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ORIGINAL ARTICLE

Open questions about metabolically normal obesity

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Subsets of obese subjects without any cardiometabolic risk factors have been repeatedly described. This raises questions whether obesity '*per se*' enhances the risk for cardiovascular or metabolic diseases and whether healthy obese subjects would benefit from a medical treatment. In order to answer these questions, as a first step, an expert consensus should be reached for the definition of metabolic normality. In fact, up to now, different parameters related to the metabolic syndrome and/or to insulin sensitivity have been utilized across studies. Once an agreement is reached, population-based studies should be undertaken to establish the incidence of metabolic normality among obese subjects. Furthermore, many other parameters such as age, sex, race, fat distribution and physical activity should be monitored to obtain results representative of a general population. Longitudinal studies aimed at investigating the evolution of the cardiometabolic profile of healthy obese subjects are also needed. In conclusion, data from the literature strongly suggest that a regular surveillance of the cardiometabolic parameters and a prevention of any further weight gain should be applied to healthy obese individuals, whereas possible benefits of a weight loss treatment are still a matter of debate.
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Introduction

Obesity is a well-established and independent risk factor for cardiovascular diseases and mortality in the general population.[1–3] However, a subset of obese subjects seems to be protected from obesity-related cardiovascular and cardiometabolic abnormalities.[4–6] This observation raises the possibility that obesity is not inevitably associated with co-morbidities and, therefore, does not necessarily need a treatment.

This review will address some questions that remain to be investigated, in order to establish sound guidelines for the management of obese subjects with a healthy cardiometabolic profile.

Which definition?

To date, there is no uniform definition for obesity phenotypes. Generally, metabolically normal obesity (MNO) describes the absence of any overt cardiometabolic disease: specifically, type 2 diabetes mellitus, dyslipidemia and hypertension in an individual with body mass index $\geqslant 30\,kg\,m^{-2}$. In addition to the absence of overt pathologies, the associations and clustering of cardiometabolic risk factors, such as metabolic syndrome components or inflammatory markers, have also been used in categorizing subjects as metabolically normal or abnormal.

The metabolic syndrome, however, is defined in at least four different ways (WHO, IDF, ATP-III and EGIR). This discordance is a possible reason for inconsistencies in the prevalence of metabolic normality reported in the literature.

Data from the European Group for the Study of Insulin Resistance (EGIR)[4] have shown that in obese subjects free from diabetes and hypertension, the prevalence of insulin resistance was relatively low (26%). Furthermore, other studies have demonstrated that both the prevalence[7–9] and the incidence[10] of cardiovascular risk factors and/or diseases are strongly related to insulin resistance. Thus, insulin sensitivity could be the key factor discriminating healthy from at-risk obese subjects.[11] Some authors have, therefore, adopted insulin sensitivity as an additional[12,13] or even the sole[6,14,15] criterion to define MNO.

The gold standard for insulin sensitivity assessment is the hyperinsulinemic euglycemic clamp technique. However, due to the complexity of this technique, different surrogate indexes have been used to estimate insulin sensitivity. Some of them[16] are derived from oral glucose tolerance test;

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others, such as the homeostasis model assessment (HOMA) index[17] or quantitative insulin sensitivity check index,[18] use glucose and insulin fasting levels.

In conclusion, the comparison of different studies investigating MNO may be difficult because of the use of different parameters to categorize subjects as metabolically healthy. Thus, the absence of harmonized criteria is the main barrier to be overcome in examining the magnitude of metabolic normality among patients suffering from obesity.

Which prevalence?

Table 1 illustrates the variability of the prevalence of MNO across the studies. Clearly, the prevalence of MNO versus at-risk obesity mainly depends on selected criteria for the definition of cardiometabolic normality. Another critical point is also represented by the cut-off values of normality for a given parameter. This is particularly true when insulin sensitivity is taken into account. For instance, the threshold value for the HOMA index largely varies across the studies,[9,13,19,20] whereas the one of glucose disposal is often obtained from pre-established stratifications of the study groups.[6,15]

Furthermore, other factors such as sex, age or family history of diabetes can largely influence this prevalence, which, in fact, varies highly according to the studies.

Among 5440 subjects who participated in the National Health and Nutrition Examination Surveys (NHANES 1999–2004), 31.7% of obese US adults showed a healthy profile, defined as the presence of no more than one of six classical cardiometabolic risk factors (blood pressure, triglycerides, fasting glucose, C-reactive protein, low high-density lipoprotein cholesterol level and insulin sensitivity).[19] In the same study, when using more stringent criteria (that is, none of the six cardiometabolic risk factors), only 16.6% of obese adults were categorized as metabolically healthy.[19]

It is interesting to note that, in this same population, only 6% of obese subjects were metabolically normal, when the cut-off point (HOMA index) for insulin sensitivity was lowered from 5.1[19] to <2.5.[20] The results of these two studies clearly underline how the nature of selected parameters and the cut-off point for the same parameter heavily condition the prevalence of metabolic normality.

In an Italian population-based study of 681 obese subjects, 27.5% did not show adverse risk factors and obesity-related metabolic and cardiovascular co-morbidities, although the authors applied numerous and strict criteria for the definition of metabolic normality.[12]

Table 1 Prevalence of metabolically normal obesity across the studies

Reference	*Study groups*	*Parameters*	*Prevalence of MNO (%)*
Kuk and Ardern[20]	6011 male and female subjects	Six parameters of metabolic syndrome (ATP-III, with the exception of waist circumference) Insulin sensitivity (HOMA <2.5)	6.0
Wildman *et al.*[19]	5440 male and female subjects	Six parameters of metabolic syndrome (ATP-III, with the exception of waist circumference) Insulin sensitivity (HOMA <5.1)	31.7
Ferrannini *et al.*[4]	1146 male and female subjects	No overt pathologies (diabetes, hypertension) Normal glucose tolerance Insulin sensitivity (Clamp)	22.0
Bonora *et al.*[9]	888 male and female obese subjects	No overt pathologies (IGT, hypertension, dyslipidemia, hyperuricemia) Insulin sensitivity (HOMA <2.8)	20.0
Aguilar-Salinas *et al.*[36]	716 male and female subjects	No overt pathologies (diabetes and hypertension) HDL cholesterol at least 40 mg per 100 ml	35.3
Iacobellis *et al.*[12]	681 obese subjects	No overt pathologies (diabetes, dyslipidemia, hypertension) No criteria for metabolic syndrome (IDF, with the exception of waist circumference) Plasma lipids: TC $<5.2\,mmol\,l^{-1}$, LDL $<3.4\,mmol\,l^{-1}$, TC/HDL <4.4, TG/HDL <3.00 Uric acid $<0.33\,mmol\,l^{-1}$ for women and $<0.42\,mmol\,l^{-1}$ for men WBC count $<10\,000$ cells per 100 ml Plasma fibrinogen $<4.00\,g\,l^{-1}$ Fasting insulin $<15\,\mu U\,ml^{-1}$	27.5
Karelis *et al.*[51]	154 obese postmenopausal women	ATP-III parameters for lipid profile and TC $\leqslant 5.2\,mmol\,l^{-1}$, LDL $\leqslant 2.6\,mmol\,l^{-1}$ Insulin sensitivity (HOMA $\leqslant 1.95$)	12.6
Messier *et al.*[22]	113 obese, sedentary postmenopausal women	Six parameters of metabolic syndrome (ATP-III, with the exception of waist circumference) Insulin sensitivity (HOMA <5.1) or	23.4
		HOMA $\leqslant 2.7$, TG $\leqslant 1.7\,mmol\,l^{-1}$, LDL $\leqslant 2.6\,mmol\,l^{-1}$, hsCRP $\leqslant 3\,mg\,l^{-1}$	23.6
Brochu *et al.*[5]	43 obese, sedentary postmenopausal women	Insulin sensitivity (clamp)	33.5

Abbreviations: HDL, high-density lipoprotein cholesterol; hsCRP, high-sensitive C-reactive protein; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; LDL, low-density lipoprotein cholesterol; MNO, metabolically normal obesity; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.

Data from 314 adult Germans[14] showed that a predefined upper quartile of insulin-sensitive obese subjects (as established by Matsuda or HOMA index) had cardiometabolic parameters closely similar to the ones measured in a normal-body-weight control group. It should be noted, however, that all the participants had a family history of diabetes and/or a previous diagnosis of impaired glucose tolerance or gestational diabetes. It is well known that all these situations are associated with reduced insulin sensitivity in both normal-body-weight and obese subjects.[21] For this reason, it is difficult to apply the results of this study to a general population.

In a cohort of 113 obese postmenopausal women, the prevalence of metabolically healthy obese subjects was 25% using methods based on insulin sensitivity (clamp, Matsuda and HOMA index).[22]

In a study of 43 obese postmenopausal women,[5] subjects were first selected on the basis of their percent body fat ($\geqslant$35%). They were then submitted to a hyperinsulinemic euglycemic clamp, and a literature-based cut-off point of 8.0 mg min^{-1} kg^{-1} lean body mass of glucose uptake was used to categorize subjects with MNO. In this way, 39.5% of the subjects were identified as metabolically normal but obese. Because of the selection of sex and menopausal status and/or the relatively small number of subjects, the results of the two last studies can be applied only to a specific category of subjects.

In a recent study, performed in a European clinically healthy population, our group showed that the prevalence of MNO, as defined by the IDF criteria and the glucose disposal rate (clamp), was about 6%.[23]

Which determinants?

Genetics

It is generally accepted that genetic background has an important role in the development of obesity and of its major related co-morbidity, diabetes. Consequently, MNO could also be the expression of a genetic trait. It has been shown, for instance, that fat deposition in the visceral area is influenced by genes.[24–26] Furthermore, human[27,28] and animal[29] studies have demonstrated that spontaneous physical activity is associated with genetic characteristics. Both the amount of visceral fat and physical activity are potential determinants of MNO. It is therefore possible that genetic background influences the metabolically normal phenotype expression by these factors. Up to now, however, no evidence supports this hypothesis.

Besides genes, epigenetic changes, that is, inheritable modifications of gene expression, can heavily contribute to the development of metabolic disturbances such as diabetes.[30] It has also been proposed[31] that, during pregnancy or lactation, a maternal metabolic deregulation could favor, in the offspring, the later development of metabolic syndrome, that is, one of the mostly used parameter for the definition of metabolic normality in obesity.

Visceral adipose tissue

Visceral adipose tissue mass, as determined by computed tomography in post-menopausal sedentary women, is smaller in MNO as compared with at-risk obese subjects.[5,6]

The role of visceral fat is confirmed by the results obtained by Jennings *et al.*,[32] who measured a smaller waist circumference in MNO in a population of African-American women. On the other hand, it is well established that visceral adipose tissue has an important role in the genesis of both insulin resistance and inflammation[33] often present in obesity. Thus, a relatively low amount of visceral adipose tissue could explain the more favorable metabolic and inflammatory profile described in MNO.[6]

Omental adipocytes have a smaller size in healthy individuals than in at-risk obese individuals.[34] This correlates with the degree of insulin resistance (HOMA established). It is of note that other studies have demonstrated that adiponectin secretion from the visceral depot is negatively related to the adipocyte size.[35] This is consistent with the finding that MNO is characterized by elevated levels of circulating adiponectin.[36] This study was conducted in 726 subjects whose body mass index ranged from 19 to $>$40 kg m^{-2}. It is interesting to note that the prevalence of metabolic normality, defined as the absence of an overt pathology such as diabetes, hypertension or dyslipidemia, declined from 85% in normal-body-weight subjects to 46–48% in obese and 23% in morbidly obese individuals, thus suggesting that increasing body mass index drastically reduces the chances of being metabolically normal. Similar results have been obtained in the Wildmann *et al.*[19] study, in which it was demonstrated that the prevalence of metabolic normality decreases with increasing age and body mass index.

Ectopic fat deposition

Obesity is often associated with ectopic fat deposition. The physiopathological mechanisms underlying this phenomenon are still unclear. On the contrary, its impact on numerous functions, such as insulin sensitivity and inflammation, are well established.[37] Uncomplicated obesity is characterized by a lower degree of ectopic fat deposition, in particular in muscle and liver.[14] This could, at least in part, explain why healthy obese subjects seem to be protected from the major obesity-linked co-morbidities.

Lifestyle

A higher degree of physical activity has been reported by some authors,[19] but not by others,[5,32] in MNO. It is not clear whether this healthier lifestyle characteristic is linked to possible genetic traits, as previously discussed, or to a more favorable socioeconomic status, which is often associated to more active leisure-time occupations.[38] This last hypothesis is not supported by data found in the study by Jennings *et al.*,[32] in which educational or economic levels did not

distinguish the metabolically healthy obese subpopulation. Whatever the cause, increased physical activity could positively influence the cardiometabolic profile of these obese subjects by a reduction of visceral fat mass,[19] which is a recognized determinant of cardiometabolic risk factors.

Up to now, no systematic investigation has analyzed the role of diet composition in MNO. Although obesity is almost invariably associated to high-fat, low-fiber and vegetable diet, it is possible that a minority of obese subjects have healthier alimentary habits that improve their cardiometabolic profile.

Psychological traits

Only one study has investigated this potentially major contributor to the healthy or unhealthy profile of obese subjects. Karelis *et al*.[39] have proposed that some psychological traits could distinguish metabolically normal obese from the 'at-risk' population. Unfortunately, these authors could not provide evidence of any specific characteristics, in terms of quality of life, self-esteem or perceived stress. These negative results may be due to the small cohort of subjects who were investigated (20 metabolically normal vs 20 at-risk obese women). In the light of the well-documented cardiometabolic consequences of stress,[40] it would be worthwhile to investigate further the potential role of stress as a discriminator between at-risk or not at-risk obesity.

Natural history of obesity

The existence of a subset of obese subjects who do not show any risk factor for cardiometabolic diseases is an indubitable fact. It remains to be elucidated whether this favorable profile represents a permanent characteristic or is just a step in the natural history of obesity, which will evolve through the appearance of risk factors and, then, of overt pathologies. Besides these two possibilities, a third intermediate and more likely scenario could be that some obese subjects potentially remain protected from the risk of co-morbidities provided that some changes, such as increase in body weight or reduction of physical activity, do not negatively interfere with their favorable cardiometabolic profile.

To answer this question, large-scale longitudinal studies are needed. Up to now, the only available data derive from two investigations. In the first,[41] an 11-year follow-up study, the authors demonstrated a significantly increased risk for diabetes in MNO, whereas they did not observe a higher incidence of cardiovascular diseases. Another 9-year follow-up study, conducted on about 6000 subjects,[20] revealed that obesity, even in the absence of metabolic alterations, is associated with an increased risk for all causes of mortality. In addition to their rather discouraging results, both these studies demonstrated that metabolically normal obese subjects were younger than their at-risk counterparts, further suggesting an age-related transition from normal to abnormal cardiometabolic profile.

Some reports seem to confirm this hypothesis: for instance, by examining a population of almost 5000 subjects, Janssen *et al*.[42] have demonstrated that, in women, 10-year duration of overweight has a significant impact on the appearance of diabetes, dyslipidemia and hypertension.

In contrast with these findings, it has been reported that an early onset of obesity is associated with higher insulin sensitivity.[5,43] No well-defined adaptative mechanisms have been evoked to explain this surprising result, which, differently from the study by Janssens *et al*.,[42] has been obtained in a very small sample (17 subjects in the study by Brochu *et al*.[5] and 30 in the study by Muscelli *et al*.[43]). This finding, therefore, needs a confirmation based on a larger number of observations.

Which surveillance and/or treatment?

Before discussing whether metabolically normal obese individuals would benefit from treatment, the usefulness of a close surveillance should be examined.

The relative lack of longitudinal studies makes difficult the elaboration of sound guidelines for both surveillance and treatment of metabolically normal obese subjects. However, it is generally agreed that there is no evidence that these subjects are permanently protected from the risk of obesity-related co-morbidities. Furthermore, the fact that metabolically normal obese subjects show a healthier cardiometabolic profile, as compared with at-risk obese subjects, does not necessarily mean that they are perfectly normal. As realistically suggested by Marini *et al*.,[15] metabolically normal obese subjects occupy an intermediate position between healthy, normal-body-weight and at-risk obese subjects, in terms of cardiovascular characteristics such as carotid intima–media thickness, systolic and diastolic blood pressure. When compared with normal-body-weight controls, healthy obese subjects also show an impaired aortic elastic function[44] and a deterioration of the endothelial function.[45]

On the basis of this evidence, a prudent attitude would be to regularly monitor the risk factors in metabolically normal obese subjects, in order to detect early a possible negative evolution of their cardiometabolic profile. In particular, a special surveillance should be applied to prevent any increase in body weight. In fact, there is no evidence that healthy obese subjects could tolerate a further increase of their fat mass, without any consequences on their cardiometabolic profile. More generally, it is well established that worsening of body weight is strongly associated with the deterioration of inflammatory and metabolic syndrome-related parameters.[46] Prevention of obesity aggravation should therefore be applied to any subgroup of obese subjects.

With regard to the possible treatment of MNO, the discussion should be limited to the usefulness of a weight loss intervention. In fact, the normality of blood pressure, glycemia and lipidemia does not justify any pharmacological

therapy in these subjects. Very few data are available about the effect of weight loss in metabolically normal obese subjects: one study reports that a 3% weight reduction significantly improved the inflammatory and lipid profile in at-risk, but not in MNO individuals.[47] The lack of effect in the healthy obese group could be explained, at least in part, by the fact that their cardiometabolic and inflammatory values are already within the limit of normality. In addition, as pointed out by Reaven,[11] the largest benefits of weight reduction are observed in those individuals who show insulin resistance, which is, by definition, absent in MNO.

More surprisingly, Karelis *et al*.[48] found a worsening in insulin sensitivity in healthy obese women after a 6-month weight reduction program. This result led the authors to suggest that healthy obese subjects may respond differently to weight loss and, therefore, such a type of intervention could be counterproductive. The implications of such a conclusion are too important to be based on a single study performed in a small group of patients (20 subjects). Although the possible adverse effect of weight loss must be considered with caution, one should remember that achieving permanent weight reduction is a difficult challenge for any obese person and the risk of weight regain is elevated. Furthermore, repeated episodes of weight loss followed by regain may have adverse health effects.[49,50] For these reasons, any weight loss program should be preceded by a careful evaluation of expected costs and benefits. This is particularly true when treating MNO. In these subjects, however, the indication for a weight reduction could come from the evaluation of other obesity-related co-morbidities, such as sleeping apnea, back pain, knee osteoarthritis or cholelithiasis.

Conclusions

An expert consensus must be established about the definition of MNO. This consensus would thus clarify whether metabolic normality has a quite elevated incidence (over 30%) in the obese population or whether it is a relatively rare observation (6%). We should also enhance our knowledge about the determinants of this favorable metabolic profile and about the possible transition from a healthy to an at-risk obesity. This last aspect should be investigated in population-based longitudinal studies. Any guideline for the treatment (if any) of healthy obese subjects can be proposed before answering these questions. A regular surveillance of the cardiometabolic risk parameters and prevention of any further weight gain seem to represent the most prudent and sound attitude in the management of metabolically normal obese subjects.

Conflict of interest

The authors declare no conflict of interest.

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