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EDITORIAL

Obesity is a chronic progressive relapsing disease of particular interest for internal medicine

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Introduction

We are pleased to announce the launch of a new web-edited "Topical Collection" that will gather both original and review articles addressing the most relevant aspects of obesity effects on body systems. We believe is about time that obesity enters fully into the internal medicine arena, and we will dedicate this Editorial to further make the case of obesity being a disease.

The initial core of this new topical collection will be represented by invited articles from leading international experts on obesity and will deal with: clinical evaluation of patients with obesity (by Barbara McGowan, from Guy's and St. Thomas NHS Foundation Trust, London, UK), mechanisms of weight loss and regain after obesity surgery (by Carel Le Roux, from the University College Dublin, Dublin, Ireland), NAFLD as the metabolic hallmark of obesity (by Andreea Ciudin from the University Hospital Vall d'Hebron, Barcellona, Spain), pharmacotherapy for chronic weight management: look into the future (by Alex Miras from the Imperial College, London, UK). But the Collection will be open, and without time limits, to any scientific contribution related to the clinical impact of obesity and its treatment.

We hope that this collection will offer the readers of internal and emergency medicine a valuable tool to overview the most recent advances, seek research collaborations, and increase their knowledge in the obesity field.

Obesity as a chronic progressive relapsing disease

Although obesity causes a very long list of disabling, social and potentially deadly complications (cardiometabolic, mechanical, neuropsychiatric and neoplastic), in some areas of medicine and among the vast majority of policymakers and stakeholders it is still believed that it is a trivial lifestyle problem due to incorrect, but yet reversible, personal choices.

For too many years, the definition of obesity was based on a correct but yet misleading assumption: "The amount of the excessive accumulation of adipose tissue that characterize obesity is equivalent, according to the first law of thermodynamic, to the difference between caloric intake and energy expenditure". According to this definition, obesity may be seen as a simple nutritional condition, caused by an excessive caloric intake, either absolute or relative to low energy expenditure. On this basis, therefore, it would be warranted to simply suggest persons with obesity to "eat less and move more". In other words, obesity as a result of wrong reversible personal choices. This erroneous view has largely contributed to the stigmatization of persons with obesity considered lazy, glutton and without will power.

Today, while the tide of the obesity pandemic is rising at alarming pace, recognizing obesity as a chronic disease should be the first and foremost step to face the many and dreadful challenges that it poses: clinical challenge, with the many complications (type 2 diabetes, arterial hypertension, atherogenic dyslipidemia, cardiovascular disease, many tumors especially of the gastrointestinal tract, obstructive sleep apnea syndrome, infertility, arthropathies, depression and many others), socio-cultural challenge; psychologic-psychiatric challenge, rehabilitation challenge and public health

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problem. Finally, obesity represents the major contributor to the alarming increase of the non-communicable diseases, that threatens health systems globally.

Obesity is, therefore, a complex disease, and although multidisciplinarity is the key, a holistic view is also needed; in this regard, the medical discipline more entitled to target complexity with the ability to look at organ systems as a whole interconnected network is internal medicine.

Disease definition

A precise and scientific definition of disease does not really exist. Certainly, a disease may be defined as a condition, caused by a specific pathogenic factor, that reduces the well-being for the appearance of specific symptoms and may be recognized by specific signs. In this regard, although it can be easily argued that obesity fulfill all of these requirements, it is also true that for many diseases listed in the International Classification of Diseases (*i.e., thypus, pemfigo, type 1 diabetes,* etc.*)* the etiopathogenetic-clinical links are more robust and do not need much of reasoning to reach a definition of disease. Perhaps, if the prevalence of obesity was very low, we could continue to consider it a form of malnutrition for excessive energy consumption; hence a utilitarian need arises: the society when faced with a danger, take special measures to deal with it. In the case of obesity, one of these measures is precisely to consider it a chronic, progressive and relapsing disease [1].

Defining obesity as a disease: more pros than cons

A brief history of the definition of obesity as a disease

The controversy surrounding the definition of obesity as a disease date back more than half a century ago. Today, in the face of a devastating and growing pandemic, it is urgent to move from philosophy to pragmatism, taking on the responsibilities of knowledgeable and experts in this field who know very well the consequences and critical issues of obesity prevention and treatment. In this sense, the progressive positions taken by the main US bodies and scientific societies must be taken into account. From the American Health Care Financing Administration that in 1977 decides that obesity is not a disease to the American Medical Association (AMA) that in 2013 recognizes obesity as a disease with multiple pathophysiological aspects that require interventions to improve treatment and prevention. Finally, in 2017, the World Obesity Federation (WOF) defines obesity as a chronic progressive and relapsing disease [2].

Among all, the position of the AMA is the one that has aroused the most intense reactions; on the one hand, the approval of both doctors, for the possibility of using more effective tools for the management of obesity and patients, for having obtained a sort of certification of their innocence. On the other hand, and conversely, some personalities in the medical world expressed concern about the removal of personal responsibility for following unhealthy lifestyles. The latter together with the concern of some patient associations for a different form of discrimination, are the main "cons".

Among the "pros", certainly the possibility of engaging politicians in national plans for treatment, as well as for prevention, which include the possibility of reimbursements for drugs that should gradually increase in number and effectiveness; the reduction of stigmatization and bullying against the obese; inclusion in the university core curriculum of obesity medicine; the protection of consumers against "seven kilos in seven days" scams, miraculous supplements or procedures that at times seriously endanger the health of those who use them; discrimination in the workplace; greater stimulus to research the mechanisms that regulate energy homeostasis and the genetics of obesity.

Personal choices against biological impact

Given that all our choices are subtended, in part, by a biology moved in turn by our genetic (and epigenetic) makeup, the strength or otherwise of the genetic determinants in the development of obesity are a valid indicator for or against the hypothesis that obesity is a disease. In other words, are the obese individuals without willpower that create problems for themselves and others, or are they affected by molecular alterations of ancestral circuits that in the presence of free access to food make it impossible not to gain weight?

That there is a genetic predisposition is demonstrated not so much by the family aggregation that could depend on exposure to similar living conditions but, above all, by the studies carried out in monozygotic twins raised together or separated in which the correlation of the body mass index (BMI) intra-pair does not change in the two conditions; and from studies of adopted children that have shown that the influence of the environment in determining the BMI of the biological and adoptive child is negligible [3]. This susceptibility to developing weight gain becomes evident in the presence of environmental conditions that favor the unlimited availability of food and a sedentary lifestyle. From these studies, it was possible to calculate that the contribution of heredity to the development of obesity varies from 40 to 70% [4].

In the last 10 years, in a progressively more advanced way from the technological point of view, the results of various so-called genome-wide association (GWAS) studies have

been published, that were able to scan the entire genome of a large number of subjects (up to a few hundreds of thousands in the latest studies), to identify genetic variants associated with BMI. The most interesting results have recently been obtained from the broader meta-analysis both in terms of subjects studied (almost 340,000) and of polymorphisms (SNPs, single nucleotide polymorphisms), from which 97 loci associated with BMI emerged [5]. Importantly, all of these loci affect genes expressed at the level of the central nervous system.

Furthermore, it is noteworthy that all the monogenic obesities identified so far concern exclusively genes encoding hypothalamic proteins (with the exception of leptin) mainly involved in the regulation of appetite [6]. Homozygous or compound heterozygous mutations of five genes involved in the signal transmission pathways within the leptin–melanocortin system are responsible for murine obesity and its corresponding forms in humans. On the basis of these data, it can therefore be stated that: (1) obesity can derive from a simple genetic defect which, in the case of leptin, can be treated with hormone replacement therapy and in the case of proopiomelanocortin (POMC) or leptin receptor gene mutations can be treated with setmelanotide, a new melanocortin-4 receptor agonist [7]. (2) All the genetic defects described so far that cause monogenic forms of obesity act by altering the hypothalamic mechanisms that regulate appetite and, above all, satiety.

From these data, it is clear the role of genetics in the development of obesity, in particular of the genetics of the molecules that regulate energy homeostasis at the level of the central nervous system.

Although the extreme inter-individual variability of body weight appears not to be compatible with a strict homeostatic control of energy deposits, the force with which our body reacts to a weight loss in each individual explains the existence of a control system that senses energy flows although react with more indulgence, for evolutionary reasons, to caloric inflow.

It has been hypothesized that there was a homeostatic system for controlling energy balance more than half a century ago, but the molecular mechanisms underlying the dialog between energy supplies and the brain have been progressively clarified starting with the discovery of leptin in 1994 [8]. At the level of the arcuate nucleus of the hypothalamus there are the two neuronal nuclei, which express, respectively, the neuropeptide-Y (NPY) and the pro-opiomelanocortin (POMC); they represent the heart of the homeostatic control unit and control the caloric intake and energy expenditure on the basis of hormonal (mainly leptin), metabolic and mechanical signals that they receive from the periphery. Leptin inhibits NPY neurons with a drying action and stimulates POMC neurons from which, by cleavage, alpha-MSH originates which, interacting with the melanocortin-4 receptor (MC4R), carries the main anorectic signal [9].

This homeostatic system, as mentioned, is not calibrated as tightly as the systems that control, for example, blood pH, water and electrolyte balance or plasma osmolality. It has evolved over hundreds of thousands of years characterized by a very poor food environment and is regulated asymmetrically: it is able to react efficiently in case of weight reduction and, on the contrary, tends to be more permissive toward weight gain.

Furthermore, the hypothalamic nuclei are influenced by many other factors, such as sight, smell, taste, the emotional sphere and the so-called hedonic system (regulated by the nucleus accumbens and the dopaminergic system): the hedonic system strongly influences the palatable food intake regardless of energy needs. The entire system is archaic and dedicated to the regulated intake of the primary source of survival: nutrients.

The set of these regulatory mechanisms comes into play powerfully when weight is intentionally lost: the body senses the threat of energy deprivation (regardless of the benefit to which it leads) and triggers a hormonal and neurotransmitter counter-reaction which, in association with the reduction of energy expenditure that characterizes weight loss, tends to bring the weight back to the original one [10]. In fact, the homeostatic centers adapt to a new set point, reached after a usually slow but progressive weight gain. For this reason, the real challenge is to maintain the weight lost.

In conclusion, the data showing how strong are the genetic, epigenetic, biological and hormonal determinants in the development of obesity are overwhelming. They potently counteract caloric deprivation inducing weight regain, even after educational and cognitive–behavioral therapy: it is therefore not a matter of wrong and reversible personal choices!

Certainly, the role of the environment is equally fundamental and obesity is part of the list of evolutionary mismatch pathologies: the progressive selection, in times characterized by poor access to food, of genes capable of both optimizing energy storage and allowing the intake of a high number of calories when available while encouraging energy conservation by avoiding physical activities when not strictly necessary, makes, today, those who are carriers more susceptible to weight gain.

When does the disease process begin?

From a pathophysiological point of view, the pathways that progressively lead to the development of the main complications of obesity have been well characterized and demonstrated [1, 2]. From a clinical point of view, different disease staging systems have been proposed and adopted [11, 12]

that start from a condition of obesity in the absence of any abnormality up to the terminal stage of extreme disability and overt organ damage.

But should obesity be considered a disease in itself or does it need complications to develop before it can be considered as such? We could argue that an obese young man who has no obvious health problem could be compared with a hypertensive or hypercholesterolemic person who has not yet developed organ damage. However, these conditions, due to the high risk of mortality from cardiovascular causes, are considered diseases and the patients in question undergo pharmacological treatment.

Two main reasons explain the resistance to consider obesity, when uncomplicated, as a disease.

The first is that prospective studies are only now beginning to be capable of calculating the risk of death (from cardiovascular causes or from cancer) in patients divided into groups with different complications. In most studies, the definition of metabolically healthy obesity is mainly based on the absence of the metabolic syndrome (or some of its components). Whether metabolically healthy obesity represents a true health condition in the obese patients has been the subject of heated debate. Recently, some evidence has suggested that obesity, regardless of whether metabolically healthy, would carry an increased risk of death and CV disease, and therefore MHO may not be so "healthy" as originally supposed. In fact, it appears that the metabolically healthy obese is such only when we make a snapshot on an obese individual who does not show any of the alterations of the metabolic syndrome. However, if instead we prospectly follow his or her fate, we would be able to witness two possible scenarios. In the first scenario, one or more of the metabolic alterations appear over time that transform our patient into unhealthy. In the second scenario, our patient, even maintaining a metabolically healthy profile, over time accumulates a CV risk that differs significantly from that of his/her normal weight counterpart [13–17]. In addition, MHO still can have the non-metabolic complications of obesity like musculoskeletal, mental or malignant diseases.

The second is linked to the concept of the "obesity paradox", that is the theoretical advantage, in terms of mortality, that overweight and obesity of the first degree would confer in some pathological areas including heart failure. Recent data would show that the paradox is only apparent. In a prospective study that included nearly 300,000 individuals from the UK Biobank [18], and which has the merit of having studied five different measures of adiposity by relating them to the number of cardiovascular events, it was found that CV risk increases linearly in almost all measurements (waist circumference, waist/hip ratio, waist/height ratio, fat mass percentage) in the absence of paradoxical observations.

In addition, it must be said that the concept of obesity paradox is most often based on cross-sectional studies and can derive from statistical bias (selection, survival) or unintentional weight losses that would invalidate the data. One of the strongest statistical biases that can lead to the "paradox" effect is the so-called inverse causality, i.e., when there is unintentional weight loss before the weight is measured and the patient is enrolled in a prospective study. This bias contributes to the conclusion that the risk of morbidity/mortality is lower in overweight and mild obesity. A recently established method of neutralizing reverse causation bias is Mendelian randomization. This methodological approach is based on the use of gene variants that predispose to obesity and which, through a complex analysis, are able to normalize the data excluding the *bias* in question.

With this approach, it has recently been shown, in a weighty prospective study with a follow-up of 18 years in over 400,000 individuals [19], that the relationship of body mass index/cardiovascular mortality tends to be linear, thus excluding any paradoxical effect.

Conclusions

According to the World Health Organization "obesity represents an unprecedented public health challenge for Europe, hitherto underestimated, poorly evaluated and not perfectly accepted as a strategic government problem associated with significant economic implications"; therefore, continue to consider it a trivial hypernutrition problem linked to reversible wrong behaviors is now completely reductive. Obesity is the cause of disabling complications that significantly shorten life expectancy. Using definitions such as "metabolically healthy obesity" is misleading and inappropriate; and the concept of the obesity paradox rests most of the time on statistical biases.

In conclusion, therefore, it is time for obesity to be fully considered a chronic, progressive and relapsing disease; it is indeed so even when, in the initial stages, it is not associated with any complication. Doctors, medical university professors, policy makers and patients must henceforth adapt to a new way of conceiving the global management of obesity. The challenge of a progressive increase in its prevalence must not catch us unprepared: networks of specialized multidisciplinary centers for obesity treatment will have to be organized that can cope as much as possible with the difficult management of obesity; the teaching of the biological bases and the clinic of obesity must be included in the core curriculum of medical courses; national plans for obesity will have to be developed as has been done, for example, for diabetes. Finally, patients and their associations must ensure that their right to health is guaranteed and that no discrimination occurs.

Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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