



## Editorial

### A DISEASE CAN BE NEITHER HEALTHY, NOR BENIGN

*C. Ionescu-Tîrgoviște*

National Institute of Diabetes, Nutrition and Metabolic Diseases "N.C. Paulescu", Bucharest, Romania

At least three papers have been published by *Diabetologia* [1-3] regarding a hypothetic obesity syndrome called "obese but metabolically healthy" (OMH or MHO), the last in the April issue of the Journal: "*Effects of lifestyle intervention in metabolically benign and malign obesity*" [3]. A wave of interest and satisfaction has been propagated among some obese people and perhaps among some doctors. Clinical feeling told me that something illogic and maybe wrong is included in associating obesity (an obvious metabolic disorder) with the terms "healthy" or "benign" (if not benefic).

Several questions must be raised. The first is related to its prevalence, approximated to ~30% of all obese patients and 10% of the whole adult population [1,3]. However, obesity is a disease with long evolution, at least if it appears before 30, 40 or even 50 years of age. A more recent paper published in *Diabetologia* by Montonen et al. [4], in a prospective study (1612 subjects) showed that the parameter *time* is extremely important for the pathogenic judgment of such a disease. The authors concluded that an increasing BMI in early adulthood (25-40 yrs) is more strongly associated with unfavorable circulating levels of obesity biomarkers later in life than is an

increase in BMI in later adulthood. Thus it will be dangerous if we will put the stamp of "metabolically healthy obese" to a child, adolescent or young adult even in the presence of apparently normal metabolic profile. The answer to the question: What real prevalence of OMH patients is found in general population? is given by two recent large prospective published studies carried out on an European population of 2011 cases [5] and, respectively, an American population of 6485 non-diabetic adults [6]. In the first study, the prevalence was of only 2.1% and in the second 4.1% of the whole population.

The second question is even more important: How much metabolically "healthy" are the obese patients included in the MHO group. The answer comes from the above mentioned American study, as part of the United States National Health and Nutrition Examination Survey (NHANES), 1999-2004. The study evaluated 843 OIR, 314 MHO and 1173 MHNW subjects. A comparison between MHO and MHNW groups showed that the so called metabolically "healthy" have an abundance of dysmetabolic signals: higher plasma insulin ( $p<0.001$ ), non-HDL-cholesterol ( $p=0.002$  in females and  $p=0.049$  in males) and C-reactive protein levels

( $p < 0.001$  in females and  $p = 0.038$  in males) and lower HDL-cholesterol levels ( $p < 0.002$ ). Moreover, MHO females had higher LDL-cholesterol ( $p = 0.012$ ) and higher systolic blood pressure ( $p = 0.02$ ). Keeping in mind these numerous dysmetabolic, biochemical and hemodynamic signals, the characterization of MHO [1,3] as metabolically “healthy” is not sustainable.

Various associations of such “biochemical signals” are observed in almost all obese people and the formulations “healthy” or “benign” are neither real, nor helpful for the patients. The designation “healthy” gives the illusion that everything is OK, thus encouraging that nothing should be done. The fact that the so called MHO patients did not respond to the intensive life style modification [1,3] does not mean that these patients might not benefit from other therapeutic options. Therefore OMH/MHO are unlikely to be ‘healthy’ phenotypes of obesity, as suggested by the term “benign” obesity.

An increase in body weight over a BMI cut off between 28-32 cannot be good news as sustainers of OMH/MHO concept suggest. Such an increase must be analyzed in the long term perspective, taking into account both metabolic and mechanical complications of obesity. Two prospective studies (one American and the other Scandinavian) mentioned by Calori [5], have clearly showed increased cardio-vascular mortality in OMH/MHO population versus normal weight healthy population, proving that there are risks associated with this type of obesity. This is why we consider that spreading a positive message in the favor of obesity is not a wise enterprise.

The attempts to divide the obese patients in OIS and OIR needs supplementary caution if keeping in mind that the “artificial” nature of the metabolic syndrome induced by a *primary* insulin resistance has been settled after two decades of contradictory discussions. After the conclusive paper published last year in *Diabetologia* [7], I thought the phantom of insulin resistance has been removed from Europe. It seems that I was enthusiastic to early, since the problematic of the insulin resistance as *primary* mechanism of metabolic syndrome diabetes has been now transferred to the explanation of MHO. However, the main flux of research goes towards the study of the obvious root of metabolic pathology which is the excess fat inside and outside the adipose tissue.

A classification of obesity must be done taking into account more objective data regarding the cellularity of the adipose tissue and the secretory profile of the adipocytes according with their number and size. From this point of view, the adipocytes could be “quiet” [8], if their lipid load is between 0.6 - 0.7  $\mu\text{g}/\text{cell}$  and their diameter  $> 90 \mu\text{m}$ , encountered in subjects with BMI  $< 27$ . The metabolic profile of these adipocytes is as a rule “clean”. Adipocytes could be considered “restless” when their lipid load is between 0.7-0.9  $\mu\text{g}/\text{cell}$  and their size  $> 100 \mu\text{m}$  in diameter in subjects with an important weight excess (but BMI not higher than 30), given especially by hypertrophic adipocytes. The number of macrophages from the adipose tissue increases and the production of proinflammatory adipokines (TNF $\alpha$ , IL6, etc.) is evident and progressive. Finally, adipocytes could be considered “aggressive” when their lipid load  $> 0.9 \mu\text{g}/\text{cell}$  and their size  $> 120 \mu\text{m}$  in

diameter in subjects with important obesity (BMI>35), produced by both hyperplasia and mainly by an excessive hypertrophy of adipocytes. It is very important to stress that proinflammatory reaction is totally or partially reversible by weight loss.

We hope that the interest for what could be named “silent obesity” sub-phenotype (the

term MHO must be deleted as inappropriate) will lead to further research and understanding of the various pathogenic pathways to help advance new therapeutic options.

## REFERENCES

---

1. **Karelis AD, Messier V, Brochu M, Rabasa-Lhoret R.** (2008) Metabolically healthy but obese women: effect of an energy-restricted diet. *Diabetologia* 51:1752–1754

2. **Perseghin G.** Is a nutritional therapeutic approach unsuitable for metabolically healthy but obese women? (2008) *Diabetologia* 51:1567–1569

3. **Kantartzis K, Machann J, Schick F, Rittig K, Machicao F, Fritsche A, Häring H-U, Stefan N.** (2011) Effects of a lifestyle intervention in metabolically benign and malign obesity *Diabetologia* 54:864-868

4. **Montonen J, Boeing H, Schleicher E, Fritsche A, Pischon T.** (2011) Association of changes in body mass index during earlier adulthood and later adulthood with circulating obesity biomarker concentrations in middle-aged men and women. *Diabetologia* 54:1676-1683

5. **Calori G, Lattuda G, Piemonti L, Garancini MP, Ragogna F, Villa M, Mannino S, Crosignani P,**

**Bosi E, Luzi L, Ruotolo G, Perseghin G.** Prevalence, metabolic features and prognosis of Metabolically Healthy Obese Italian individuals. The Cremona Study (2011) *Diabetes Care* 34:210-215

6. **Manu P, Ionescu-Tirgoviste C, Tsang J, Napolitano BA, Lesser M.L, Correll CU** (2011) Dysmetabolic signals in “metabolically healthy” obesity. *Obesity Research & Clinical Practice* ORCP-D-11-00041R2

7. **Simmons RK, Alberti KG, Gale EA, Colagiuri S, Tuomilehto J, Qiao Q, Ramachandran A, Tajima N, Brajkovich Mirchov I, Ben-Nakhi A, Reaven G, Hama Sambo B, Mendis S, Roglic G.** (2010): The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. *Diabetologia* 53:600-605

8. **Ionescu-Tirgoviste C.** (2011) Insulin resistance - what is myth and what is reality? *Acta Endocrinologica* VII(1):123-146