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OBESITY AND CARDIOVASCULAR RISK

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Current state of knowledge

The World Health Organization (WHO), according to the International Classification of Diseases, defines obesity as the abnormal or excessive accumulation of fat, resulting from an interaction of genotype and the environment, creating an energetic imbalance that involves the integration of social, behavioral, cultural, physiological, metabolic, and genetic factors[1].

The World Obesity Federation (WOF) has characterized it as a chronic, recurrent, and progressive disease, emphasizing the need for immediate action for prevention and control[2].

According to world data from the WHO, the prevalence of obesity has tripled since 1975. 39% of the population over 18 years of age is overweight and of these, 13% are obese[3]. Data from Latin America, in the Argentine Republic, the prevalence of excess weight by self-report (overweight and obesity together) in the 4th Edition of the National Survey of Risk Factors (ENFR) was 61.6%, comparatively higher with respect to previous editions[4]. In the 2020 European Health Survey, in Spain the prevalence of obesity is 16% and overweight is 37.6% and increases in all age groups up to 75 years[5].

Overweight and obesity are associated with increased morbidity and mortality and increasing health costs, mainly in low- and middle-income countries[4].

In 2010, it was estimated that globally, overweight and obesity caused 3.4 million deaths, 3.9% of years of life lost, and 3.8% of disability-adjusted life years (DALYs)[6].

Numerous studies have shown a relationship between obesity and cardiovascular diseases (coronary heart disease, acute myocardial infarction, heart failure, cardiac arrhythmias) and that weight loss in overweight and obese people, reduces cardiovascular disease risk factors such as diabetes, hypertension, dyslipidemia, and sleep apnea, among others[7].

Obesity can contribute to elevated cardiovascular morbidity and mortality through both direct and indirect mechanisms. Directly, it triggers structural and functional adaptations to accommodate excess body weight, fosters the development of an inflammatory and prothrombotic state. Indirectly, it amplifies the risk through associated factors like insulin resistance, type 2 diabetes, visceral adiposity, hypertension, and hyperlipidemia[8].

Enhanced cardiac imaging techniques allow early detection of altered heart structures and functions in patients with obesity, enabling the treatment of subclinical medical conditions and, therefore, preventing cardiovascular events.

The WHO defines CVD as the leading cause of death worldwide, with a rate of 17.7 million deaths per year, and obesity as an independent risk factor for CVD and mortality from all causes[9].

The goal of a proper evaluation of a patient with obesity is to gather information to confirm the diagnosis, determine the severity of the disease and related comorbidities, identify triggers and drivers, and guide appropriate care in an unbiased and stigma-free clinical setting.

Healthcare professionals should initiate patient-centered care, discussing values and treatment goals, fostering reflection, and encouraging responsibility to promote long-term improvements.

Diagnosis and evaluation

The rise in non-communicable diseases (NCDs) compounded by an aging population is leading to a surge in healthcare demands. Within the scope of obesity, the intricate nature of the disease, characterized by multifaceted factors, poses a challenge in seamlessly integrating knowledge, research findings, and translating them into comprehensive clinical care[10].

The diagnosis of obesity is established with a body mass index (BMI) $\geq$ 30 kg/m^2. Although BMI is a highly useful, simple, and easy-to-apply assessment method, it serves as a surrogate measure for fat mass, with adiposity being the truly critical body compartment regarding the development of comorbidities[11].

The INTERHEART study demonstrated that central obesity is more strongly linked to cardiovascular risk than total adiposity expressed by BMI[12].

For most populations, the presence of overweight (BMI ≥ 25 kg/m^2) represents a higher risk and requires additional evaluation of other anthropometric, hemodynamic, and biochemical parameters.

Considering the limitation of BMI in determining fat composition and distribution, the use of waist circumference (WC) has been recommended as a surrogate measure of abdominal or visceral fat, as there is epidemiological evidence suggesting that WC can help identify individuals at higher risk of cardio-metabolic disease. Currently, the recommended WC cutoffs should be adapted to the ethnic group and geographical area. In general, they should be < 90-94 cm in males and < 80 cm in females[13]. Higher values suggest a greater risk of visceral adiposity and the development of cardio-metabolic comorbidities[13].

WC is not a direct measure of visceral fat and requires considerable training and standardization among different healthcare team members conducting the measurement and analysis to ensure reproducibility.

Thus, recognizing the coexistence of various obesity phenotypes based on body composition and cardio-metabolic risk profiles is crucial. This includes individuals who are obese but have a normal weight, exhibiting greater visceral adiposity, hyperinsulinemia, insulin resistance, dyslipidemia, and elevated circulating proinflammatory cytokines. Identifying this type of obesity early is exceptionally important because patients and doctors may underestimate cardiovascular risk due to the normal weight, overlooking potential metabolic cardio risks. Early intervention for these patients can be beneficial in treating and preventing complications related to obesity, possibly leading to changes in adipose distribution before a significant alteration in body weight or BMI occurs[15].

The initial approach, communication, and attitude of the physician during an evaluation of a patient with obesity is a significant determinant of the success of treatment and the patient's health.

Individuals grappling with obesity often encounter weight bias in their surroundings, leading to feelings of discrimination and, consequently, a reluctance to seek treatment and defer preventive care. Stigmatization contributes to unfavorable outcomes, fostering disordered eating, heightened depression rates, and reduced levels of physical activity[16].

The use of structured interview formats (such as Obesity Canada's 5As of Obesity Management ™) helps facilitate discussions about obesity in primary care. An adaptation of the 5As template has been developed by Obesity Canada for use in clinical practice. The main components of this framework include:

1. (ASK) ASK permission to discuss weight and exploring readiness;
2. (ASSESS) Evaluating risks related to obesity and the underlying causes of obesity;
3. (ADVICE) ADVICE on health risks and treatment options;
4. (AGREE) AGREE on health outcomes and behavioral goals;
5. (ASSIST) Assisting in accessing appropriate resources and providers.

Using and analyzing the information collected in the obesity assessment, the Edmonton Obesity Staging System (EOSS) was developed to understand the severity of the disease and guide the intensity of treatment required.

The EOSS has been proposed to guide clinical decisions based on the evaluation of obesity and in each BMI category, it is a measure of the mental, metabolic and physical impact on the patients' health and uses these factors to determine their stage of obesity. It utilizes these factors to determine the obesity stage (from stage 0 with no obesity-associated risk factors to stage 4 with obesity associated with severe disability).

Finally, when conducting an obesity assessment and aiming for long-term success, it is important to evaluate each patient's needs, readiness for change, intrinsic motivation, and values and goals when initiating a personalized treatment plan[17].

Recommendations

Research has primarily focused on inadequate food intake and reduced physical activity as postulated causes for the increasing prevalence of obesity. However, this simplistic approach does not recognize the possibility of diverse contributions. For example, in some individuals, an increase in food intake may predominate, while in others, decreased energy expenditure may prevail.

Increased hunger may result from heightened orexigenic signals dominating over anorexigenic signals in the hypothalamus, as well as emotional eating triggered by stress-related events and psychological aspects. In addition to perceived hunger and stress influencing eating behavior, at the other end of energy homeostasis, a decrease in resting energy expenditure, as well as a low adaptive thermogenic response, can also determine an obesity phenotype[18].

In some people living with obesity, elevated nutrient absorption may predominate due to hormonal changes, gastrointestinal secretion, and anatomo-histological characteristics, while in others, increased fat accumulation through adipogenesis may prevail.

Changes in the quantity and diversity of the intestinal microbiome can disturb homeostatic humoral and neural pathways, digestion, and absorption, requiring detection by the intestine's endocrine cells, activation of neuroendocrine pathways to regulate gastrointestinal motor, secretory, and absorptive functions, as well as metabolic

control. The specific characteristics and quantity of individual adipose tissue, type, distribution, and function must also be considered[19, 20].

Therefore, the individual's genotype, adipose tissue type, enteral cells, and microbiome interact with macronutrient intake, appetite, metabolism, and thermogenesis. The interplay between genetic makeup and individual characteristics shapes personalization and responses to macronutrients, dietary patterns, habits, and lifestyle. These factors are pivotal for a holistic and comprehensive grasp of energy homeostasis, a consideration crucial in the age of precision medicine.

The evaluation components for a patient with obesity to assess treatment include:

- *A history centered* on obesity, must include a clinical interview, medical and surgical history, medications, allergies, and social and family history. Key elements include the detection of sleep disorders, sexual disorders, and psychological abuse, description of eating patterns, physical activity, screen time, internalized weight bias, mood, and anxiety disorders, as well as substance abuse. Medications that may increase body weight should be identified.

It is crucial to assess the evolutionary history of weight in patients with obesity, along with their nutritional history related to eating habits and regular physical activity.

The evaluating physician should also identify and document the patient's values and goals regarding treatment.

- *A physical examination* focused on obesity with routine measurements and anthropometrics, including height, weight, BMI, and waist circumference. Blood pressure should be measured with an appropriately sized cuff based on the patient's arm circumference. Neck circumference and airway permeability are also useful for estimating the risk of sleep apnea, in addition to routine cardiorespiratory and gastrointestinal examinations along with a general skin examination to rule out findings (dermatitis, intertrigo, erysipelas). Joint and gait examinations are recommended to assess mobility barriers. A superficial endocrine examination includes palpation of the thyroid gland and detection of signs of Cushing's syndrome and polycystic ovary syndrome. If these signs are present, should be followed by additional biochemical studies.

- *Diagnostic tests* are commonly ordered during the initial assessment of obesity to identify metabolic problems and tailor therapy. Screening for metabolic syndrome with HbA1c or fasting glucose, complete blood count, kidney function, total cholesterol, LDL, serum triglycerides and HDL, uric acid, and transaminases is recommended in most patients. Those at high risk of fatty liver disease, including those with type 2 diabetes or metabolic syndrome, should be examined with an abdominal ultrasound.

- *Additional tests:* ECG. Echocardiogram is recommended for personalized evaluation.

- *Other studies:* Exercise test, polysomnography, and image and laboratory studies according to the patient's clinical evaluation[17, 21].

Interventions in patients with obesity are based on the following strategies:

A. **Habit changes** are enhanced with specific techniques such as those developed in motivational interviewing. It is a patient-centered counseling approach aimed at improving positive behavior change. The stages of change that can be assessed during motivational interviewing include pre-contemplation, contemplation, preparation, action, maintenance, and relapse.

The general principles of motivational interviewing include empathy (creating a space for communication, understanding, collaboration, support, encouragement, and listening), avoiding arguments (recognizing types of resistance, arguing, denying, ignoring, and then moving forward through reflection; shifting the focus, reframing), developing discrepancies (developing mismatch between where I am today and where I want to be in the future), resolving ambivalence, and addressing uncertainty through the desire for change; and supporting self-efficacy is affirming favorable outcomes by focusing on the patient's successes and highlighting their skills and strengths. The eating behavior in individuals with increased body fat often reflects the imbalance of physiological forces that strongly resist weight loss and weakly support weight gain. Eating behavior is affected by the 5 senses (sight, smell, hearing, taste, and touch) and can also be influenced by mental stress, emotions, habitual time signals, environment, information gap, and reward factors. Eating behavior can be affected by eating disorders (e.g., binge eating disorder and bulimia nervosa).

B. **Obesity nutritional treatment** is more effective when dietary interventions are evidence-based, whether quantitative or qualitative, and enhance patient adherence.

The most suitable nutritional therapy for weight loss is one that is safe and effective, considering eating behaviors, meal patterns, cultural backgrounds, traditions, food availability, time constraints, financial issues, nutritional knowledge, culinary skills, and medical conditions potentially affected by the nutrition plan.

Fat restriction in the diet leads to a greater reduction in total cholesterol and LDL, while carbohydrate restriction in the diet leads to a greater reduction in serum triglycerides and an increase in HDL cholesterol. Carbohydrate reduction may lead to a greater reduction in serum glucose and hemoglobin A1c.

The patient should be encouraged to:

• Eating patterns that maximize satiety, such as meal timing, nutrient composition (high fiber, moderately high protein, moderately low glycemic load, higher volume), and appetite awareness training.

• Consumption of proteins and healthy fats, vegetables, green leafy vegetables, fruits, berries, nuts, legumes, and grains.

• Dairy products (taking into account caloric content).

• Read labels rather than marketing claims.

• Avoid eating for reasons other than hunger.

• Avoid frequent snacking.

• Use portion control.

• Being habitually aware of food stimuli may allow a better opportunity for stimulus control.

The changes in body composition associated with **physical activity** in subjects with obesity are based on the decrease in the percentage of fat mass, which in principle requires a negative energy balance.

Routine physical activity can strengthen body composition, endocrine and immune adipocyte body processes; improve musculoskeletal metabolism, cardiovascular, pulmonary, mental, sexual, and cognitive health. Dynamic training promotes weight loss and can help prevent weight gain or regain. Resistance training can improve body composition, prevent loss of muscle mass during weight loss, and increase resting energy expenditure.

The prescription of physical activity should be personalized with an ideal standard of 30 min/day 5 days a week for overweight and obese patients, with a progressive increase in volume and intensity.

Aerobic physical activity can be combined with 2-3 sessions of resistance exercise at least twice a week comprising 8 to 10 exercises involving large muscle groups.

Monitoring of physical activity can be done through a variety of activity logs as well as body composition measurements by a reliable technician. Physical inactivity behavior may be related to comfort, lack of time, fatigue, disinterest, and environment[22].

C. **Pharmacological treatment** is based on complementing nutritional, physical activity and behavioral therapies. The indication for pharmacological treatment is based on patients with BMI>30 kg/m^2 or BMI>27 kg/m^2 with comorbidities.

Biological and behavioral phenotypes define the heterogeneity of obesity and pharmacological treatment can be directed to improve weight loss[23].

Patients have an average weight loss of around 5 to 10%, with greater weight loss in hyper-responders and less than 5% weight loss (or even weight gain) in hyporesponders and no clinical improvement. (e.g., at least 3-5% loss of initial body weight) after 12 to 16 weeks on an anti-obesity medication. Alternative medications may be considered, or dosage increased if appropriate or discontinuation of treatment, it should always be evaluated in a personalized way according to the characteristics of the individual[23, 24].

The objectives:

• Treat the disease.

• Facilitate the management of eating behavior.

• Slow progression of weight gain/recovery.

• Improve health, quality of life and body weight of overweight or obese patients.

• Bariatric surgery can be an effective complement to improve weight loss or prevent weight regain.

The medications currently supported by evidence for treating obesity include the following (please refer to their approval status in each country):

1. Orlistat is a gastrointestinal lipase inhibitor, taken in 3 tablets of 120 mg per day, it is contraindicated in patients with chronic malabsorption syndrome and cholestasis.

2. Liraglutide is a glucagon-like peptide 1 (AGLP1) receptor agonist at a dose of 3.0 mg per day subcutaneously for the treatment of obesity contraindicated in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2.

3. Naltrexone/bupropion is a combination of an opioid antagonist and an antidepressant; it is contraindicated in patients with uncontrolled hypertension, chronic use of opioids, seizure disorders, and withdrawal of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs.

4. Semaglutide AGLP1 approved at a dose of 2.4 mg weekly in adults who are obese or overweight and with comorbidities such as type 2 diabetes, high blood pressure or high cholesterol. Has similar contraindications to liraglutide[26].

5. Tirzepatide glucose-dependent insulinotropic polypeptide and AGLP1 approved for the treatment of obesity by the FDA. The most frequent adverse effect has been gastrointestinal (nausea, diarrhea, or constipation)[27].

D. **Bariatric surgery** (BS) is the most effective and efficient treatment for people suffering from severe obesity, in the medium and long term, with evidence that demonstrates a strong impact on the comorbidities of obesity (type 2 diabetes, high blood pressure, sleep apnea, hepatic steatosis, etc.) and reduction in mortality from all causes, improvement in life expectancy and quality of life. The main health effects are related to the induction of substantial weight loss and not to the surgery per se. BS is considered on an individual basis when conventional treatment fails[28].

Patients with indications for BS should be referred to specialized centers, where they can be fully and objectively informed, psychologically prepared and treated by a dedicated and accredited multidisciplinary team.

Patients treated with this method require lifelong follow-up and additional medical management. Eating habits need to be adapted to the new gastrointestinal physiology, and nutritional deficits often arise, depending on the type of bariatric procedure, due to restriction of food intake after any BS procedure, as well as malabsorption of nutrients induced by long-term bypass procedures (e.g., proteins, various vitamins, minerals, and trace elements). Therefore, multivitamin supplements should be prescribed according to the surgical procedure used and

periodic laboratory monitoring is recommended to avoid nutritional deficiencies.

The management of diseases associated with obesity must be adapted according to weight loss.

Finally, there may be relapse in body weight gain that generally occurs after 10 years.

Adequate medical management of post-bariatric follow-up requires much attention. The provision of a multidisciplinary post-bariatric follow-up program is an integral part of the clinical pathway in BS centers[16].

Careful patient selection is critical to the success of the treatment, the indications being the following:

- Body mass index (BMI) greater than 40 kg/m^2 with or without comorbidities.

- BMI greater than 35 kg/m^2 with one or more comorbidities, in patients in whom weight loss could improve this condition: type 2 diabetes, arterial hypertension, dyslipidemias, Pickwick's syndrome, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea-hypopnea syndrome (OSAHS), cardiorespiratory diseases, gastroesophageal reflux (GER), significantly impaired quality of life and severe psychological disorders related to obesity, among others.

BS covers different surgical techniques, the four most applied procedures are the Roux-en-Y gastric bypass (PGB), laparoscopic vertical gastrectomy or gastric sleeve (GV), the laparoscopic adjustable gastric band and the biliopancreatic diversion. The most used in our environment are GV and BPG. In the first, a restrictive mechanism predominates, whereas gastric bypass generates a greater disabsorptive metabolic action[29].

Most studies and meta-analyses that demonstrated benefits with BS refer to an age between 18 and 65 years. In people under 18 and over 65, the risk-benefit must be evaluated since the primary objective is to improve quality of life.

Contraindications for BS are:

• Presence of major psychiatric disorders (psychosis; manic, hypomanic, mixed, or depressive episode), mental retardation and bulimia nervosa.

• Presence of death and/or suicidal ideation.

• Abuse of alcohol or other psychoactive substances.

• Short-term life-threatening illnesses term.

• Patient who cannot understand medical directives or nutritional and/or psychological guidelines.

• Pregnancy.

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