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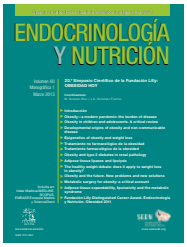

20.º SIMPOSIO CIENTÍFICO OBESIDAD HOY

The healthy weight debate: does it apply to weight loss in obesity?

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Given the difficulty in reversing over the next decades the underlying factors that are driving current obesity trends, a comprehensive, pro-active, long-term strategy and sustainable response to deal with the challenges posed by this epidemic is urgently needed. In the current scenario encouraging the instauration of programmes for early competent diagnosis, treatment and prevention is mandatory. Overweight and obesity are serious health issues that will only worsen without thoughtful and evidence-based interventions that address individual and societal attitudes alike as well as their environmental context. Although many people resolve to lose weight the perception of both the general population and the health care providers may be disappointing, in the sense, that most of the patients give up trying after a short period of time, and few will sustain the weight lost in the long term. Noteworthy, in overweight and obesity treatment any intervention which causes a negative energy balance is guaranteed to be effective in producing weight loss. It has been estimated that affecting energy balance by only 50-100 kcal/d, an easily attainable target, could prevent weight gain in most of the population. Even more, evidence-based guidelines and studies have recognised the clinical benefits of moderate 5-10% weight loss, which is achievable using a variety of available interventions.

Introduction

While in the last century smoking was the main modifiable risk factor for the development of cardiovascular diseases (CVD), during the past few decades our obesogenic environment characterized by an increasingly sedentary lifestyle and dietary habits have changed this landscape identifying obesity as one of the principal contributors.[1,2] The relation between body mass index (BMI) and mortality was already established in the 1980s, with an increased risk for obese individuals and especially for morbid obesity even at young ages. More recently, the relationship between BMI and all-cause mortality has been examined in a pooled analysis of 19 prospective studies, which included 1.46 million white non-Hispanic adults with over 160.000 deaths and a 10-year follow-up.[3] Both overweight and obesity were associated with increased all-cause mortality with the hazard ratios being broadly similar for men and women. In this study the contrast between the pattern observed among healthy subjects who never smoked highlights particularly the strong association with BMI in a sub-group that is minimally confounded by smoking or prevalent illness. Nowadays, it is known that adipose tissue lies at the heart of the increased mortality-BMI relation.[4]

Long thought of as a passive organ for the mere storage of excess energy in the form of triglycerides, in the last decades adipose tissue has been recognized as an extraordinarily active and dynamic endocrine organ with pleiotropic functions that go beyond body weight homeostasis and appetite control to extend to glucose and lipid metabolism as well as quite diverse biological processes such as immunity, reproduction, bone remodelling and the whole range of CV functions including vascular tone regulation, fibrinolysis, coagulation and angiogenesis.[5-7] When adipose mass enlarges a recruitment and activation of monocytes takes place. The enlarged adipocytes together with the infiltrated macrophages produce an altered

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adipokine secretion profile, characterized mainly by an increase in proinflammatory cytokines and acute phase reactants such as tumour necrosis factor alpha, interleukin 6, C reactive protein, serum amyloid A, leptin, or adipsin, among others, together with a decrease of the beneficial adipokines due to their insulinomimetic and cardioprotective effects, such as adiponectin and omentin. These adipokines will exert their effects both locally as well as at distance on key organs contributing to the development of the main co-morbidities.[8]

Relevance of body composition assessment

BMI is the measure used to classify individuals in lean, overweight or obese. However, strictly speaking, obesity is not defined as an excess of body weight relative to height but as a state of increased adiposity of enough magnitude to produce adverse health consequences. Although the BMI is a useful tool in epidemiological studies, it is highly imprecise in estimating body fat at an individual level. For this reason, it is extraordinarily important to try to perform body composition analyses whenever possible to accurately discern in each individual the amount of body fat irrespective of the BMI. When simultaneously performing the comparison of the BMI with the body composition analysis performed by air-displacement plethysmography or the BOD-POD® in over 6,500 individuals, a misclassification in a relevant number of subjects became evident in the BMI-based categorization.[9] Interestingly, a huge number of subjects classified as lean according to BMI is either overweight or even obese when looking at their actual body fat content (Fig. 1). In fact, it was observed that among the subjects classified as lean by BMI, 29% are actually obese.

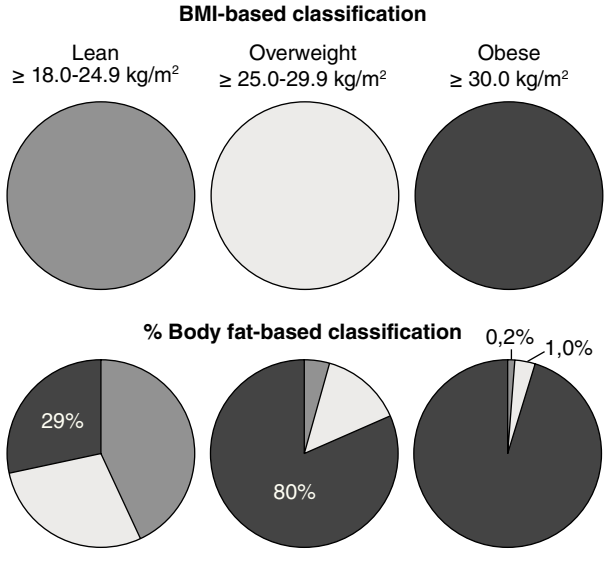

Figure 1 Comparison of the proportion of individuals classified as lean, overweight and obese according either to body mass index (BMI; upper panel) or body fat percentage (determined by air displacement plethysmography) in the Clínica Universidad de Navarra (CUN) series with over 6,500 volunteers.

For the BMI encompassing the overweight category, 80% of individuals was really obese, while the misclassification in the opposite direction is very small, with only 0.2% of BMI-based obese individuals being lean and 1.0% being overweight.

The immediate, pragmatic question that arises is whether this misclassification has any clinical implications. To address it we analyzed a subgroup of individuals who were non-obese or obese by BMI, but that were matched for body fat so that both had an average body fat of 31% for males and 41% for females. Noteworthy, cardiovascular risk factors were broadly similar between these groups of increased adiposity irrespective of BMI as opposed to the individuals with a normal body fat content.[9] In fact, elevated waist circumference, systolic and diastolic blood pressure, glucose, insulin, triglycerides, total and LDL-cholesterol, fibrinogen and C reactive protein together with a decrease in HDL-cholesterol concentrations were observed in the increased adiposity groups. In a different analysis we focused on individuals with a BMI below 25 kg/m², but separating them according to their glycemic state. In spite of the lack of differences in BMI between both groups, prediabetic/type 2 diabetics exhibited a significantly increased body fat content both in men and women.[10] This was particularly relevant in men over 40 years of age, where subjects can even have a normal waist circumference but already high adiposity. Taken together these findings provide clear evidence that by using only the BMI and waist circumference measurements we are loosing opportunities to help patients that have an increased cardiometabolic risk, which makes them more prone to develop comorbidities.

Given our awareness that not all physicians have access to reliable body composition determination equipments, our next step consisted in designing and validating a useful tool that could be used in the clinical setting due to its predictive capacity based on readily and easily measurable variables. We developed an equation, the CUN-BAE, standing for Clínica Universidad de Navarra — Body Adiposity Estimator.[9] The clinical usefulness of the CUN-BAE was tested in a comparison study of the equation with plentiful other anthropometric indices as regards its correlation with actual body fat percentage in a large cohort of 6,510 Caucasian subjects from both sexes (67% female) representing a wide range of ages (18-80 years) and adiposity. In addition, a validation study was carried out in a separate cohort of almost 1,500 individuals as well as a further analysis (n = 634) pertaining the clinical usefulness of the prediction equation with cardiometabolic risk factors.[11] Noteworthy, body fat percentage calculated by the CUN-BAE showed the highest correlation with the actual body fat per cent value compared with other anthropometric measures or adiposity estimators. Similar agreement was found in the validation sample. Moreover, in general, body fat percentage estimated by the CUN-BAE exhibited better correlations with cardiometabolic risk factors than BMI as well as waist circumference in the subset of 634 subjects. CUN-BAE is an easy-to-apply predictive equation that can be thus used as a first screening tool in clinical practice. Furthermore, our equation may be a good tool for identifying patients at increased cardiovascular and type 2 diabetes risk.[11]

Need to go beyond BMI and focus on subphenotypes

Thus, it is important not only to determine the total amount of body fat but also where it is located. The fat distribution is one of the main factors conditioning the development of obesity-associated comorbidities.[4,7] Importantly, specific depots of abdominal adiposity as well as lipid content within the muscle and liver are differentially associated with metabolic risk factors, obesity and insulin resistance. In this context, subjects with greater intra-abdominal adipose tissue (IAAT) and hepatic fat than predicted by clinical anthropometric indices may exhibit an elevated risk of metabolic diseases despite a BMI within the normal range. Therefore, the accurate quantification of these potentially hazardous depots together with the identification of novel subphenotypes that recognize individuals at potentially increased metabolic risk is needed. In this line, the group of Prof. Bell has calculated a reference range for total and regional adipose tissue as well as ectopic fat in liver and muscle in healthy subjects.[12] The relationship between age, body-mass, BMI, waist circumference, and the distribution of adipose tissue, using whole-body magnetic resonance imaging (MRI), in 477 white volunteers (243 male, 234 female) was studied. Furthermore, proton magnetic resonance spectroscopy (MRS) was used to determine intrahepatic and intramyocellular lipid content. The study identified a large variation in IAAT, abdominal subcutaneous adipose tissue (ASAT), and liver fat depots not fully predicted by clinically obtained measurements of obesity applying the determination of BMI and waist circumference. These findings highlight the emergence of a previously unidentified subphenotype coined as "TOFI" standing for "thin outside, fat inside", which is accompanied by an increased metabolic risk in the setting of an apparently normal or even lean phenotype.[12]

Need for redefining success in obesity management

Clinical guidelines recommend weight loss as a primary treatment strategy for obesity reduction. Weight loss goals range from 5-10% of initial body weight. However, it has to be stated that intentional weight loss in adults may not be necessarily associated with adiposity reduction (Fig. 2) and, consequently, an improvement in many of the health complications of obesity. Moreover, emerging evidence supports the notion that a lifestyle-modification program characterized by a balanced diet and an increase in physical activity can reduce adiposity as well as the risk of obesity-related comorbid conditions despite minimal or no weight loss (Fig. 3). The benefits of such an approach include appreciable reductions in abdominal obesity, visceral fat and cardiometabolic risk factors, and increases in both skeletal muscle mass and cardiorespiratory fitness.[13] It is therefore important that clinicians are aware of focusing more on adiposity than on body weight or BMI per se. This approach should be translated to the patient to face collaboratively the serious challenge of obesity management. Thus, clinicians should encourage positive lifestyle changes in their patients by counselling them about the importance of improving their body composition. More emphasis on the role of physical activity as a treatment and (or) preventive strategy for combating obesity should be placed. While most of the research has focused solely on reductions in total body weight it is equally important to focus on fat mass and cardiorespiratory fitness as indicators of treatment success.[14] Given that fat deposition in the visceral adipose tissue as well as in the liver and skeletal muscle plays a major role in the development of obesity-related health risks, these depots should emerge as relevant new targets for obesity treatment.

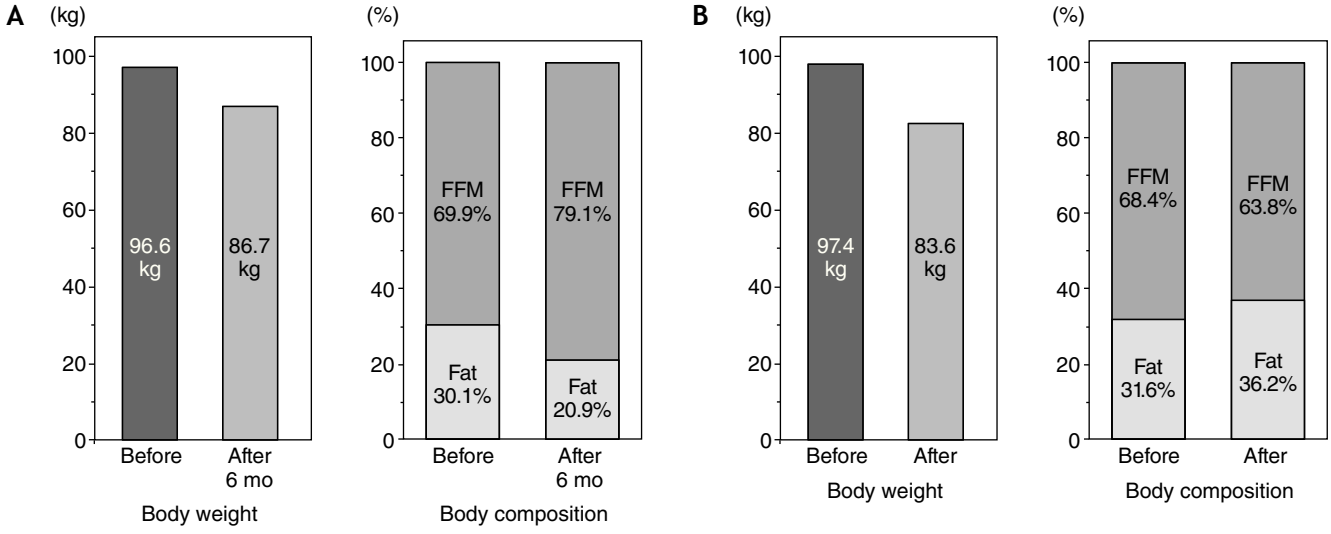

Figure 2 Relevance of body composition analysis in treatment evaluation. Example of parallel body weight and body fat reduction 6 months after following a lifestyle intervention (A) as opposed to an increase in body fat percentage in spite of a significant body weight loss during the same follow-up time (B).

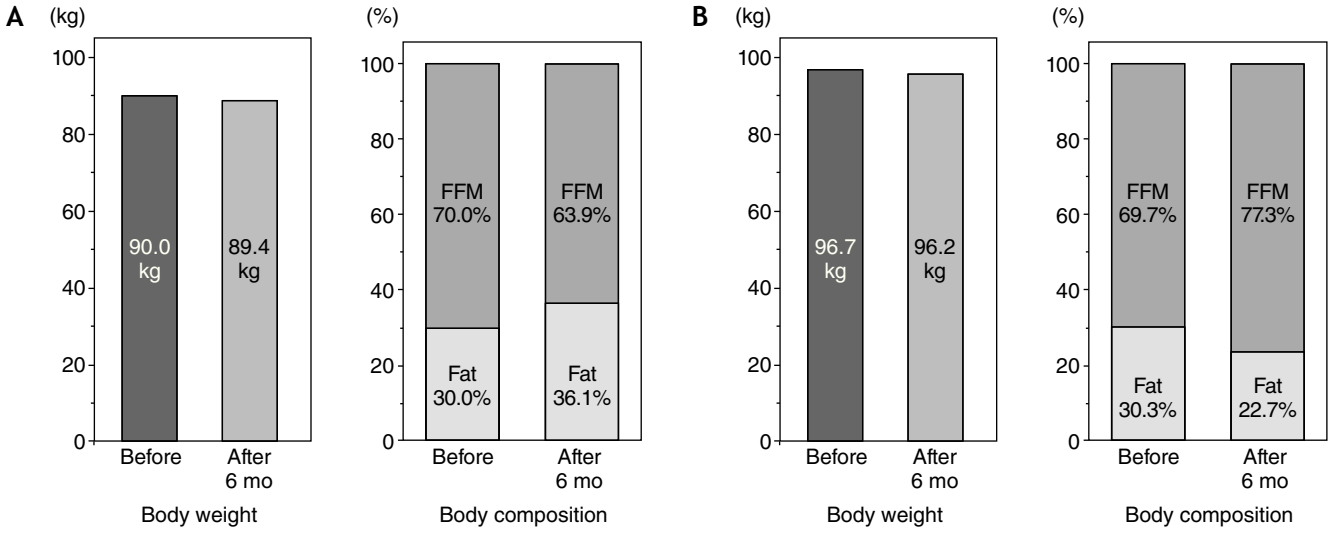

Figure 3 Importance of body fat assessment in the evaluation of real treatment success. Example of a successful body fat reduction 6 months after following a lifestyle intervention despite the lack of changes in body weight (A) as opposed to an unsatisfactory body fat increase without changes in body weight during the same follow-up time (B).

This approach and reasoning can and should be applied to evaluate the success of bariatric surgery. While there is no doubt that bariatric surgery is the most effective treatment for carefully selected patients,[15] it has also to be stressed that in the long-term the amelioration of some of the cardiometabolic conditions such as hypertension or hypercholesterolemia decreases over time and even looses statistical significance after 10 years of undergoing the bariatric procedure, probably in relation to an increase in the above-mentioned relevant body fat compartments.[16]

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Conflicts of interest

The author declares that she has no conflicts of interest in this article.

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