of 22 prospective studies (n = 584,799), patients with obesity without MetS had 45% higher risk for cardiovascular events than subjects without MetS but with normal BMI[12]. In addition, in another meta-analysis of 97 cohort studies (n = 1,800,000), only 50% of the excess risk for coronary heart disease in patients with obesity was due to the presence of T2DM, dyslipidemia or hypertension, suggesting that MHO is also associated with increased cardiovascular risk[13].

Given the high risk of patients with MHO to progress to MUO and to experience cardiovascular events, aggressive and multifactorial management aiming at weight loss and at control of metabolic comorbidities is essential. However, in a meta-analysis of 12 studies (n = 1,827), diet induced smaller reductions in body weight, blood pressure and trigluceride levels in patients with MHO than in those with MUO and also had no effect on insulin resistance and on glucose and hsCRP levels[14].

In conclusion, MHO is quite prevalent among patients with obesity. Even though these subjects have less pronounced metabolic abnormalities compared with patients with MUO, they are at increased risk for progressing to MUO and for developing CVD. Accordingly, diet, exercise and appropriate pharmacotherapy should be recommended to patients with MHO as strongly as in those with MUO.

Conflict of interest

None to declare.

ΠΕΡΙΛΗΨΗ

Μεταβολικά υγιής παχυσαρκία: Είναι πράγματι αβλαβής;

Νικόλαος Κουρρής, Κωνσταντίνος Τζιόμαλος

Α΄ Προπαιδευτική Παθολογική Κλινική, Τμήμα Ιατρικής, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Νοσοκομείο ΑΧΕΠΑ, Θεσσαλονίκη, Ελλάδα

Τα τελευταία χρόνια, μια ομάδα ασθενών με παχυσαρκία αλλά χωρίς καρδιομεταβολικές διαταραχές έχει κινήσει το ενδιαφέρον της επιστημονικής κοινότητας και έχει χαρακτηριστεί ως μεταβολικά υγιής παχυσαρκία. Η υποκατηγορία αυτή φαίνεται να είναι αρκετά συχνή μεταξύ των ασθενών με παχυσαρκία. Επιπλέον, οι

ασθενείς με μεταβολικά υγιή παχυσαρκία έχουν αυξημένο κίνδυνο να εμφανίσουν μεταβολικές διαταραχές και να εκδηλώσουν καρδιαγγειακά συμβάματα. Συνεπώς, δίαιτα, άσκηση και κατάλληλη φαρμακευτική αγωγή πρέπει να συνιστώνται εξίσου εμφατικά σε παχύσαρκους ασθενείς που δεν έχουν ακόμη εμφανίσει μεταβολικές διαταραχές.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Παχυσαρκία, μεταβολικά υγιής παχυσαρκία, καρδιαγγειακός κίνδυνος, μεταβολικό σύνδρομο*

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