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Metabolically Healthy Obese and Metabolically Obese-Normal Weight individuals

Konstantinos Kantartzis

PD Dr., Consultant in Internal Medicine, Department of Internal Medicine IV, and Institute of Diabetes Research and Metabolic Diseases at the University of Tübingen, Germany
Department of Internal Medicine IV, Division of Endocrinology, Diabetology, Angiology, Nephrology and Clinical Chemistry, University of Tübingen, Germany and Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the Eberhard-Karls-University of Tübingen, Germany, German Center for Diabetes Research (DZD), Tübingen, Germany

Obesity, defined as a BMI over 30 kg/m^2, is well known to be closely associated with insulin resistance and related cardiometabolic risk factors, eventually leading to type 2 diabetes, cardiovascular disease, and possibly to malignancies[1]. However, a subset of obese patients do not display this traditional cardiometabolic risk profile. These are known as the 'metabolically healthy obese' (MHO). Conversely, although normal weight individuals with a BMI in the range 20-25 kg/m^2 seem to have the lowest all-cause mortality[2], a subset of them shoulder an increased risk of developing metabolic and cardiovascular diseases ('metabolically unhealthy normal weight'-MUNW). Metabolic health definitions are based on the absence of insulin resistance, type 2 diabetes, dyslipidemia, hypertension and systemic inflammation, but greatly vary in terms of the number and cutoffs of these risk factors between different researchers and different studies[3]. Due to this inconsistency, there is a high degree of variability in the reported prevalence of the MHO and MUNW phenotypes. Most studies however suggest that in any given moment about 1 out of 4 obese and about 1 out of 10 normal weight individuals demonstrate the MHO and MUNW phenotypes, respectively[4-6].

While the existence (and the relatively high prevalence) of MHO and MUNW individuals in cross-sectional studies is not questioned, there is an ongoing discussion whether these individuals retain their status in the long-term, i.e. whether the MHO display about the same and MUNW a worse metabolic and cardiovascular risk compared to 'metabolically healthy' normal weight (MHNW) humans. In this respect, large meta-analyses of longitudinal studies (many of them with more than 10 years duration) have shown that both, the incidence of cardiovascular events and all-cause and cardiovascular mortality of MHO individuals are somehow higher compared to MHNW individuals, but much lower compared to 'metabolically unhealthy' obese (MUO) individuals. Of particular note, MUNW individuals display cardiovascular morbidity and mortality rates almost as high (or even higher in some analyses) as MUO[7-9]. MHO and MUNW status seem to confer a similar risk of developing diabetes in the future, which is higher than the respective risk of MHNW but clearly lower than the risk of MUO[10,11]. These data imply that MHO and MUNW may constitute only tem-

porary states. Nevertheless, large observational studies have suggested that about 2/3 of MHO and MUNW subjects retain their status (and the respective cardiometabolic risk) after a follow-up of 6-10 years[12,13]. About one-third of MHO lose their 'metabolic health' being rendered to MUO. Interestingly, at follow-up, this population shows a 4-5 times higher prevalence of diabetes and cardiovascular events compared to those who retain their MHO status. In contrast, one-third of MUNW gain their 'metabolic health' and display similar to MHNW prevalence of diabetes and cardiovascular disease at follow-up[12,13].

The precise mechanisms leading to MHO and MUNW phenotypes are not known. Nevertheless, elegant studies in transgenic animal models and humans suggest that the status of metabolic health is associated with a specific body fat distribution, i.e. low visceral fat mass, low liver fat content and high amounts of subcutaneous fat, a favourable adipokines and cytokines profile (mainly high adiponectin levels), and a low grade of adipose tissue and systemic inflammation[4,14,15]. In this setting, hepatokines, i.e. several proteins that are exclusively or predominantly secreted from a fatty liver and directly affect glucose and lipid metabolism, may play a particularly important role[16]. The best studied hepatokine, fetuin-A, for instance, is an endogenous inhibitor or insulin receptor, thus inducing insulin resistance, and has been shown to induce inflammation by interacting with free fatty acids and thereby activating toll-like receptors-4[16-18]. In an effort to clarify whether the same mechanisms contribute equally to the pathogenesis of the MHO and MUNW phenotypes, we recently analyzed data from 981 subjects at increased cardiometabolic risk, because of overweight or obesity, a family history of type 2 diabetes, a personal history of gestational diabetes, or of having prediabetes during an OGTT. We identified fatty liver, visceral obesity, low percentage of subcutaneous leg fat (gluteofemoral) mass, high insulin resistance, low insulin secretion capacity and low cardiorespiratory fitness on a cycle ergometer as being determinants of the 'metabolically unhealthy' status both in normal weight and obese subjects[6]. However, the relative contribution of fatty liver, visceral obesity and insulin resistance is greater in obese than in normal-weight individuals, whereas the relative contribution of low percentage of subcutaneous leg fat mass is greater in normal weight individuals (that is, gluteofemoralf at may be a major determinant of the MUNW phenotype)[6]. Gluteofemoral fat was shown to release higher, compared to subcutaneous abdominal adipose tissue, amounts of the insulin-sensitizing lipokine palmitoleate[19,20]. This may constitute a possible mechanism partly explaining the protective effect of this fat depot.

Genetics certainly play a role in the pathogenesis of the MHO and MUNW phenotypes, but their relative importance remains elusive. Association studies in large cohorts suggest that the effect maybe exerted by affecting body fat distribution. The Frayling groupfor instance, using data from about 200.000 individuals from the UK Biobank and 5 other studies, showed that 11 single nucleotide polymorphisms (SNPs) are associated with a 'favourable adiposity', i.e. a higher BMI and higher body fat mass, but lower waist-to-hip ratio and lower prevalence of type 2 diabetes, hypertension and heart disease[21]. Conversely, certain other SNPs and genetic loci were reported to be related to high insulin resistance and high prevalence of diabetes and hypertension, but a low BMI and lower subcutaneous (particularly gluteofemoral) adipose mass, i.e. to a MUNW-like phenotype[21-23].

The knowledge of the pathophysiology may be relevant for making proper treatment decisions. For MUNW, there are not consensus guidelines or clinical practice recommendations. Obviously, a healthy lifestyle should be always recommended, and pharmacological treatment of hyperglycemia, hyper- or dyslipidemia and hypertension should be added whenever this is considered to be necessary. Nevertheless, if low subcutaneous leg fat plays indeed a key role in the pathogenesis of MUNW, thiazolidinediones (TZDs) may represent a particularly attractive approach, because of their ability to promote adipose tissue differentiation while simultaneously improving hyperglycemia. However and in addition to their known side-effects, TZDs did not prove to be effective in treating lipodystrophies (a kind of 'extreme MUNW'), and this applies even in the cases resulting from peroxisome-proliferator–activated receptor γ mutations[24].

With regard to MHO, the main question is whether the general guidelines for obesity should apply also in individuals 'metabolically healthy'. Only few studies have tested the effectiveness of a

lifestyle intervention, the first-choice treatment of obesity according to the guidelines, in MHO individuals[25-29]. A reduction in visceral and liver fat and an improvement in insulin sensitivity were observed. However, the magnitude of the response was mostly rather limited and generally smaller than the response of the MHO to the same lifestyle intervention. Although all these studies refer to short-time lifestyle interventions (up to 9 months) and therefore had no 'hard' endpoints (diabetes, cardiovascular events), their results suggest that structured, time-consuming and costly lifestyle intervention programs may not be justified in MHO individuals. Considering however, as mentioned before, that the long-term risk of losing the 'metabolic health' status is about 30%, it is reasonable to advise these people to follow a healthy lifestyle and remain under continuous medical supervision.

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