Characterization of metabolically healthy but obese individuals: Should we add vitamin D to the puzzle?

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The heterogeneity of metabolic risk factors associated with obesity is well established. Accordingly, a unique subgroup of obese individuals has been categorized as having a metabolically healthy obese (MHO) phenotype [1]. To date, many studies have characterized the MHO individual. In general, despite similar total body fat mass, the MHO phenotype is associated with favourable ectopic fat (i.e. lower levels of liver and visceral fat), insulin sensitivity, lipid (i.e. lower levels of triglycerides and higher HDL-cholesterol levels), blood pressure, liver enzyme (i.e. lower levels of AST and ALT), inflammation (i.e. lower hsCRP and IL-6 levels) and hormonal (i.e. higher levels of adiponectin) profiles compared with obese subjects with risky cardiometabolic profiles dubbed the metabolically unhealthy obese (MUO) [1]. In addition, the physical activity and dietary profiles of MHO individuals appear to be comparable to those of MUO subjects [2]. Indeed, despite clinical recognition of the MHO phenotype, factors underlying this favourable metabolic profile remain to be elucidated.

One interesting factor that may contribute to a better understanding of the protective metabolic profile of MHO individuals is vitamin D. There is evidence to suggest that vitamin D may be negatively correlated with insulin resistance, insulin secretion, the number of components of the metabolic syndrome, subclinical inflammation and non-alcoholic fatty liver disease [3]. There is even evidence to suggest that vitamin D may be implicated in the development of type 2 diabetes [3] and, despite conflicting results in human interventional trials, several authors have suggested potential clinical benefit for glucose control when vitamin D levels are maintained above 30 ng/mL in patients with established type 2 diabetes [4]. These studies provide tantalizing evidence that vitamin D may be involved in the protective metabolic profile of MHO individuals.

In this edition of Diabetes and Metabolism, a report by Esteghamati et al. [5] has investigated levels of serum 25-hydroxy vitamin D in MHO individuals and compared them with MUO subjects. In this cross-sectional study, 4391 obese Iranian adults were recruited. MHO subjects were identified by the absence of the metabolic syndrome using the criteria of the International Diabetes Federation (IDF) and the more stringent definition proposed by Karelis et al. [6], which incorporates an index of insulin resistance (HOMA-IR) and traditional metabolic risk factors (HDL, triglycerides and LDL) as well as a subclinical inflammation marker (high-sensitivity C-reactive protein [hsCRP]). The prevalence of MHO subjects was 41.9% and 38.4% when using the IDF and Karelis definitions, respectively. Besides a favourable metabolic profile, serum 25-hydroxy vitamin D was significantly higher in MHO vs. MUO individuals according to both definitions (IDF: 20.2 vs. 17.3 ng/mL, respectively; Karelis: 24.6 vs. 16.2 ng/mL, respectively). Furthermore, the authors subdivided the MHO and MUO phenotypes into vitamin D deficient (< 20 ng/mL) and non-deficient groups. The authors observed that the vitamin D deficient group was associated with a greater number of metabolic disturbances in MUO than in MHO subjects. Collectively, this study adds 25-hydroxy vitamin D to the list of differences between MHO and MUO patients, and highlights the role of serum 25-hydroxy vitamin D as a possible underlying biomarker that may explain, at least in part, the protective and risky profiles of MHO and MUO individuals, respectively. However, due to the cross-sectional approach used in the study, no conclusions as regards causal associations between the MHO profile and serum 25-hydroxy vitamin D could be made.

Interestingly, a recent systematic review has indicated that many prospective studies have observed a relationship between low 25-hydroxy vitamin D and a wide range of chronic health disorders (i.e. inflammation, glucose dysregulation) [7]. However, the findings of randomized interventional trials have shown that vitamin D supplementation was not associated with a decreased risk of health disorders. This supports the hypothesis that 25-hydroxy vitamin D might not be a causative effect in the previous observational studies. The authors of this systematic review suggested that low 25-hydroxy vitamin D levels may be due to the inflammatory response during the development and progression of disease. In support of this concept, studies have shown that MHO individuals display a favourable inflammation profile [8] and, in turn, this may explain the higher vitamin D levels in the MHO phenotype.

Furthermore, there is evidence to suggest that persistent organic pollutants (POPs) could be contributing to lower levels of vitamin D [9]. Therefore, to add to the current literature, a
recent study from our laboratory showed that the MHO phenotype was associated with lower plasma levels of multiple POPs from different classes (i.e. dioxin, polychlorinated biphenyl [PCB], octylphenol [OP] and polybrominated diphenyl ether [PBDE]) compared with MUO subjects [10]. Interestingly, close to 70% of the detectable POPs were significantly higher in MUO than in MHO subjects. This study brings new information as to the possible causative effect that could explain the protective metabolic profile of MHO individuals.

A great deal of attention has been recently given to the risk of mortality and chronic diseases in MHO individuals [11]. That is, several studies have reported that the MHO profile may be associated with a decrease in risk of early mortality, type 2 diabetes and cardiovascular disease, while others have shown no beneficial effects. For example, in a 15-year follow-up, MHO individuals were not associated with an increased risk for all-cause cancer and cardiovascular disease mortality compared with non-obese insulin-sensitive subjects [12]. In contrast, in a 30-year follow-up, overweight and obese middle-aged men without the metabolic syndrome (fitting the MHO phenotype) showed an increased risk for cardiovascular events and mortality [13]. Moreover, the clinical significance of the MHO individual has been recently questioned in a meta-analysis and supports the idea that the MHO subject does not have a benign condition [14]. The authors of this meta-analysis showed that MHO individuals have an increased risk for cardiovascular events and all-cause mortality compared with normal-weight healthy subjects. However, it should be noted that the relative risk in MHO subjects was 1.24, which was approximately half of that reported in MUO individuals (2.65). Therefore, given the differences in relative risk, this could suggest a certain protection against adverse outcomes of obesity in MHO subjects. In addition, obesity increases the risk of kidney disease, some types of cancer, orthopaedic problems, depression, asthma, sleep apnoea, back pain, skin infections and cognitive decline. Thus, we cannot exclude the clinical significance of this unique subgroup, as obesity is associated with many other health outcomes. Collectively, we believe there is clinical utility in separating metabolically healthy and unhealthy obesity to study the variation of metabolic risk factors associated with obesity and the risk of certain chronic diseases.

Currently, there are many different methods that have been used for the identification of MHO subjects [11]. The contradictions reported in the literature could be explained by the use of these multiple methods. In general, the absence of metabolic risk factors (i.e. blood pressure, triglycerides, HDL-cholesterol and glycaemia) found in the metabolic syndrome and insulin resistance indexes with specific cut-off points are used to identify MHO individuals. Moreover, the prevalence of MHO individuals may vary widely from 3.3% to 57.5% of the obese population, depending on how obesity is identified as well as which metabolic markers and cut-off points are used to identify MHO subjects [11]. Therefore, the true prevalence of the MHO phenotype in the obese population is currently unknown. Although the MHO individual has been well recognized, there has been no consensus on a standardized definition. Once a standard definition is achieved, all previous longitudinal and interventional studies could reanalyze their data to either confirm or correct their previous results. However, as there is no established standard definition to date, future studies may wish to consider using multiple definitions to confirm their findings, which was the case in the study by Esteghamati et al. [5], who used two definitions to confirm their data. We believe that a strict method for the identification of MHO individuals is warranted in order to identify ‘true’ MHO subjects with no apparent metabolic risk factors, chronic diseases, psychological problems and functional limitations associated with obesity. In support of this concept, mortality rates are increased with higher Edmonton obesity staging system scores; a 5-point ordinal classification system that considers comorbidity (i.e. metabolic risk factors, physical symptoms and psychopathology) and functional status, in overweight and obese individuals [15].

Taken altogether, Esteghamati et al. [5] raise some interesting clinical questions in the fascinating and controversial field of the MHO phenotype, such as:

- whether vitamin D should be considered a clinical marker in the identification of a healthy metabolic profile;
- whether vitamin D can predict the progression of MHO status to MUO, as there is evidence to suggest that one-third of MHO subjects could be converted to MUO during a 5- to 10-year follow-up [16].

Interventional studies with vitamin D supplementation are also needed to examine whether it can increase the probability of converting MUO subjects to MHO individuals.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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References


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