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How cardiologists can manage excess body weight and related cardiovascular risk. An expert opinion

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ABSTRACT

Obesity is an important independent cardiovascular (CV) risk factor and a chronic inflammatory disease related to the development of insulin resistance, type 2 diabetes, dyslipidaemia, coronary artery disease, hypertension, heart failure, atrial fibrillation and obstructive sleep apnoea. Body Mass Index (BMI) values >27 kg/m^2 are associated with an exponential increase in the risk for Major Adverse Cardiac Events (MACE). On the other hand, weight reduction can significantly reduce metabolic, CV and oncological risk. Orlistat, bupropion/naltrexone, liraglutide and semaglutide, combined with lifestyle changes, have proven to be effective in weight loss; the last two have been tested in randomized clinical trials (RCTs) with CV outcomes only in diabetic patients, and not in obese patients. To fill a fundamental gap of knowledge, the SELECT trial on patients with obesity and CV disease treated with semaglutide is ongoing, aiming at MACE as the primary endpoint.

The battle against the social and clinical stigma towards obesity must be counteracted by promoting an awareness that elevates obesity to a complex chronic disease. Several actions should be implemented to improve the management of obesity, and cardiologists have a key role for achieving a global approach to patients with excess weight also through the correct implementation of available treatment strategies.

Obesity, already recognized as a chronic disease back in 1999, can be considered one of the main public health problems, affecting 650 million individuals worldwide. It's a consequence of complex interactions between genetic, behavioral, socio-cultural, biological and metabolic factors and represents an important cardiovascular (CV) risk factor, correlated to an increased risk of arterial hypertension, metabolic syndrome, insulin resistance, type 2 diabetes (T2DM) and dyslipidaemia. In clinical practice, obesity is identified through the evaluation of the Body Mass Index (BMI) (ratio between weight in kilograms divided by the square of height in meters), which however is not able to discriminate between fat mass and lean mass, nor to identify the presence of abdominal fat, that is associated with CV risk and other chronic conditions. BMI values >27 kg/m^2 are associated with an exponential increase in the risk for Major Adverse Cardiac Events (MACE) [1].

Abdominal circumference is a simple and reliable indicator of the presence and quantity of abdominal adipose tissue, which can be used in the baseline assessment of CV risk, and in the monitoring of a weight loss treatment.

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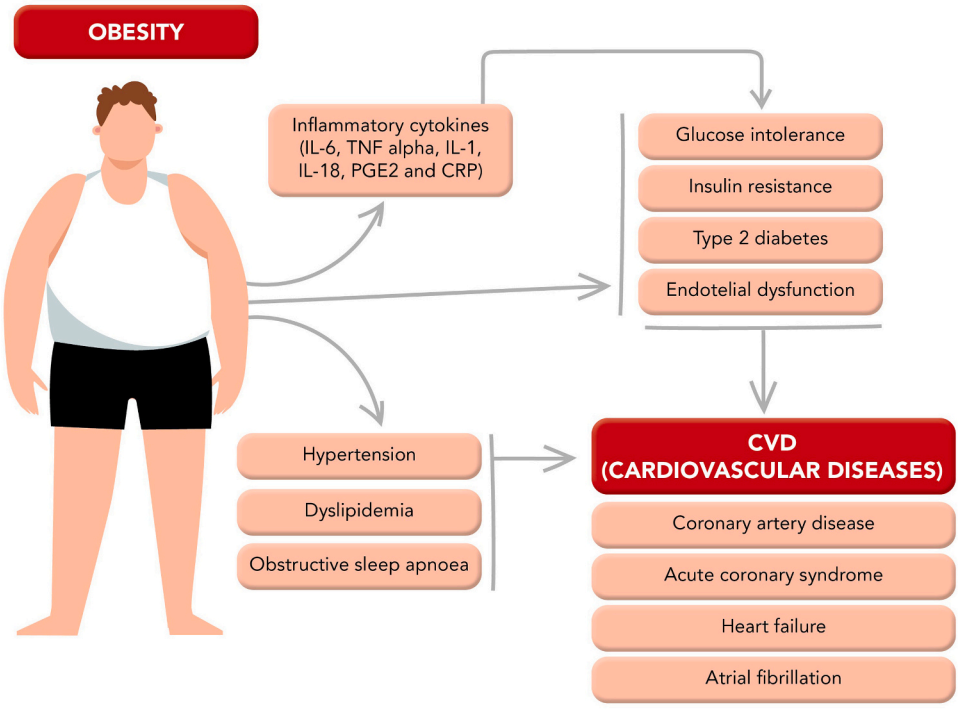

Fig. 1. Relationship between obesity and cardiovascular diseases.

Obesity is a chronic inflammatory condition, with increased levels of inflammatory cytokines (IL-6, TNF alpha, IL-1, IL-18, PGE2 and CRP) [2]. This leads to the development of insulin resistance and CV and metabolic abnormalities: coronary artery disease (with 2–4% increase in myocardial infarction) [2], hypertension (3 mm Hg increase in mean arterial blood pressure and 2.3 mm Hg in diastolic pressure, per each 10 kg increase in weight) [3,4], heart failure (1 unit increase in BMI brings to 5–7% increase in risk) [5], atrial fibrillation [6], T2DM [7], dyslipidaemia [2], obstructive sleep apnoea (Fig. 1) [8].

With respect to heart failure (HF), there is a strong association especially with HF and preserved ejection fraction (HFpEF). In the ALLHAT trial, which enrolled patients with arterial hypertension and one additional cardiovascular risk factor, a high BMI at enrollment was the strongest predictor for development of HFpEF [9]. Longitudinal noninvasive studies over a 4-year time interval revealed close correlation between diastolic left ventricular stiffness and BMI [10,11].

Even a moderate weight reduction (10–15%) can significantly reduce metabolic and CV risk: prevention to progression to type 2 diabetes from impaired glucose tolerance, improvement in systolic and diastolic blood pressure, increase in HDL cholesterol [12].

Cardiologists play a key role in identifying and screening obese patients and prescribing personalized treatment, including lifestyle counselling, nutritional interventions, psychological therapies, sometimes medications and, in severe cases (BMI >40 kg/m^2 or BMI >35 kg/m^2 in the presence of associated comorbidities), bariatric surgery. This latter treatment is unfrequently performed in patients with a prior atherothrombotic event to prevent event recurrences. A complete clinical evaluation of patients with obesity allows to better estimate the individual CV risk profile. In any case, the residual CV risk in these patients with correctly treated comorbidities (especially T2D, dyslipidaemia and hypertension) should be considered [13]. It is likely that the chronic inflammatory state associated with obesity, and persistent even after correction of other risk factors, is one of the causes.

Nutritional interventions and regular physical activity represent the first approach to obesity. However, their feasibility and efficacy may be limited, particularly in the long-term. In this case it is not advisable to delay the beginning of an appropriate pharmacological treatment (combined with an adequate diet and a correct lifestyle), which may rapidly promote a stable reduction in body weight with beneficial clinical consequences.

Several drugs have been developed to promote weight loss and, above all, to maintain the achieved weight. Orlistat selectively binds to the lipases of the gastrointestinal tract, inhibiting them and reducing the absorption of about 1/3 of the lipids introduced by diet, which are then eliminated with the faeces; these effects induce an average weight loss of about 5% at 6 months [14]. Randomized control trials (RCTs) have demonstrated that orlistat is superior to placebo in inducing greater and more stable decrease in weight, waist circumference, blood pressure, fasting blood glucose, total cholesterol, low density lipoprotein cholesterol (LDL-C), triglycerides and risk of T2DM [15], but CV outcome studies are not available. The bupropion/naltrexone combination has shown to induce weight loss as early as the 4th week of therapy, with an overall weight loss 4.8% higher than placebo. A reduction in glycated haemoglobin ($<7\%$) and triglycerides, with an increase in HDL-C was also observed [16]. Liraglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist, that induces reduction in appetite and delay in gastric emptying, enhances pancreatic insulin secretion and reduces inappropriate glucagon secretion; it is indicated in obesity or in adult or in patients with overweight with BMI ≥ 27 kg/m^2 (in the presence of at least one weight-related comorbidity) at the maintenance dosage of 3 mg, after a step-up titration. In clinical studies it has shown to induce greater weight loss than caloric restriction. In the LEADER study (*Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results*), performed in diabetic patients treated with subcutaneous liraglutide 1.8 mg or placebo, CV outcomes (CV death, myocardial infarction, fatal stroke) were evaluated, resulting lower in the treatment group than in the placebo group ($p < 0.001$ for non-inferiority and $p = 0.01$ for superiority) [17].

A RCT conducted on 185 obese or overweight patients suffering from metabolic syndrome, treated with liraglutide 3 mg or placebo, demonstrated a decrease in visceral abdominal tissue of 12.49% vs 1.63% in the placebo group ($p < 0.0001$), of adipose cells in the liver, fasting blood glucose and CRP after 36 weeks of therapy [18].

In the SCALE program (four Phase III randomized placebo-controlled

Table 1
Enrolment, objectives and endpoints of the STEP studies. Modified from [20].

Study	STEP 1 NCT03548935	STEP 2 NCT03552757	STEP 3 NCT03611582	STEP 4 NCT03548987	STEP 5 NCT03693430
Enrolled patients	1961	1210	611	902	304
EOT (weeks)	68	68	68	68	104
Objectives	WM in overweight or obese adults	WM in overweight or obese adults with T2D	WM + IBT in overweight or obese adults (US only)	WM in overweight or obese adults (maintenance)	Long term WM in overweight or obese adults
ENDPOINTS					
Change of weight from baseline to EOT, %	X	X	X	X	X
WL ≥5% from baseline to EOT	X	X	X	X	X
WL ≥10% from baseline to EOT	X	X	X	X	X
WL ≥15% from baseline to EOT	X	X	X	X	X
Change in abdominal circumference, cm	X	X	X	X	X
SAP mm Hg	X	X	X	X	X
Physical functioning, SF-36	X	X	X	X	NA
Physical functioning, IWQOL-Lite-CT	X	X	NA	NA	NA

EOT: end of therapy; IBT: intensive behavior therapy; SAP: systolic arterial pressure; T2D: type 2 diabetes; WL: weight loss; WM: weight management.

studies involving a total of 5358 patients treated with liraglutide in daily doses up to 3 mg), the drug therapy was associated with greater weight loss, improvement of blood glucose levels, increased time to T2DM onset in patients with or without prediabetes, and more patients who maintained weight loss. Furthermore, liraglutide treatment significantly improved systolic blood pressure, waist circumference, and obstructive sleep apnoea severity [19].

Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1, and acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. Semaglutide reduces body weight and fat mass through lowering caloric intake thanks to a general decrease in appetite. The STEP program (*Semaglutide Treatment Effect in People with Obesity*, a program of phase 3 randomized placebo-controlled, multinational trials) investigated the efficacy and safety of subcutaneous semaglutide 2.4 mg once weekly as an adjunct to behavioral therapy and low-calorie diet, in the treatment of obesity and overweight in a large population of diabetic and non-diabetic subjects (Table 1) [20]. A greater reduction in weight, abdominal circumference and blood pressure, as well an increase in physical efficiency measured with the SF-36 physical functioning score and the physical function domain (5-items) score (IWQoL-Lite-CT) were observed in the treatment group compared to the control group [21–24].

In addition, participants treated with semaglutide, as compared to placebo, reported a greater improvement with respect to cardiometabolic risk factors and a greater increase in physical functioning [25].

A meta-analysis of 4.582 patients from the STEP 1–4 studies found a 30% reduction in the risk of CV disease in the treatment group compared with placebo ($p = 0.001$) [26].

The knowledge gaps in the treatment of obesity are mainly related to CV outcomes, both under specific drug therapy and after bariatric surgery, and could be addressed by long-term prospective studies. For this purpose, the SELECT trial (*Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity*), a randomized, double-blind study, on non-diabetic patients with overweight or obesity and CV disease treated with semaglutide 2.4 mg/week s.c. or placebo, is ongoing, and its primary endpoint is a decrease in the percentage of MACEs [27].

While waiting for new data from the ongoing studies, it is important to promote awareness of obesity as a chronic disease, and to increase the willingness of physicians to address it as a primary clinical problem.

The social stigma towards overweight and, even more, obese patients is still high and has a heavy impact on the effectiveness of treatment strategies; in the paediatric population it leads to bullying and negative interference in the development of self-esteem and can paradoxically favour a greater food intake [26]. In general, the quality of care appears to be lower among people with obesity, and discrimination has been observed in the workplace [28].

The battle against the social and clinical stigma towards obese patients must be counteracted by promoting the awareness for obesity being a severe condition. Several actions should be implemented to improve the management of this disease, like national regulatory initiatives, recognition of obesity as a complex chronic disease among all healthcare professionals, creation and organization of multidisciplinary structures.

In conclusion, obesity is an outstanding clinical problem, whose pathophysiological mechanisms are increasingly been known. The treatment of comorbidities, in particular dyslipidaemia, T2DM, hypertension, obstructive sleep apnoea, remains an essential part of the clinical management, but the approach to patients with overweight or obesity must be comprehensive and overarching. The role of cardiologists is fundamental not only in dealing with the associated comorbidities, but also in approaching patients with obesity in their entirety and in setting up the appropriate therapy. Effective pharmacological treatments are progressively being introduced into the clinical practice of various specialists. These therapies have proven to be effective and safe in allowing stable loss of body weight, and evidence of their potential role in reducing CV risk is promising.

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