REVIEWS

Structural and functional ventriculo-arterial changes in obesity: mechanisms, implications and reversibility after weight loss

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Article received on the 19th of February 2013. Article accepted on the 5th of March 2013.

Abstract: Obesity is a public health problem, being the fifth cause of death worldwide. Adverse cardiovascular prognosis of obesity is linked to: endothelial dysfunction, abnormal left ventricular geometry, systolic and diastolic left ventricular dysfunction, heart failure, increased arterial stiffness, coronary artery disease, dilated left atrium and atrial fibrillation. Pathophysiologic mechanisms of structural and functional cardiovascular changes of obesity are complex: cardiac metabolism disturbances, mitochondrial dysfunction, impaired insulin signalling, inflammation, neuro-hormonal activation, impaired production of adipokines, fibrosis, changes in the extracellular matrix and cardiomyocytes apoptosis. Obesity is characterized by a mixed left ventricular overload, with predominance of one component (pressure or volume), depending on which a certain type of cardiac remodelling appears (eccentric or concentric hypertrophy, concentric remodelling), with specific prognostic implications. The main modalities of obesity treatment are diet, physical activity, behaviour modification, pharmacological therapy and bariatric surgery. Favorable metabolic and blood pressure changes were demonstrated after losing weight by any means, but reversibility of cardiac morphological changes (mainly regression of left ventricular hypertrophy) and of left ventricular diastolic and systolic dysfunction were demonstrated only after bariatric surgery. Described effects are probably due to a large and sustained weight loss.

Keywords: obesity, left ventricular remodeling, vascular dysfunction, weight loss, reversibility

Rezumat: Obezitatea reprezintă o problemă de sănătate publică, fiind a cincea cauză de mortalitate în lume. Prognosticul cardiovascular nefavorabil al obezității este legat de: disfuncție endotelială, geometrie anormală a ventriculului stâng, disfuncție sistolică și diastolică ventriculară stângă, insuficiență cardiacă, rigiditate arterială crescută, boala coronariană ischemică, dilatarea atriului stâng, fibrilație atrială. Mecanismele fiziopatologice ale modificărilor structurale și funcționale cardiovasculare din obezitate sunt foarte complexe: perturbări ale metabolismului cardiac, disfuncție mitocondrială, alterări ale semnalului insulinei, inflamație, activare neuro-hormonală, dereglarea producției de adipokine, modificări ale matricei extracelulare, fibroza și apoptoza cardiomiocitelor. Obezitatea este caracterizată de un mecanism mixt de suprasarcină ventriculară stângă: de presiune și de volum, cu predominanța uneia dintre componente, în funcție de care apare un anumit tip de remodelare ventriculară stângă (hipertrofie excentrică sau concentrică, remodelare concentrică), cu implicații prognostice specifice. Principalele modalități de tratament ale obezității sunt: dieta, activitatea fizică, modificările comportamentale, terapia farmacologică și chirurgia bariatrică. Modificări metabolice favorabile și scăderea tensiunii arteriale au fost demonstrate prin scăderea ponderală prin orice metodă, însă numai după chirurgia bariatrică au fost descrise reversibilitatea modificărilor morfologice cardiace (în principal regresia hipertrofiei ventriculare stângi) și a disfuncției ventriculare stângi diastolice și sistolice. Efectele descrise sun cauzate probabil de scăderea ponderală amplă și susținută.

Cuvinte-cheie: obezitate, remodelare ventriculară stângă, disfuncție vasculară, scădere ponderală, reversibilitate

THE MAGNITUDE OF THE PROBLEM

Obesity is now considered a major clinical and epidemiological problem, a worldwide epidemy with a rapid increase of its incidence.

Obesity epidemiology

The global prevalence of excessive weight has doubled in the last 30 years and is at a level of approximately 33% for obesity and 50% for overweight and obesity. In the world there are currently registered 200 million obese men, 300 million obese women and 1.4 billion overweight subjects, there are regions (from U.S.A.) where overweight and obese individuals account for over 65% of the population. Equally worrying is the current number of obese adults and high prevalence of obesity among children – in 2010 more than 40 million of children younger than 5 years were overweight[1,2].

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In Romania, epidemiological studies conducted between 2000-2005 have shown a obesity prevalence in the general population of 28%, with a distribution of 26.3% in males and 35.1% in females; in patients with coronary heart disease, obesity had a higher prevalence: 31% – of which 29% in men and 34% in women; in the study "Urziceni" body mass index (BMI) in adults with average age of 25 years was 27.4 kg/m^2 (corresponding to overweight), and 30.6% of them had high cholesterol level and excess weight (overweight or obesity)[3,4].

Obesity is a major public health problem, which is reflected in the constant concern of the medical world to develop comprehensive guidelines for the identification, evaluation and treatment of obesity. In Europe, obesity applies directly for 6% of the funds allocated to health; health expenditure in individuals with obesity is twice higher than in normal weight subjects[5].

Definition and classification of obesity

There are many definitions of obesity. The most used is based on body mass index (BMI = weight / height^2); a BMI between 18.5 to 24.9 kg/m^2 is normal, 25 to 29.9 kg/m^2 defines overweight and BMI > 30 kg/m^2 defines obesity[6].

There are five classes of obesity: class 1 - BMI 30 to 34.9 kg/m^2, class 2 – BMI 35 to 39.9 kg/m^2, class 3 – BMI 40 to 49.9 kg/m^2, class 4 – BMI 50 to 59.9 kg/m^2, class 5 BMI ≥ 60 kg/m^2 [6].

The excess weight **prognosis** is extremely unfavourable: obesity is the fifth cause of death worldwide, giving 2.8 million deaths/year, with a mortality that increases by 30% at every BMI augmentation of 5 kg/m^2 [7].

In the most recent version of "European Guidelines on Cardiovascular Disease Prevention in Clinical Practice" it is shown that obesity and overweight are both associated with an increased risk of cardiovascular death, with a direct and linear relationship between BMI and all causes mortality. It emphasizes that optimal body mass index with the lowest mortality is 20-25 kg/m^2, it points out that greater weight reduction does not confer additional cardiovascular protection[6].

Although it's the first guide that mentions "obesity paradox"[8] in patients with coronary artery disease (possibly better prognosis in patients with obesity undergoing coronary revascularization procedures), it shows that existing data in this respect are contradictory and do not provide other recommendations in addition to those described above[6].

Obesity prognosis

Obesity potential "adverse effects" are related to: insulin resistance, high blood pressure, systemic proinflammatory and prothrombotic status, albuminuria and dyslipidemia (increased serum levels of total cholesterol, LDL-cholesterol, other forms of non-HDL cholesterol, triglycerides, apolipoprotein B, small dense LDL particles and decreased concentrations of HDL cholesterol and apolipoprotein AI)[6].

METABOLIC AND CARDIOVASCULAR OBESITY DISORDERS

Major cardiovascular and cerebrovascular abnormalities seen in obesity are: endothelial dysfunction, increased sympathetic nervous system activity, abnormal left ventricular (LV) geometry, systolic and diastolic LV dysfunction, heart failure, coronary artery disease, dilated left atrium, atrial fibrillation, stroke[6].

Pathophysiological mechanisms of cardiovascular changes in obesity

Pathophysiologic mechanisms of structural and functional cardiovascular changes of obesity are complex[9]:

- Changes in cardiac metabolism.
- Mitochondrial dysfunction and increased oxidative stress.
- Impaired insulin signalling: insulin resistance, hyperglycaemia and diabetes mellitus.
- Inflammation – the association between obesity and inflammation is considered one of the main links of increased incidence of myocardial infarction and heart failure in obese subjects. In patients with obesity and heart failure it has been demonstrated increased serum levels of proinflammatory cytokines: interleukin 6, interleukin-1β, atrial natriuretic peptide and tumor necrosis factor, without a compensatory increase of antiinflammatory cytokines: interleukin-10 or transforming growth factor β[10].
- Neuro-hormonal activation – in obesity there is an overactive sympathetic nervous system.

Hypersympathetic state leads to left ventricular hypertrophy by increasing myocardial contractility, by increasing blood pressure, but also through direct hypertrophic effects of catecholamines; in addition, obesity has been demonstrated hyperactivity of the renin-angiotensin-aldosterone secretion mechanism, incriminated mechanism being angiotensionogen secretion from adipocytes of visceral fat.

- Production of adipokines disorder with decreased levels of "protective" adipokines (adiponectin) and increase of and proinflammatory and proate-

rogene adipokines (leptin, insulin, angiotensinogen)[10].

- Changes of extracellular matrix and fibrosis: in experimental models of obesity induced in laboratory animals, there was an increase in fibrosis in the wall of the coronary arteries and increased accumulation of collagen in the cardiac interstitium[9,11].
- Apoptosis: experimental studies in obese animals showed an increase in cardiomyocyte apoptosis associated with increased ceramide and triglyceride levels in these cells[9].
- Sleep-apnea syndrome – is very common in obese patients and most studies have been shown to be associated with the presence of left ventricular hypertrophy by the following mechanisms: increased sympathetic tone, chronic hypoxia, diurnal and nocturnal exacerbation of hypertension and excessive changes of intrathoracic pressure during obstructive periods[13].

Overload types and LV geometry changes in obesity

Volume overload was initially considered the primary pathophysiologic mechanism leading to cardiac remodeling in obesity. Thus increased metabolic needs of obesity is accompanied by circulating blood volume expansion, increased stroke volume and cardiac output, then by the appearance of eccentric LV hypertrophy[9,12]. It was subsequently reported an increased predominance of concentric LV hypertrophy in patients with obesity, a remodeling pattern typical of left heart pressure overload. Pressure overload mechanisms of obesity are related to the coexistence of systemic hypertension, to the "nondipper" profile (no nocturnal decrease in blood pressure) and to increased arterial stiffness reported in obese patients[9,13].

Obesity is therefore characterized by a mixed LV overload with predominance of one component (pressure or volume), depending on which (as well as on other factors: ethnicity, age, gender, comorbidity, hormonal status, genetic factors) a certain type of cardiac remodeling appears, with specific prognostic implications[12].

Left ventricular geometry evaluation and prognosis

Parameters defining the geometry of the LV are relative wall thickness and LV mass[14].

The most accurate determination of LV mass is by magnetic resonance imaging, followed by three-dimensional echocardiography[14].

LV mass can be calculated from two-dimensional echocardiography parameters by Devereux formula, a necropsy validated equation[15] and indexed to height in meters to the power of 2.7 as previously described[14].

LV Mass (g) = 0,8*(1,04*[(IVS+LVEDD+PW)^3 - LVEDD^3]+0,6

IVS = interventricular septum thickness, PW = LV posterior wall thickness, LVEDD = LV end-diastolic diameter.

The LV mass has to be indexed to the power of 2.7 to minimise the interference of obesity in the estimate of ventricular mass (LV mass indexed to body surface area is known to underestimate the prevalence of LV hypertrophy in overweight and obese patients)[16].

LV mass index = LV mass/height^{2,7}.

To evaluate the concentricity of LV geometry, LV wall thickness (LV posterior wall + interventricular septum) was divided by LV end-diastolic dimension to generate relative wall thickness.

Based on LV Mass index and relative wall thickness, LV geometry can be divided into[14]:

- normal geometry: normal LV mass index, normal relative wall thickness.
- concentric remodelling: normal LV mass index, increased relative wall thickness.
- eccentric hypertrophy: increased LV mass index, normal relative wall thickness.
- concentric hypertrophy: increased LV mass index, increased relative wall thickness.

Prognostic implications of LV geometry changes

Type of LV remodeling is very important in practice, since each left ventricular geometric pattern was found to have symptoms, evolution and special prognostic implications in general population. Thus, subjects with concentric left ventricular hypertrophy showed the greatest limitation of exercise capacity by reduced systolic and chronotropic reserve. Also concentric hypertrophy, in the Framingham study, had the worst cardiovascular prognosis, followed by eccentric hypertrophy, eccentric remodeling and normal LV geometry[17]. Despite normal LV mass, concentric remodeling was, in another study, an independent predictor of cardiovascular risk in hypertensive patients[18]. The "LIFE" study has shown an increased risk of ischemic stroke associated with concentric remodeling, increased risk of cardiovascular death associated with eccentric hypertrophy and concentric remodeling and an increased risk of myocardial infarction in both concentric and eccentric hypertrophy[19].

It is very likely that in obese patients, electrocardiogram present a low sensitivity in detecting LV hypertrophy, since obesity is known as one of the situations that are associated with low QRS voltage on ECG[20].

LV geometry changes in obesity are **asymptomatic** in the early stages but **may later develop into heart failure** with LV systolic dysfunction or, more commonly, to diastolic dysfunction and preserved ejection fraction; the latter is also associated with a poor long term prognosis[21].

LV systolic function in obesity

Studies on LV systolic function in obese patients provide conflicting information: some authors reported predominantly systolic dysfunction, most normal ejection fraction and others supernormal systolic function[9]. Perhaps the results depend on other features of the different lots of obese patients; it is always very difficult to separate the "pure" cardiac effects of obesity from the cardiac effects of its comorbidities (diabetes, hypertension, etc.), the latter being known to be associated more frequently with coronary artery disease, which often evolves in LV systolic dysfunction[9].

A previous study showed that inducing obesity in hypertensive mice with concentric LV hypertrophy leads to a rapid progression to left ventricular systolic dysfunction, independent of BP or glycosylated hemoglobin values. Several mechanisms have been incriminated: cardiomyocyte apoptosis, activation of mitochondrial collagenases and leptino-resistance[22].

Diastolic function in obesity

Diastolic dysfunction is often described in obesity. Increased LV filling pressures lead to left atrial dilation, increased risk of atrial fibrillation and secondary embolic stroke[9].

Vascular function in obesity

Extensive studies demonstrating that obesity is an independent predictor of cardiovascular disease, correlated to research results showing the important role of arterial stiffness in cardiovascular morbidity-mortality led to hypothesis of vascular dysfunction in obesity.

Numerous works then confirmed increased levels of arterial stiffness in obese subjects (measured locally, in the ascending aorta or common carotid artery or by pulse wave velocity measuring), independent of age, sex, race or blood pressure levels, but the results are divergent over the role of general adiposity or abdominal adiposity in the induction of increased arterial stiffness. Thus, the study by Orr et al. demonstrated that moderate weight gain in normal weight patients is followed by increased arterial stiffness and reduced arterial compliance in interrelation with abdominal adiposity level without correlation with overall adiposity level[23].

Wildman et al. demonstrated increased pulse wave velocity in direct relation to the degree of overall obesity (BMI) independent of ethnicity (both Caucasian subjects and in Afro-Americans) and showed that vascular dysfunction is present in all age groups adults, including obese youth (20-30 years)[24].

Children with obesity are also characterized by increased arterial stiffness and endothelial dysfunction, as demonstrated Tounian et al., long term effects becoming increasingly important, given that 77% of children overweight children become obese into adulthood[25].

Endothelial dysfunction, arterial stiffening and other micro- and macrovascular changes described in obesity result in an increased incidence of atherosclerotic events in this group of patients and in cardiac structural and functional abnormalities[9].

OBESITY TREATMENT

The main modalities of obesity treatment are diet, physical activity, behavior modification, pharmacological therapy and bariatric surgery[6,26].

Diet, physical activity and behavioral changes

Reducing total calories intake and regular exercise are essential for weight control. Overweight control is dependent on achieving a balance between intake and energy expenditure. Various types of diets differ in: total calories, macronutrient composition (protein, carbohydrates and lipids), energy value and glycemic index[27].

Behavioral attitude change (long-term lifestyle changes) leads to a gradual weight loss and represents the basis of all obesity treatments.

According to a Cochrane review, behavioral and cognitive-behavioral therapy is very useful for weight loss when added to diet and exercise programs[27].

Medication

Generally, the contribution of drugs is modest and, in the past, some products had severe side effects[27].

Orlistat inhibits intestinal lipases, preventing hydrolysis and absorption of lipids. Weight loss is usually modest and cause gastrointestinal disorders, but has a very good lipid-lowering effect. This product should be used in combination with a complete and balanced diet[28].

Sibutramine increases the feeling of satiety after food intake through its metabolites that inhibit the uptake of norepinephrine and serotonin. It was however associated with sinus tachycardia and increased blood

pressure[28]. In 2010, the European Medicines Agency recommended suspension of marketing authorizations for sibutramine following a six-year study which showed an increased risk of non-fatal but serious cardiovascular events in patients with a known or high risk for cardiovascular disease[29].

Rimonabant is an inhibitor of endocannabinoid receptors, which seems to be able to induce a modest but sustained weight loss in combination with a caloric controlled diet. Rimonabant may improve glucose tolerance, may beneficially affect lipid metabolism and is associated with a modest reduction in blood pressure, but it was also associated with significant psychiatric disorders (anxiety and depression)[30].

In July 2012, the U.S. Food and Drug Administration approved two new drugs for the treatment of obesity: Lorcaserin (serotonin 2C receptor antagonist) and an extended release combination between Phentermine (previously used in short term treatment of obesity) and Topiramate (formerly known as antiepileptic and antimigrain). Both drugs are indicated, as an adjunct, in obese patients that already made exercise and maintain a reduced calorie diet.

Although diet, exercise and behaviour modification are essential for weight loss success, in many cases, especially in the long term, are difficult to maintain and are followed by weight regain.

In this situation, bariatric surgery is an extremely important and is indicated in patients with BMI> 40 kg/m^2 or BMI> 35 kg/m^2 in the presence of comorbidities[6].

Bariatric surgery

Bariatric surgery is practiced around the world for 34 years and the main types of bariatric interventions are[26]:

- gastric banding – mounting laparoscopic adjustable silicone ring.
- longitudinal gastrectomy ("gastric sleeve") – longitudinal cutting of the stomach, with removal of its dorsal portion (about 80% of its volume) and hunger centres - is a recently practiced intervention (in the last 5 years), with very good results on weight loss without being followed by malabsorption.
- gastric-folding - performing folds in the gastric wall, followed by folds surgical suture with absorbable wires.
- gastric bypass – complete isolation of a small portion of the stomach that connects to the gut - it's the most often practiced bariatric intervention in the U.S. for the last 20 years.
- bilio-pancreatic diversion - the most severe way interfere with the absorption of food calories and nutrients, which consists of almost complete gastric resection and connection to the distal small intestine, requiring further supplements in the form of vitamins and minerals, in order to avoid anemia, osteoporosis and other diseases caused by malabsorption.

Weight loss is 40-80% of excess weight in the first year and it is long term maintained.

Most bariatric procedures are performed laparoscopically, thus presenting the advantages of minimal hospitalization and faster postoperative recovery[26].

Reversibility of metabolic and ventriculo-vascular changes after weight loss

Removal of subcutaneous fat by liposuction was not associated with significant metabolic changes[9].

Pharmacotherapy was associated with weight loss, improved lipid profile and insulin resistance, but none of the drugs used to date had significant effect on cardiac dimensions or the pulmonary artery pressure[9].

A meta-analysis on 16.867 patients with severe obesity treated by bariatric surgery (mainly aggressive interventions, most frequently gastric bypass) has shown, after a mean follow-up of 34 months, a significant reduction in cardiovascular risk factors (low level blood pressure, improved lipid and glycemic status) and a 40% decrease in coronary risk assessed by the Framingham score[31].

Another recently published meta-analysis, performed on 19.543 subjects with severe obesity undergoing bariatric surgery, with mean follow up of 57.8 months, showed an excess weight loss of approximately 54% (16-87%), relief or cure of hypertension in 63% of subjects, of diabetes mellitus in 73% of cases and of dyslipidemia in 65% of cases. Echocardiographic data was available in 713 patients and showed improvement of LV mass and diastolic function[32].

Important studies, over a period of 1-2 years follow-up after gastric bypass, showed reverse cardiac remodeling after weight loss by decreasing LV mass and its geometry normalization and decreased right ventricular dimensions; morphological changes were accompanied by improved diastolic function and decreased LV filling pressures, as by biventricular systolic function improvement[33-36].

It was assumed that bariatric interventions *per se* would have a positive role in cardiovascular prognosis

beyond weight loss by bridging of neuro-hormonal gastrointestinal circuits[33]; however, this hypothesis cannot be verified because it is impossible to find a group of patients that have adopted dietary or medical methods and have achieved weight loss of similar magnitude and duration to that secondary to bariatric surgery.

The above studies demonstrated favourable cardiovascular changes after gastric bypass; however, limited data exists regarding the cardiovascular system effects of less radical interventions, without risk of malabsorption, such as recently practised laparoscopic longitudinal gastrectomy ("gastric sleeve").

PERSPECTIVES

Extent and duration of cardiovascular benefits obtained by weight loss by any means are currently poorly known. Bariatric surgery produces greater and long-term weight loss and cardiovascular benefits are therefore probably more important[33].

Given the high and growing prevalence of obesity in the world as well as increased experience and number of cases treated by bariatric surgery, studies over the effects of bariatric surgery on cardiac and vascular structure and function are needed.

Abbreviations: BMI = body mass index, LV = left ventricle, IVS = interventricular septum thickness, PW = Left ventricular posterior wall thickness, LVEDD = Left ventricular end-diastolic diameter.

Conflict of interests: None declared.

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