

Preface

On the Molecular Mechanisms Underpinning the Development of Obesity

Obesity and overweight are defined as abnormal or excessive body fat accumulation, possibly due to an imbalance of excess energy intake and reduced energy expenditure. This excessive fat accumulation can reach levels capable of affecting health, thus contributing to an increased risk of developing certain disorders.

The existence of obesity seems almost as ancient as humans, and from an evolutionary perspective it is very tempting to consider as a strategy for storing food reserves. In fact, during most time of human history, obesity could be an advantage character in times where food was scarce. The ability to store energy as fat from the least possible amount of food intake might have constituted a selective advantage. Thus, during many times in human history obesity was considered beneficial. Only in the XVIII century people start realizing that excessive body fat could have a negative impact in life quality. With the documentation of morbid complication and increased mortality associated with obesity it started to be recognized as a cause of ill health. In 1997 the World Health Organization (WHO) declare it a global epidemic and worldwide public-health crisis. Actually, the WHO considers overweight and obesity major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer. In 2010, overweight and obesity were estimated to cause more than 3.4 million deaths worldwide. Following an intense debate and controversy, in 2013 the American Medical Association recognized obesity as chronic disease in an attempt to reverse the epidemic rise of obesity. According to this decision, the diagnosis and treatment of obesity becomes a professional obligation for physicians. All these health consequences contribute to important economic costs for health systems, with estimates suggesting that obesity is responsible for approximately 1–3 % of total health expenditure in most countries (in United States the estimates point to a cost of 5–10 % of health expenditures).

Obesity was first considered a problem only of wealthy nations, however currently it has an important impact in developing countries, affecting economy, pro-

ductivity and health worldwide. According to WHO the obesity levels across the world nearly doubled in the past 30 years, and the current numbers are scary. In 2008, more than 1.4 billion adults (20 years of age and older) were overweight, which corresponded to 20% of world population. From those, almost 200 million men and 300 million women were obese. In 2012 more than 40 million children under the age of 5 were overweight or obese. In developed countries from The Organization for Economic Co-operation and Development (OECD) around 53% of the population are overweight or obese, with 21 from the 34 countries of OECD having a prevalence above 50% in adults. Over the past 10 years the obesity prevalence increased more than 40% in countries like Denmark, France or Sweden and the OECD average raised from 13% in 2000 to 18% in 2010. In a recent study reporting obesity trends worldwide from 1980 to 2013 found an increase not only in the proportion of overweight or obese adults (both men and women), but also in children and adolescents. According to the study, the proportion of adults with a BMI of 25 kg/m² or greater increased in 33 years from 28.8 to 36.9% in men, and from 29.8 to 38% in women. In children and adolescents the prevalence of obesity and overweight has increased in developed countries (23.8 and 22.6%, in boys and girls, respectively), but also in developing countries with an increase around 5% from 1980 to 2013.

But how is obesity defined? As it was mentioned overweight and obesity are an excessive accumulation of body fat, which is difficult to measure. Therefore, measures based on quantitative anthropometric characteristics are used to define obesity. Currently, the body mass index (BMI), which is a simple index of weight-for-height, is most commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m²). The BMI is a measure that was devised in the 19th century by Adolphe Quetelet, although only in 1972 did it become a world reference for measuring body fat. Decades of research have shown that BMI provides a good estimate for body fat, although more sophisticated and accurate measures are also being used nowadays. Currently, it is widely accepted that BMI is a reliable and easy way to access to body fat, and those are two of the most important advantages of its use as an obesity measure. Also importantly, several studies related the risk of developing health problems and risk of death with BMI. According to WHO for a healthy adult the BMI should range from 18.5 to 24.9 kg/m². Overweight is defined as a BMI of 25–29.9 kg/m², whereas obesity is defined as a BMI above 30 kg/m². If for adults these cutoffs are more or less conventional, the definition of children obesity based in BMI was more controversial. Depending on the age and gender, it is normal for children and adolescents to have different amounts of body fat, thus several scales based in age and gender are currently used (WHO, United States the Centers for Disease Control and Prevention, and International Obesity Task Force). Despite the great advantages and the broad use, BMI have also some limitations. For example, being an indirect measure of body fat it does not distinguish between body fat and lean body mass. Also, it is not so accurate in younger ages compared to adults and it does not take into account normal differences between gender or ethnic groups. Thus, other indirect methods were developed to measure body fat (for example

waist circumference or waist-to-hip-ratio), and currently more sophisticated direct methods such as magnetic resonance imaging or dual energy X-ray absorptiometry are being used. However, despite all these methods and techniques, BMI remains the simple, cheap and most used measure of obesity.

Obesity and overweight arises in a simple way as an energy imbalance between calories consumed and calories expended. However, currently obesity is understood as a multifactorial disorder. If it is clear the effect of environment and food consumption in obesity, it is also widely accepted the effect of a genetic component in the increased risk of developing obesity. Moreover, it becomes increasingly clear the contribution of other mechanisms (like epigenetics, neurotrophic factors, microRNAs) in obesity. However, the factors underlying the development of obesity are still largely unknown. If in monogenic forms of obesity, the gene and the particular causing mutation is identified, in polygenic forms of obesity the contributions of mutations and genes are not yet completely understood. What emerges from the last decades of research is that obesity is a complex trait resulting from interplay of an obesogenic environment and a genetic background. In this book entitled: *Molecular Mechanisms Underpinning the Development of Obesity* we try to provide a state-of-the-art revision about the molecular mechanisms that could be in the basis for developing obesity, reviewing the current knowledge in areas like monogenic and polygenic obesity forms; but also providing an updated view of the emerging knowledge about epigenetics, microRNAs, and neuronal aspects that may also contribute to obesity.

Clévio Nóbrega

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Nobrega, PhD, C.; Rodriguez-Lopez, PhD, R. (Eds.)

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