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Narrative Review

Obesity phenotypes and their paradoxical association with cardiovascular diseases

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ABSTRACT

The pro-inflammatory state of the visceral adipose tissue (VAT) is supposed to accelerate cardiovascular (CV) and metabolic diseases in obese subjects. Some studies have recently reported an improved CV prognosis in certain obese and overweight patients as compared with leaner ones. This phenomenon, known as the "obesity paradox" (OP), has been described in many chronic diseases. This narrative review is based on the material searched for and obtained via PubMed and Web of Science up to May 2017. The search terms we used were: "obesity, paradox, adipose tissue" in combination with "cardiovascular, coronary heart disease, heart failure, arrhythmias". Using the current Body Mass Index (BMI)-based obesity definition, individuals with different clinical and biochemical characteristics are gathered together in the same category. Emerging evidence point to the existence of many "Obesity phenotypes" with different association with CV risk, accordingly to physical and life-style features. In this narrative review, we discussed if obesity phenotypes may be associated with a different CV risk, potentially explaining the OP. As a globally accepted definition of obesity is still lacking, we emphasized the need of a new approach, which should consider the heterogeneity of obesity. Better defining "obesities" and related CV risk is critical to markedly improve the classical BMI-based definition of obesity.

1. Introduction

In the last decades, the prevalence of obesity has increased worldwide, reaching epidemic proportions [1]. From 1975 to 2014, mean body mass index (BMI) globally increased in both women and men [2]. Body weight gain is due to a chronic positive energy balance, occurring when energy expenditure is less than energy intake. Even though a number of studies suggest that the major cause of obesity could be related to an abnormal food intake [3], some behavioral changes have recently occurred (e.g. the great reduction in occupation-related activity and household management energy expenditure) [4], giving additional explanations for the ongoing global weight gain. Moreover, the development of obesity is strongly associated with socio-economic status and environmental factors, which may determine epigenetic modifications throughout gene-environment interaction [5]. Adipose tissue dysfunction in obese subjects causes abnormal inflammation by an imbalance in adipocytokines production, which is associated with the development of cardio-vascular diseases (CVDs) and of several site-specific cancers [6–8]. Despite a considerable number of data supporting these notions, in several studies overweight and obese patients have shown a better prognosis as compared with leaner ones, a phenomenon known as "obesity paradox" (OP) [9,10]. Several potential explanations for this paradox have been recently suggested. They include the presence of statistical errors in studies on OP, such as the reverse causation and the collider stratification bias [11,12]. Other authors underlined the influence of the duration of follow-up and the level of physical activity (PA) [13,14]. However, there is not a global consensus and the debate on the existence of the OP is still opened.

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Moreover, obese subjects seem to have heterogeneous phenotypes, each one associated whit different degree of cardiovascular (CV) risk. At this regard, some authors coined the term Metabolically Healthy Obesity (MHOB) referring to an obese phenotype without metabolic syndrome and presenting lower CV risk as compared with other obese phenotypes [15]. The opposite condition is represented by Metabolically Obese Normal Weight (MONW), a subgroup of individuals with normal BMI but characterized by obesity-related metabolic complications [16].

In order to potentially explain the OP, we focused in the following paragraphs on the different association between obesity phenotypes and CV risk. Critical points and future perspectives on OP definition were also discussed. Our search was based on publications on PubMed and Web of Science up to May 2017. The search terms we used were: “obesity, paradox, adipose tissue” in combination with “cardiovascular, coronary heart disease, heart failure, arrhythmias”.

1.1. Adipose tissue composition and adipocytokines

Adipose tissue (AT) is now considered as an endocrine organ with several functions in different physiological pathways that overwhelmed its “classical role” in energy homeostasis and thermoregulation. It is a dynamic tissue, able to expand in response to excessive food intake and to release nutrients throughout lipolysis in case of food scarcity. In the human body two principal types of AT can be recognized: the brown adipose tissue (BAT), localized in supraclavicular and paravertebral regions, and the white adipose tissue (WAT). The latter includes subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) surrounding abdominal organs. The excess of fat deposition in VAT and in deep SAT has been associated with increased mortality and morbidity risks [17,18]. There are several possible explanations for these correlations. First of all, this kind of fat is more prone to lipolysis, showing a strong resistance to the anti-lipolytic action of insulin. As a consequence, patients' liver is exposed to a high concentration of free fatty acids throughout the portal vein circulation, thus causing an alteration of its metabolism with an increased release of triglyceride-rich lipoproteins and glucose. Secondly, VAT has a pro-inflammatory profile, favoring the development of CV and metabolic diseases [19], as discussed below. Finally, some individuals are unable to produce new adipose cells in SAT in response to a positive energy balance. As result, fat accumulates in usually lean tissues, such as liver, heart and skeletal muscle [20]. Some ectopic fat depots seem to have a systemic action, while others, such as both pericardial and perivascular fat, are postulated to have predominantly local effects [21]. However, all of them have shown an association with an altered cardio-metabolic profile. Chronic positive energy balance leads to deep AT remodeling characterized by an increase in adipocyte size (hypertrophy) and number (hyperplasia) together with the modifications in immune cell subset AT composition [22]. Both under physiological and pathophysiological conditions, adipocytes can secrete > 50 cytokines, hormones and peptides, known globally as adipocytokines, which play an important role in local and systemic regulation of energy homeostasis and inflammation [19,23]. In particular, hypertrophic adipocytes in obese individuals showed an unbalanced adipocytokines production, with an increased secretion of a number of pro-inflammatory mediators, such as leptin, resistin, interleukin (IL)-6 and tumor necrosis factor-α (Fig. 1) [19]. The switching to this pro-inflammatory pattern has been associated with some obesity comorbidities, including CVDs, insulin resistance, diabetes and cancer [24]. Noteworthy, also the transforming growth factor-1 has been associated with detrimental effects of BMI, especially with hypertensive renal disease [25,26].

2. Current definition of obesity

The World Health Organization (WHO) defines obesity as an abnormal fat accumulation [27]. In the clinical practice, obesity is currently diagnosed by the assessment of BMI [28], a surrogate measure of body fat (BF) based on the person's weight adjusted for height. Independently from age and sex, obesity is categorized in different classes, accordingly with BMI increase. Whereas a BMI between 25 and 29.9 kg/m^2 defines overweight patients, those with BMI > 30 kg/m^2 are categorized as obese. Among them, a BMI between 30 and 34.9 kg/m^2 identifies a class I obesity, between 35 and 39.9 kg/m^2 class II, and > 40 kg/m^2 a class III, also known as morbid obesity (Table 1). Lower BMI thresholds were recently proposed to define obesity in Asians, considering the higher percentage of BF and the elevated prevalence of CVD even at BMI < 25 kg/m^2 in these ethnic groups [29], while adjustments for other races are still missing. Different classes of obesity have been associated with progressive hemodynamic impairment and changes in cardiac structure [30]. Significantly higher values of left ventricular (LV) mass are typical of all classes of obesity compared with lean controls. Similarly, elevated LV filling pressure due to impaired diastolic filling or relaxation is frequently recorded in classes II and III. Accordingly, an obesity-related form of heart failure (HF) with preserved ejection fraction (HFpEF) has been also characterized [31]. However, myocardial dysfunction in obese patients has been recently associated with poor metabolic health rather than simply BMI or fat mass [32]. Indeed, BMI is not able to discriminate between fat mass and muscle mass, despite the latter is associated with lower risk of premature death [33,34]. Moreover, fat localizations cannot be represented by BMI, whereas abdominal adiposity is recognized to be more closely associated with CVD and other chronic diseases than other adipose depots. Many studies have suggested to use other anthropometric measures to better evaluate VAT amounts, such as waist circumference (WC) [22] and waist-to-hip ratio (WHR) (Table 1) [35]. To date, WC measure is recommended in overweight and class I obese patients with a cut-off point of 102 cm in men and 88 cm in women [36]. Krakauer and colleagues proposed a new algorithm to measure of body shape, A Body Shape Index (ABSI), based on WC, weight and height [37]. A high ABSI indicates a WC higher than expected for a given height and weight and it is associated with higher central fat distribution and mortality [37]. Accordingly to BMI limits, it has been recently shown that BMI has a J-shaped relationship with CV death, whereas all visceral adiposity measures have displayed a positive linear association [38]. Those different relationship should been considered designing clinical studies and analyzing their results.

3. Definition of obesities

Data coming from recent literature suggest the coexistence of various phenotypes with a different CV risk profile within the same BMI category.

3.1. Metabolically Healthy Obesity

The metabolically healthy obese (MHO) phenotype refers to a subset of obese individuals in which high BMI is associated with a healthy metabolic profile, characterized by high insulin sensitivity, favorable lipid profile and low pro-inflammatory cytokine levels in plasma and AT (Fig. 2) [39,40]. Moreover, MHO patients have a lower amount of VAT and liver fat than metabolically unhealthy obese (MUO) subjects [39]. They have a lower risk for CV events and mortality which is comparable to normal weight subjects [41,42]. MHO subjects have shown lower intima media thickness values, supporting the evidence of a less prone-to-atherosclerosis phenotype [43]. Furthermore, in MHO myocardial function is preserved independently on BMI or fat mass [32]. The prevalence of MHO is about 10–30% in European obese adults and is higher in women than in men decreasing in older patients [44]. Even if MHOB has been described as a benign condition, many studies have shown instead that MHOB increases the risk for CVD, chronic kidney disease, and fatty liver disease [28,45–47]. Hence, the MHO phenotype does not seem to be a harmless condition, especially