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REVIEW

Bariatric surgery and prevention of cardiovascular events and mortality in morbid obesity: Mechanisms of action and choice of surgery

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Abstract *Aims:* Obesity is associated with increased cardiovascular (CV) morbidity and mortality. Weight loss improves several risk factors for CV diseases, but anti-obesity medications and lifestyle interventions have failed to modify primary CV endpoints. This paper reviews bariatric surgery in prevention of CV diseases and CV mortality, and analyzes the possible mechanisms involved.
Data synthesis: In morbidly obese patients bariatric surgery results in stable weight loss and in long-term reduction in the prevalence and incidence of obesity-related comorbidities; controlled trials have shown superiority of bariatric surgery over medical therapy in inducing significant weight loss and improvement of CV risk factors. Bariatric surgery induces several metabolic improvements (resolution of type 2 diabetes mellitus, improvement of lipid metabolism and of insulin resistance, reduction of visceral fat, of subclinical endothelial dysfunction and inflammation), and functional improvements (reduction of hypertension, of sympathetic overactivity, of left and right ventricular hypertrophy), which can explain the protective effect towards CV disease.
Conclusions: Reduction of CV diseases is mediated by the pleiotropic effects of weight loss through surgery. Available data do not allow conclusions on the comparative efficacy of different surgical techniques; the choice of the surgical technique for a single patient remains an open question, and it is likely that the degree of prevention of CV diseases depends, among other factors, on the baseline conditions of patients. Large prospective studies are needed to address this issue in morbidly obese patients.

Introduction

Obesity and morbid obesity: epidemiology issues

The growing epidemics of obesity is multifaceted: recognized as a social issue in industrialized countries [1], it is now expanding worldwide. Morbid obesity, defined by a body mass index (BMI) $\geq$ 40 kg/m^2, is increasing at an even more accelerated pace than obesity characterized by

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a BMI between 30 and 40 kg/m^2 [2]. In the US, UK, and Australia, for instance, the prevalence of obesity has more than doubled in the past 25 years [3]. Currently, 67% of the US population is overweight or obese, and in most European countries the prevalence ranges between 40% and 50% [3]. Obesity-related (and overweight-related) morbid conditions include hypertension, cardiovascular (CV) diseases, dyslipidemia, type 2 diabetes mellitus, sleep apnea (OSAS), degenerative joint diseases and depression [4]. Obesity and morbid obesity are associated with progressively increasing morbidity and mortality [5–7], and, unsurprisingly, with reduced life expectancy [8].

Despite the adverse impact of overweight and obesity on most CV risk factors and on heart failure [8,9], controversial findings were reported by authors who studied patients with heart failure or acute coronary heart disease; in these studies, overweight and mildly obese patients did not carry an excess mortality risk, showing, if any, a better survival [10–13], a phenomenon known as "obesity paradox". Accepted with skepticism at the beginning, the obesity paradox is now of evidence for patients with CV disease more than for the general population [14–17]; however, this phenomenon has little to share with treatment of obesity, as data come from longitudinal studies [14], not from intervention studies; as such, confounding factors (patients with cachexia, no data on fat distribution or body composition, on biochemistry, on physical fitness), rather than BMI itself, might be involved [14–17].

Effects of weight loss

In obese individuals with type 2 diabetes and arterial hypertension or dyslipidemia, even a modest weight loss leads to a better control of blood glucose levels, blood pressure, and lipid profile [18]. Given the fact that weight loss also positively affects other intermediate risk factors for CV disease [19–21], it might also reduce the incidence of CV events. Epidemiological studies have shown that intentional weight loss, at least in obese type 2 diabetes, is associated with improved survival [22]. Unfortunately, a randomized study has failed to confirm this finding [23]. Moreover, long term interventions with 10–20 years follow-up, while able to consistently prevent diabetes, have not prevented CV events [24,25]. Similarly, lifestyle intervention and antiobesity treatments have either shown no effect on primary CV end points, or an increased incidence of CV events in treated patients in comparison to controls [26,27]. Taken together, non-surgical weight loss trials have failed to show a consistent benefit in terms of CV events in obese subjects [23–27].

Bariatric surgery

Bariatric surgery results in sustained and stable weight loss in morbidly obese patients [28]. Several surgical approaches have been proposed and utilized in the last 50 years [29]. Weight loss is accompanied by long-term reduction in the prevalence and incidence of several obesity-related comorbidities, in particular type 2 diabetes [30]. The superiority of bariatric surgery over conventional medical therapy in inducing significant weight loss and concomitant control of CV risk factors in patients with morbid obesity has been proven in controlled and randomized clinical trials [31–33], and is supported by results of meta-analyses based on a review of a large number of clinical studies, which have evaluated short and long-term patients' outcomes [34–37]. There is now reliable evidence that with bariatric surgery clinical benefits induced by weight loss ultimately translate into a reduction of the increased mortality risk that characterizes morbid obesity.

Bariatric surgery and prevention of mortality

A series of studies published 1997–2007 reported lower long-term mortality (follow-up periods 2.5–12.0 years) in patients undergoing bariatric surgery than in controls; these studies were the object of a systematic review and meta-analysis [38], showing the beneficial effects of bariatric surgery on CV (risk reduction 42%), all-cause mortality (risk reduction 30%), and of global (CV plus all-cause) mortality (risk reduction 45%); a slightly superior efficacy of Roux-en-Y gastric by-pass (RYGB) over LGB for CV mortality was also reported [38]. More recent results from the Swedish Obesity Study (SOS study) have substantiated this finding showing a reduction of total and fatal CV events by 33 and 53% respectively among bariatric surgery patients compared to control patients after adjusting for baseline conditions [39]. Studies have later shown an improved life expectancy over controls also for surgery patients suffering from cardiovascular diseases [40]; obese patients undergoing bariatric surgery show a lower risk of mortality than control patients, but the risk remains higher than in non-obese subjects [41]. The results of the above meta-analysis [38] have been substantiated by a more recent one, detailing that patients undergoing bariatric surgery have a reduced risk of myocardial infarction, stroke, cardiovascular events and mortality compared to non-surgical controls [42].

All the above data seem therefore to confirm the hypothesis that in surgery-treated patients, stable long-term weight loss and reduction of CV risks factors may determine a reduction of CV events and CV mortality. Current guidelines have therefore suggested LGB a reliable weight management approach for individuals with BMI $\geq$ 35 kg/m^2 and one or more comorbidities of obesity [43]. As a result, this approach has been widely applied in Europe for morbid obese patients [44,45], allowing the evaluation of the possibility that weight loss could be associated with a significant reduction of CV events in LGB-treated or in RYGB-treated patients. Retrospective and prospective uncontrolled studies with LAGB and with RYGB showed a significant stable long-term reduction in blood glucose, systolic and diastolic blood pressure, total cholesterol, triglycerides, and a statistically significant decrease of the 10- and 30- year estimated CVD risk [44–46].