ARTIGO ORIGINAL

Cirurgia bariátrica em pacientes infectados pelo HIV: revisão de literatura

Bariatric surgery in HIV-infected patients: review of literature

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The author has no conflicts of interest to disclose.

ABSTRACT

Obesity is now a common problem among HIV-infected patients receiving antiretroviral therapy (ART). Until recently, HIV infection has been considered a contraindication to bariatric surgery for various reasons. Insurance carriers have considered HIV a terminal disease, and surgeons have been reluctant to operate HIV-infected patients because of this, as well as the associated risk of infectious transmissions, although this has been changing. Gastric bypass surgery may be an option for some patients who have failed diet and therapeutic lifestyle changes, modification in ART or other treatment modalities for HIV/ART-related lipohypertrophy and obesity. However, few data are available regarding HIV-related outcomes after such surgery and its impact on ART tolerability. The aim of this study is to review bariatric surgery in HIV-infected patients.

Keywords: HIV, obesity, bariatric surgery

INTRODUCTION

The World Health Organization has estimated that 36.7 million persons were affected with HIV/AIDS worldwide, in 2015.[1] In Brazil, there are 798,366 people living with HIV/AIDS, until 2015.[2]

The advent of highly active antiretroviral therapy (HAART) has dramatically reduced the progression of HIV to AIDS.[3-5] HAART has improved longevity while maintaining nearly undetectable viral loads. Less than one-quarter of deaths among HIV-infected persons receiving care are due to AIDS, whereas up to half are due to noninfectious causes such as cardiovascular disease (CVD), non-AIDS-related malignancies, and renal disease.[6,7] However, long-term HAART has been associated with lipodystrophy syndrome[8-11], which is characterized by central fat accumulation in the abdomen, breasts, and dorsocervical spine (“buffalo hump”), and lipoatrophy of the face, limbs, and buttocks. Metabolic features of lipodystrophy syndrome include hypertriglyceridemia, hypercholesterolemia, insulin resistance (IR), type II diabetes mellitus (T2DM), and lactic acidemia. The use of protease inhibitors (PI) has also been associated with accelerated coronary artery disease and myocardial infarction.[12,13]

Until recently, HIV infection has been considered a contraindication to bariatric surgery for various reasons. Insurance carriers have considered HIV a terminal disease, and surgeons have been reluctant to operate HIV-infected patients because of this, as well as the associated risk of infectious transmissions, but this has been changing. The aim of this study is to review bariatric surgery in HIV-infected patients.

Definition and consequences of obesity

The standard classification of obesity is expressed in terms of body mass index (BMI). Obesity is defined as a BMI > 30 kg/m^2 and might be further subdivided into classes.[14] BMI calculated as weight (kg)/height (m^2). Classifications of BMI: Underweight, < 18.5; Normal or acceptable weight, between 18.5 and 24.9; Overweight, 25 to 29.9; Obese, > 30; Grade 1, between 30 and 34.9; Grade 2, between 35.0 and 39.9; Grade 3, > 40 (severe, extreme, or morbid obesity); Grade 4, > 50; and Grade 5, > 60[15].

The prevalence of obesity is increasing as it reaches worldwide epidemic proportions with a worrying trend toward severe obesity.[15,16] This is not without effect on public health. At least 2.8 million people die each year as a result of being overweight or obese.[15] Chronic accumulation of excess body fat leads to a variety of metabolic changes. Indeed, visceral obesity is associated with an increased risk of developing CVD, but it also causes inflammation.[17] Obesity promotes hypertension, dyslipidemia, IR, sleep apnea, T2DM, and induces a variety of structural changes in cardiovascular functions.[18]

Obesity and HIV

Only a decade ago, HIV disease was a progressively fatal illness accompanied by severe wasting. Nowadays HAART has transformed the HIV disease into a chronic illness, accompanied by obesity.

Evolution of metabolic abnormalities

Since the identification of AIDS in 1981, metabolic abnormalities associated with HIV infection have varied over the time. During the early years, between 1981 to 1995, wasting syndrome was the hallmark of AIDS. Pronounced loss of weight, lean body mass and fat mass were attributed to several factors, including opportunistic infections, living below the poverty level, low CD4+ cell count, and high viral load. Although the incidence of wasting syndrome has declined dramatically since the introduction of ART, wasting still occurs, especially in individuals who are not receiving ART.[19]

Shortly after the introduction of HAART in late 1995, several new metabolic abnormalities were reported and linked to its use.[20] These abnormalities included lipodystrophy (fat redistribution), dyslipidemia, and IR. Whereas the etiology of lipodystrophy syndrome (fat redistribution along with dyslipidemia and/or IR) remains poorly understood, it has been associated with the use of all classes of antiretroviral medications, particularly the nucleoside reverse transcriptase inhibitor stavudine and the PI ritonavir. The prevalence of this metabolic disorder has been difficult to determine because of the lack of precise diagnostic criteria; however, it has been estimated to occur in up to 60% to 80% of individuals treated with ART.[21]

Recently, reports suggest that HIV-infected patients are gaining weight and beginning to approach weight levels seen in the general U.S. population, in which approximately two out of every three adults are overweight (BMI > 25) and one in every four adults is obese (BMI > 30).[22] Overweightness and obesity are considered the main responsible for the increasing prevalence of metabolic syndrome (MS). Components of MS include abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, IR with or without glucose intolerance, and proinflammatory and prothrombotic states[23], many of which overlap with correlates of lipodystrophy syndrome.

Thompson-Paul *et al.*[24] compared obesity prevalence among HIV-infected adults receiving care and the U.S. general population, to identify that obesity correlates among HIV-infected men and women. It was a cross-sectional data collected in 2009 and 2010 from 2 nationally representative surveys: Medical Monitoring Project (MMP), and National Health and Nutrition Examination Survey (NHANES). Weighted prevalence estimates of obesity, defined as body mass index > 30.0 kg/m^2, were compared using prevalence ratios (PR, 95% confidence interval [CI]). Correlates of obesity in HIV-infected adults were examined using multivariable logistic regression. Demographic characteristics of the 4,006

HIV-infected adults in MMP differed from the 5,657 adults from the general U.S. population in NHANES, including more men (73.2% in MMP versus 49.4% in NHANES, respectively), black or African Americans (41.5% versus 11.6%), persons with annual income lower than $20,000 (64.5% versus 21.9%), and homosexuals or bisexuals (50.9% versus 3.9%). HIV-infected men were less likely to be obese (PR 0.5, CI 0.5-0.6) and HIV-infected women were more likely to be obese (PR 1.2, CI 1.1-1.3) compared with men and women from the general population, respectively. Among HIV-infected women, younger age was associated with obesity (<40 versus >60 years). Among HIV-infected men, correlates of obesity included black or African American race/ ethnicity, annual income higher than $20,000 and lower than $50,000, heterosexual orientation, and mean CD4+ T-lymphocyte cell count higher than 200 cells/ml. Obesity is common, affecting 2 in 5 HIV-infected women and 1 in 5 HIV-infected men.

HIV-infected patients are becoming increasingly overweight and obese at diagnosis and during HIV treatment. The prevalence of overweight is around 30-40%, and obesity affects 6-34% of men and 21-30% of women.[25] Weight gain seems to be secondary to improved health status and can be a consequence of HIV treatment. These patients could develop many comorbidities, such as CVD, MS, T2DM and others.[26,27]

Obesity management

Weight management programs may be important components of HIV care.[28] A potential option to reduce obesity and the metabolic dysregulation associated with excess weight in HIV-infected patients is the bariatric surgery. Bariatric procedures, including gastroplasty, adjustable gastric band (AGB), sleeve gastrectomy (SG), gastric bypass (GBP), and jejunoileal bypass, represent the more successful approaches to weight loss compared to other methods in morbid obesity, decreasing morbidity and mortality.[29,30] The efficacy, safety, and durability of bariatric surgery for the treatment of obesity and cardiometabolic disease determinants, such as diabetes, hypertension, and dyslipidemia, have been documented in the general population.[31-34] However, there are few data regarding the outcomes for those with HIV infection undergoing bariatric surgery.

Bariatric surgery

Literature shows that, in the presence of severe obesity, the only treatment that allows significant substantial long-term weight loss and that cures or durably improves comorbidities is the bariatric surgery.[35] Sustainable weight loss requires a comprehensive strategy that encompasses nutrition, exercise, emotional, and cognitive aspects. Basically, there are three principal treatments for severe obesity: (1) changes in lifestyle habits, (2) pharmacotherapy, and (3) bariatric surgery.

Lifestyle modifications for successful weight loss include (a) reducing calorie intake; (b) increasing physical activity; (c) monitoring food intake, physical activity, and weight; (d) setting realistic weight loss goals; and (e) assessing and managing stress. To be successful, weight loss initiatives must also take into account patient preferences, lifestyle, and readiness to lose weight.[36]

A variety of bariatric surgery procedures is available to treat severe obesity. There are several guidelines describing eligibility for bariatric surgery, most of which are somewhat similar. The National Institutes of Health, the American Diabetes Association,[37] the International Diabetes Federation,[38] and other organizations[35,39] issued consensus statements identifying bariatric surgery as the only proven effective option for sustainable weight loss and weight control inducing beneficial clinical outcomes in severe obesity.[40] They have proposed bariatric surgery therapy for adult patients with BMI > 40 kg/m^2 or BMI > 35 kg/m^2, with obesity-related comorbidities such as systemic hypertension, T2DM, and obstructive sleep apnea, that are difficult to control with lifestyle changes or pharmacotherapy. All guidelines emphasized a general statement indicating that all candidates must have tried and failed appropriate nonsurgical weight loss measures. The risk-benefit ratio needs to be adequately evaluated and explained for each individual. Currently, there is no clear consensus regarding the upper age limit and the possible cardiovascular, pulmonary, and/or endocrine contraindications to bariatric surgery. These issues should be addressed one by one with the surgeon and other specialists at the time of the preoperative evaluation. Exclusion criteria for bariatric surgery include current drug or alcohol abuse and an uncontrolled and severe psychopathologic condition, which prevents patients from understanding the risks, benefits, expected outcomes, and lifestyle changes required with bariatric surgery.[41] Patients referred for bariatric surgery should undergo a comprehensive medical history, physical examination, blood chemistry, 12-lead electrocardiogram, chest radiograph, and formal pulmonary function testing if clinically indicated.[42] For patients with known cardiac disease and patients who have an increased perioperative cardiovascular risk, supplemental preoperative evaluations[42,43] and formal cardiology consultation should be judiciously performed.[43,44]

Types of bariatric surgical procedures

Bariatric surgery procedures promote weight loss and improvement in comorbidities through mechanisms of restriction and malabsorption. Classically, bariatric surgery has been described as either restrictive or hybrid surgery, which is a combination of both mechanisms. Restrictive approaches limit the amount of food consumed by reducing the size of the stomach, whereas hybrid approaches limit the absorption of nutrients by bypassing portions of the intestine in addition to restricting the stomach.[45]

Restrictive surgeries

Restrictive surgeries, aimed at reducing food intake, include AGB and SG. The AGB is an implanted inflatable band device at the topmost part of the stomach; the device is connected to a reservoir port placed just under the skin. Band adjustment is performed with saline injections through the reservoir port in the office on a routine basis for the “adjustment” of the upper stomach pouch outlet. The pouch quickly fills with food and the band slows the passage of food from the pouch to the lower part of the stomach, allowing the patient to achieve appetite control and satiety. The SG is a longitudinal resection of the stomach, which preserves its vagal innervation, starting from the antrum, 5-6 cm from the pylorus, and finishing at the fundus, close to the cardia. Approximately 75% to 80% of the stomach is resected and the remaining gastric sleeve is calibrated with a French bougie. The ideal approximate remaining stomach size after the procedure is approximately 150 ml.[46]

Malabsorptive surgeries

Hybrid surgeries include Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) with duodenal switch (BPD-DS), in which both procedures mix restriction and malabsorption of food but to different degrees. The RYGB remains the most commonly performed bariatric procedure in North America and worldwide.[47] The RYGB procedure consists of reducing the size of the stomach to a small pouch of 15 ml by stapling off a section of it and connecting it to the small intestine further down in the digestive system. The length of the alimentary loop can be modified but most of the time it is standardized at 150 cm, ensuring that RYGB has a greater restrictive than malabsorptive component. The biliopancreatic diversion, a malabsorptive procedure, introduced by Scopinaro et al. in 1979,[48] yields very good and sustained weight loss. The procedure was later modified by Hess and Hess[49] and Marceau[50] into the BPD-DS. The BPD-DS surgery involved a gastric restriction with an SG and the malabsorption results from the small intestinal bypass. The duodenum is transected approximately 4 cm distal to the pylorus and anastomosed to a 250 cm alimentary limb of the ileum. The biliopancreatic limb, which consists of the distal duodenum, jejunum, and proximal ileum, contains the biliopancreatic secretions and is attached to the alimentary limb approximately 100 cm from the end of the ileum or the ileocecal valve area. Biliopancreatic secretions, therefore, mix with the ingested food in this distal 100 cm common channel of the small intestine.[50] The BPD-DS surgery has a more important malabsorptive component when compared with the RYGB surgery.

Bariatric surgery in HIV-infected patients

In 2005, Flancbaum *et al.*[51] reported the first series of six HIV-infected patients from a prospectively maintained database of 892 patients (0.71%) undergoing bariatric surgery between June 1999 and December 2003. Six HIV-infected patients (4 women, 2 men; with a mean age of 43 years, ranging 28-56 years; mean preoperative weight of 142 kg, ranging 110-174 kg; mean preoperative BMI of 50, ranging 42-59) underwent RYGB. The mean duration of HIV infection was 9 years; 33% were receiving HAART at the time of surgery, which was discontinued perioperatively for 2-3 days. Average CD4 cell count was 619 cells/mm^3 (ranging 361-1096 cells/mm^3). There were no deaths or postoperative infectious complications. Mean percent excess body weight (EBW) loss was 33% at 3 months, 47% at 6 months, and 61% at 12 months. Mean percent initial body weight loss was 19% at 3 months, 26% at 6 months, and 33% at 12 months.

Fazylov *et al.*[52] reported 2 cases of morbidly obese, asymptomatic HIV-infected patients who underwent laparoscopic Roux-en-Y gastric bypass (LRYGB) surgery. The first patient was a 44-year-old woman with a history of borderline diabetes mellitus, morbid obesity, and HIV disease that was diagnosed in 2001 – she was not taking any medications. Her BMI was 42 kg/m^2, with an EBW of 90 lb. Preoperatively, her CD4 count was 368 x 106 cells/mm^3 and her viral load was 422 HIV RNA copies per ml. In 2004, she underwent an uneventful LRYGB surgery, with a 15-20-cm^3 gastric pouch, a 90-cm Roux limb, and a retrocolic/retrogastric gastrojejunostomy created with a 21-mm circular EEA stapler. Thirty months after the surgery her BMI was 28.3 kg/m^2. Her EBW loss was 72 lb (80%) at her last follow-up visit. The second patient was a 47-year-old woman with a significant history of morbid obesity and HIV disease, which was diagnosed in 2000. She had no other co-morbid diseases. She had a BMI of 54.1 kg/m^2 and an EBW of 180.5 lb. Preoperatively, her CD4 count was 891 cells/mm^3. Her viral load was not recorded. Her medications were stavudine, lamivudine, and lopinavir and ritonavir. In 2005, she underwent an uneventful LRYGB surgery, with a 15-30-cm^3 gastric pouch, 125-cm limb, and retrocolic/retrogastric gastrojejunostomy, created with a 21-mm EEA stapler. She had an uncomplicated postoperative course. Her BMI at 18 months was 37.9 kg/m^2. Her EBW loss at 18 months was 100.7 lb (57.9%). She continued to do well and had maintained her weight loss at the last follow-up visit.

Selke *et al.*[53] reported a case series of seven subjects with HIV infection who underwent bariatric surgery. Viral suppression was maintained in five of the six subjects who were receiving ART prior to surgery, including three subjects who experienced surgical complications. The median (range) decrease in postoperative BMI was 10 kg/m^2 (6-28 kg/m^2). Improvements were also seen in serum lipid fractions with median (range) changes in total cholesterol of -19 mg/dL (-61 to +3 mg/dL) and triglycerides of -185 mg/dL (-739 to +35 mg/dL). Four of the subjects had a postoperative reduction in their metabolic medication prescriptions. Three of the subjects experienced postsurgical complications. The authors concluded that bariatric surgery may provide an effective treatment modality for obesity and its related comorbidities in the HIV-infected population while not modifying virologic suppression.

Fysekidis *et al.*[54] retrospectively evaluated eight consecutive patients who underwent an SG, its effect on weight loss and its impact on the treatment and on the markers of HIV infection. Seven out of eight patients were females. The mean age was 46 years, with a median preoperative BMI of 42 kg/m^2. The mean duration of HIV infection and CD4 cell count were 13.4 years and 457 cells/mm^3, respectively. The mean weight loss was 37 kg in 20 months, the excess BMI loss was 80.8±30.9 %, and the excess weight loss was 81.5±28.9% with one minor complication. CD4 counts remained unchanged. Three patients had therapy modifications that were unrelated to bariatric surgery. Two patients had a therapeutic drug monitoring before and after the intervention. Plasma concentrations remained in therapeutic levels after the SG. Most comorbidities disappeared postoperatively, decreasing the cardiovascular risk. The SG was safe and effective with no consequences on CD4 counts and viral load in HIV-infected obese patients.

Eddy *et al.*[55] reported a case of a 44-year-old HIV-infected female that underwent bariatric surgery in 2012. Diagnosed in 2007, she had been on HAART for four years with a suppressed viral load (less than 34 copies per ml) and CD4 count of 680 cells/mm^3 at the time of surgery. Prior to surgery, her weight had stabilized at 154 kg. She had a medical history of recurrent cellulitis and asthma. Preoperatively, the patient was taking Atripla® (tenofovir/emtricitabine/efavirenz). The choice of regime was further limited by the size of the pouch opening which was 1 cm in diameter. This meant that tablets initially could not pass into the pouch and therefore could not be given to the patient. A regime of zidovudine liquid, nevirapine tablets dispersed in liquid ("off license" use) and lamivudine liquid was commenced. Due to the volume restriction of the pouch, this had to be interspaced by 30-minunte pauses. Two months postoperatively, the pouch had increased in size to allow larger tablets to be taken. Two years post-surgery, she had lost 73 kg (47% of her body weight). She had complete resolution of her cellulitis and reduced frequency of inhaler use. CD4 count has remained high (819 cells/mm3) and viral load remained undetectable.

Poucher *et al.*[56] reported bariatric surgery in HIV-infected patients using laparoscopic procedures like those used for all obese patients. They evaluated six patients who underwent an SG. For four of them (1 man and 3 African women, median age of 37.5 years, median BMI of 48 kg/m^2) they have long term follow-up before (6-12 months) and after surgery (18-36 months). Two patients had comorbidities: one had hypertension, treated with perindopril/valsartan, and sleep apnea, treated with nightime CPAP; the second had treated sleep apnea. Before surgery, two patients were receiving ART. All patients had a CD4 count higher than 475 cells/mm^3 and laboratory parameters were within normal range. Median percent excess body weight loss was 61%, at 18 or 36 months after the surgery. All comorbidities resolved with weight loss at 6 months. The success of surgery was evaluated using the BAROS score (quality of life, co-morbidities, and weight loss), as proposed. The median BAROS score was 7/9, corresponding to a good result. No postoperative complication was reported and all patients were discharged on day 3 or 4. Using the patient as their own control, we observed no significant alterations of CD4 cell count and HIV plasma viral load before and after surgery.

Zivich *et al.*[57] performed a retrospective cohort study of HIV-infected patients who underwent bariatric surgery while receiving care at the Partnership Comprehensive Care Practice (PCCP), a multidisciplinary HIV clinic affiliated with Drexel UniversityCollege of Medicine. They included all HIV-infected patients who underwent AGB, SG, or RYGB between January 2005, and July 2014. The researchers collected data from the electronic medical records regarding HIV viral load, CD4+ T-cell count, weight, BMI, metabolic parameters (random glucose, HbA1C, LDL, HDL), blood pressure, postoperative complications, use of acid suppression therapies, and changes in ART regimens. During the study period, 7 patients (4 men and 3 women) underwent a bariatric surgery procedure: 3 of them underwent SG, 2 underwent AGB, and 2 underwent RYGB. The median age at the time of the procedure was 40 years (ranging 24-50 years) and the mean (SD) preoperative BMI was 49.1 (12.2) kg/m^2. The median CD4+ T-cell count at the time of the procedure was 598 cells/μL (ranging 297-1857 cells/μL). The median follow-up time at the PCCP following the procedure was 27 months (ranging 10-60 months). There were 2 patients with intolerance of oral medications in the postoperative period leading to prolonged time periods without ART administration. In both instances, undetectable HIV viral loads were again obtained after ART regimens were restarted. There were no significant changes in CD4+ T-cell counts pre- and postprocedure ($p = 0.35$) or the proportion of undetectable HIV viral loads ($p = 0.76$). There were no intraoperative complications for any patients. After the procedure, 2 patients had their ART regimens changed for reasons other than patient preference. In both of these instances, the ART regimen change was prompted by the use of atazanavir in patients receiving antacid therapy. Other medication changes during the postoperative period included cessation of oral antihypertensive therapy (1 patient) and cessation of oral hypoglycemic therapy (1 patient), with therapeutic targets reached in the absence of medications. The mean BMI after surgery was 41.2 (11.7) kg/m^2, which was significantly reduced from baseline ($p < 0.01$). Overall, the smallest reduction in BMI was observed after AGB, while larger reductions in BMI were observed after SG and RYGB. Random glucose concentrations and HbA1c values were significantly reduced after surgery, whereas lipid parameters remained essentially unchanged. Statistically significant decrements in both systolic and diastolic blood pressure were also observed. In summary, SG and RYGB were safe and effective among morbidly obese HIV-infected patients.

Drug Absorption

The changes in drug absorption induced by bariatric surgery have been poorly studied and may differ according to the alteration of gastrointestinal anatomy and physiology, the presence of drug interactions, and the reduction in body mass. In literature, there are few publications reporting the drug alteration after GBP surgery in non-HIV patients, notably drugs used in depression, some antibiotics, and thyroxin in hypothyroidism[58-60]. The authors concluded that these modifications were not critical in the management of the disease.

The effect of bariatric surgery on drug absorption may be specific to the drug or the type of operation. The various stages of drug absorption could be modified: disintegration/dissolution, mucous membrane exposure, transport through the gut, and transport across the intestinal epithelium. Gastric disintegration mixture could be significantly reduced after GBP and SG. Drug dissolution and solubility can potentially be affected by the increase in gastric pH in GBP and SG or by the use of anti-acid therapy. Most anti-HIV treatments are absorbed in the ileum. The absorption can be changed after GBP due to the reduced availability of bile acids to improve the solubility and reduced drug exposure to the intestinal mucosa. The changes in the volume of distribution of lipophilic drugs may be increased in obese patients and decreased after surgery. Few reports suggested no modifications or small changes; after oral administration, post-GBP achieved sufficient serum concentrations for lopinavir, whereas administration through the jejunal tube did not.[61] In a case of gastrectomy, lopinavir/ritonavir plasma levels were not affected.[62]

Conclusion

Bariatric surgery may be an effective and reasonable treatment modality for obesity and its related comorbidities in people living with HIV infection who have failed more conservative therapy with diet and therapeutic lifestyle changes. Close involvement between the surgical team and HIV multidisciplinary team is recommended for patients undergoing bariatric surgery. Risks and benefits of bariatric surgery should be considered on a highly individualized basis in patients with asymptomatic HIV infection. In conclusion, bariatric surgery did not modify in a negative way the course of HIV infection in morbidly obese patients, while it significantly improved comorbidities, thus reducing the cardiovascular risk. Large-scale studies are needed to determine surgical complication rates in this population and to assess the impact of bariatric surgery on CD4 cell counts and viral suppression. Prospective studies are needed to propose an optimal management of HIV-infected patients with morbid obesity.

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Recebido em 11/09/2016
Revisado em 20/10/2016
Aceito em 05/11/2016

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