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Impact of Gastrointestinal Surgery on Cardiometabolic Risk

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Abstract Bariatric surgery has gained acceptance as the only treatment with long-term efficacy for severe obesity. Recent publications emphasize the usefulness of bariatric surgery in the reduction of long-term cardiometabolic risk, cardiovascular disease incidence and mortality, and the management of uncontrolled type 2 diabetes (T2DM), an important cardiovascular risk factor in individuals with severe obesity. The present review article offers a brief overview of the literature published over the past several months relevant to cardiometabolic outcomes in bariatric surgery patients. A recent report from the Swedish Obese Subjects (SOS) study specifically reported a reduced incidence of cardiovascular events on long-term prospective follow-up after bariatric surgery. In addition, abundant studies have been recently published on gastric bypass surgery showing high T2DM remission rates as well as improved blood lipids and inflammatory markers after surgery. Sleeve gastrectomy is increasingly performed as a stand-alone operation. Recent reports on this surgery pertaining to cardiometabolic risk showed variable T2DM remission rates that may possibly be explained by age of the patients and duration of T2DM. Available data suggest a possible favorable impact of the surgery on CRP levels and improvements in the blood lipid profile. How sleeve gastrectomy compares to other surgical approaches will require further study. Biliopancreatic diversion with duodenal switch has been reported to offer some of the best long-term weight loss for obese patients. Approximately 9 out of 10 patients treated with this surgical procedure show long-term remission rates of T2DM. Significant improvements in the cardiometabolic risk profile are also observed after BPD-DS; they are especially pronounced regarding dyslipidemia. In conclusion, bariatric procedures improve the cardiometabolic risk profile, a phenomenon that appears to be only partly explained by the magnitude of the weight loss. Significant variations are observed with respect to the type of surgery and patient characteristics. More research is clearly needed on the short and long-term cardiometabolic outcome of obesity surgeries.

Keywords Cardiometabolic risk · Bariatric surgery · Roux-en-Y gastric bypass · Biliopancreatic diversion · Sleeve gastrectomy · Lipid profile · Inflammatory markers · Excess weight loss

Introduction

The obesity pandemic, afflicting over 300 million adults, has widened beyond industrialized nations to include developing regions, adding significance to obesity's impact on the health of societies and associated healthcare costs [1, 2]. Severe obesity is associated with numerous co-morbidities contributing to increased mortality risk [3], as well as physical and psychological disorders [4–6]. Associations between morbid obesity and the risk of hypertension, coronary artery disease, diabetes, cancer and respiratory conditions have also been well-documented [7–11]. Lifestyle and medical interventions are poorly effective for severely obese patients [12–15], and bariatric or weight loss surgery (also recognized as metabolic surgery) has gained acceptance as the only treatment with durable, long-term effects for this condition [16–18] in terms of weight loss and improvements

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in diabetes and other intermediate risk factors for cardiovascular disease [9].

Bariatric procedures promote weight loss and improvement in comorbidities through multiple mechanisms. Classically, however, bariatric operations have been described as either restrictive, malabsorptive, or a combination of both. Restrictive approaches limit the amount of food consumed by reducing the size of the stomach, whereas malabsorptive approaches limit the absorption of nutrients by bypassing portions of the intestine [12, 16]. Among procedures used to induce weight loss, the Roux-en-Y gastric bypass (RYGB), an operation with both a restrictive and malabsorptive component and subsequently resultant hormonal mechanisms, remains the most commonly performed bariatric procedure in North America and globally [19–21]. The sleeve gastrectomy (SG), a more contemporary primary bariatric procedure, was initially developed in the early 90's as an acid-reducing and restrictive component of a biliopancreatic diversion with duodenal switch (BPD-DS) [18, 22]. It was later offered laparoscopically as a first step of a two-staged approach to the BPD-DS to reduce perioperative complications in high-risk patients; the second step, or the duodenal switch component, was then performed after some weight loss had been obtained [11, 12]. However, it was observed that some patients experienced appreciable weight loss with the SG alone and did not require a second-stage surgery, thus avoiding a malabsorptive procedure [18]. The popularity of SG as a stand-alone operation has increased due to its perceived technical simplicity and favourable early outcomes [18]. Another major weight loss operation is the BPD-DS, which consists of both the SG and an intestinal bypass component where the first part of the duodenum is anastomosed with 250 cm of ileum measured from the ileocecal valve (alimentary limb). The distal duodenum, jejunum, and proximal ileum, which contain biliary and pancreatic secretions, receive no nutrients; and this biliopancreatic limb of intestine is anastomosed to the distal ileum 100 cm from the ileocecal valve. This common limb becomes the only major site for lipid absorption [23, 24].

Research into bariatric surgery began more than 50 years ago [25], and numerous publications have documented various aspects of the commonly performed operations. The aim of this review article is to provide an overview of the literature published in the past several months relating to cardiometabolic outcomes after bariatric surgery.

Bariatric Surgery and Cardiometabolic Disease: Highlights of 2012

The development of cardiovascular disease and associated morbidity and mortality represents an important risk related to obesity. There have been many publications related to bariatric surgery over the past few months; three major studies, however, are worth highlighting here for their relevance in terms of how bariatric surgery improves cardiovascular risk factors, including diabetes mellitus [26••, 27••, 28••]. The Swedish Obese Subjects (SOS) study is an ongoing, nonrandomized, matched, prospective, controlled study in which more than 4,000 patients were enrolled and followed forward over time in Sweden. Reports on the primary endpoint of the SOS project, overall mortality, were published in 2007, where a 23.7 % overall unadjusted (30.7 % adjusted) mortality decrease was observed in bariatric surgery patients at 10 years compared with a well-matched nonsurgical control population [29]. This improvement in overall mortality after bariatric surgery, which has also been demonstrated in smaller retrospective studies, along with the repeated observations of the beneficial effect of bariatric surgery on diabetes, dyslipidemia and hypertension, suggest that such surgery directly influences cardiovascular disease. The most recent report from the SOS project [27••] describes the impact of obesity surgery on the predefined endpoints of myocardial infarction and stroke, reported as total (fatal and non-fatal) cardiovascular event incidence rates. The study groups included 2,010 bariatric surgery patients (BMI≥34 kg/m^2 in men; BMI≥38 kg/m^2 in women) receiving gastric bypass (13.2 %), gastric banding (18.7 %) or vertical banded gastroplasty (68.1 %) and 2,037 contemporaneously matched obese controls receiving usual medical care. Over a median follow-up of 14.7 years (range: 0–20 years), bariatric surgery was associated with a reduction in the number of cardiovascular deaths and first time cardiovascular events (fatal or non fatal), after controlling for the cardiometabolic risk profile at baseline [27••]: Compared with controls, for total cardiovascular events, the adjusted hazard ratio (HR) of bariatric surgery was 0.67 (95 % CI: 0.54-0.83; P<0.001); and for fatal cardiovascular events, the adjusted HR was 0.47 (95 % CI: 0.29-0.76; P=0.02). Of note is that weight loss was only about 16 % at 15 years in the treatment group, whereas overtime the control group showed weight changes around a maximum of 1 %. Interestingly, secondary subgroup analyses of the SOS data failed to demonstrate an association between initial BMI and postoperative health benefits of bariatric surgery. Even the magnitude of surgery-induced weight loss did not predict cardiovascular events in this cohort. This puts into question the current clinical practice of using BMI as a main indication and eligibility criterion for bariatric surgery, when cardiovascular benefits are realized independent of differences and changes in body weight [30, 31]. Further post-hoc analysis of the SOS data revealed that, unlike baseline BMI or the magnitude of postoperative weight loss, a high baseline insulin level was in fact a predictor of cardiovascular events in the study. These results point to the important role of bariatric surgery in improving the cardiovascular risk profile, in addition to decreasing the overall incidence of fatal and non-fatal cardiovascular events in severely obese patients in the long term. They also suggest that weight-independent mechanisms rather than weight loss alone may explain part of the cardiometabolic benefits of surgery. In addition, while the majority of surgical patients in the SOS cohort underwent procedures infrequently offered today, similar positive results are expected to be observed, and with perhaps greater magnitude, when the more frequently performed malabsorptive procedures, RYGB and BPD-DS, are offered.

In addition to the latest update from the SOS group, two other studies recently examined, through a prospective randomized design, the impact of bariatric surgery on diabetes control when compared with current medical therapy [26••, 28••], thereby addressing an important and common cardiovascular disease risk factor in severely obese patients. When Mingrone et al. randomized patients between biliopancreatic diversion, RYGB, or standard medical therapy, better glycemic control was observed in the surgical groups after 2 years. In addition, no remission from diabetes was seen in the medical group, whereas remission rates were 75 % and 95 % after RYGB and BPD, respectively [28••]. Schauer et al. showed that after 1 year, a glycated haemoglobin level of ≤6 % was achieved in 42 % after RYGB, 37 % after SG, and in only 12 % after intensive medical therapy, when patients were randomized between these three arms [26••]. Together, the short- and long-term results from these three seminal studies published in 2012 clearly emphasize the important role bariatric surgery plays in the management of uncontrolled T2DM, as well as of long-term cardiovascular disease risk in individuals with severe obesity.

Recent Studies on Cardiometabolic Outcomes of Bariatric Surgery

Roux-En-Y Gastric Bypass

A large number of reports were published in the past 2 years on the metabolic effects of RYGB surgery. A detailed review of all these studies is beyond the scope of this article. This section will summarize some of the recently published works on cardiometabolic outcomes of RY gastric bypass.

In general, gastric bypass surgery tends to result in significant improvements in the cardiometabolic risk profile that are proportional to the magnitude of weight loss [19, 32–34]. For example, recent studies showed that 12-month post-surgery T2DM remission rates ranged from 64 % to 96 % [19, 35–40]. Interestingly, two of the studies reporting remission rates in the range of 60 % were performed in Asian populations with initially lower BMI values compared to other populations [35, 36]. The other study with a remission rate of around 60 % comprised a small number of subjects with T2DM [38]. In the remaining studies, T2DM remission rates after gastric bypass averaged approximately 92 % over a follow-up time of 1 to 6 years [19, 37, 39, 40].

Such changes have been accompanied by improvements in circulating lipid levels. For example, a retrospective study performed in 949 participants showed that plasma concentrations of triglycerides, HDL-cholesterol and LDL-cholesterol were all significantly improved one year after Roux-en-Y surgery [41•]. These improvements were predicted in part by the amount of lost weight [41•]. A small prospective study assessing apolipoprotein B levels showed a 22.9 % reduction at 3 months and 32.1 % reduction at 6 months [38]. Changes in the ApoB100/ApoA1 ratio were significantly correlated with changes in cholesterol, LDL-cholesterol and triglyceride levels [38]. Short-term changes in the blood lipid profile in response to gastric bypass have been examined in another study of patients stratified according to initial BMI value [42]: triglyceride levels were significantly reduced in all BMI categories 30 days following surgery, and then improved further at 6 months. However, HDL-cholesterol showed a transient decrease at 30 days, specifically in the subgroups with initial BMI values above 40 kg/m^2. HDL-cholesterol levels improved later during the follow-up, but this change was of lower magnitude compared to improvements in triglyceride levels [42]. This transient decrease in HDL-cholesterol levels has also been reported in other weight loss studies [33, 37] and has been suggested to result from the dramatic reductions in caloric and lipid intake immediately after surgery, which reduce lipid levels overall [42].

Age at the time of surgery is deemed a significant predictor of 10-year Framingham risk score [34]. Specifically, subjects younger than 45 years experienced a greater improvement in cardiometabolic risk compared to older patients; this was reflected in a better risk score at follow-up [34]. A study also showed some impact of initial obesity level on the cardiometabolic response to surgery as metabolic improvements appeared to be observed more readily among patients with an initial BMI value lower than 50 kg/m^2 [34].

Inflammatory markers were specifically examined in a number of RYGB studies. Previously, lifestyle intervention studies had been shown to decrease circulating levels of the inflammatory marker C-reactive protein (CRP) in obese individuals [43, 44]. Similarly to diet-induced weight loss, gastric bypass was shown to reduce CRP levels [32, 41•, 45–47]. For example, in 431 patients followed for an average of 325 days post-operatively, CRP values were above 3 mg/dL in only 9.8 % of patients, compared with 34.6 % that were above this cut-off value before surgery [41•]. Regarding other inflammatory markers or adipose tissue-derived cytokines, one prospective study showed no significant impact of gastric bypass on IL-6 and IL-10 levels, although leptin, PAI-1 and CRP levels decreased significantly at three and six months of follow-up. Fibrinogen and IL-1Ra levels decreased significantly and adiponectin significantly increased only at 6 months of follow-up [32]. Recent studies showed significant increases in interferon-gamma synthesis and peripheral blood mononuclear cell secretion of IL-12, IL-18 [48]. Others have shown that circulating IL-6 and TNF-alpha were not affected by surgery [46]. Studies on adiponectin changes in response to gastric bypass also report significant increases in adiponectin levels 3 and 6 months after surgery [32, 45–47].

Sleeve Gastrectomy

As mentioned, SG is increasingly performed as a stand-alone obesity surgery [18]. Outcomes after SG remain short and intermediate-term in nature. Recently, percentage excess weight loss (%EWL) at 12 months after SG has been reported to range from 43.6 % to 96.2 % [49–53, 54•, 55, 56]. The study with the highest %EWL was performed in a sample of teenagers [50]. When excluding studies performed in adolescents, the average 12-month %EWL was 61.2 % [51–53, 54•, 55, 56]. This is more in line with our experience with the SG, where an average of 52 % EWL is observed at 12 months. Population characteristics need to be, of course, considered when comparing these parametric statistics. Available studies indicate a possible inverse correlation between initial body mass index (BMI) and %EWL at 12-months [49–53, 54•, 56, 57]. A study in 174 patients directly addressed this question by showing that participants with BMI values above 50 kg/m^2 had a 7–10 % lower excess weight loss compared to those with BMI values below 50 kg/m^2, at least for the 6- and 12-month follow-up [51]. This trend is less apparent in other studies, one of which has been performed on a noticeably older population [56]. Studies are not unanimous as to whether the efficiency of SG is as good as the Roux-en-Y regarding %EWL. While some studies support the notion that outcomes of SG may be as good as that of the RYGB [40, 58, 59•], others report no significant difference between the two procedures. Moreover, many have documented better %EWL with the RYGB than with SG [39, 40, 58, 59•]. The active weight loss phase seems shorter for the SG than for the Roux-en-Y. According to recent studies, weight loss slows down approximately one year after SG compared to one to three years for Roux-en-Y surgery [19, 32–34, 36–38, 40, 50, 54•, 56, 58, 59•, 60–62].

Early results of the SG show that it is able to induce improvements in metabolic comorbidities. Recent studies reporting percentage of T2DM remission following SG are summarized in Table 1. Remission rates have been reported to be highly variable, with values ranging from 18.2 % to 93.8 % [49–51, 53, 54•, 56, 57, 61, 63]. Many factors have been proposed to explain such wide variability. The highest resolution rate was 93.8 % and was observed in young (<21 years old) obese individuals [49]. The shorter duration of T2DM in this young population may explain the observed results. Casella et al. reported a T2DM resolution rate of 31 % in 16 obese with diabetes for >10 years, compared with 100 % resolution in a group of 40 who had diabetes for <10 years T2DM duration [61]. The lowest %T2DM remission (18.2 %) was observed in a super-obese population [57]. At this point, it remains premature to conclude that the SG is as effective as the RYGB in terms of T2DM resolution.

Two comparative studies, however, have not observed any significant difference between both surgeries [40, 59•]. Interestingly, the latter study which included 786 patients undergoing Roux-en-Y and 811 patients undergoing SG noted a better remission rate in the SG group with 90.9 % compared to 86.6 % for the Roux-en-Y group [59•]. However this case-control study did not match patients for comorbidities and the HbA1c level at baseline reflected worse control in the RYGB group. Another study performed in 30 diabetic patients undergoing Roux-en-Y and 30 diabetic patients undergoing SG reported discordant results, with a 93 % T2DM remission rate at 1-year for the first group compared to 47 % in the second group [39]. These findings appear to be more consistent with the results of the recently reported randomized trial by Schauer et al. showing a control of HbA1c at <6 % in 37 % of the SG group at one year [26••].

Since inflammation is emerging as a predictor of cardiovascular disease, inflammatory changes after SG have also been evaluated. One recent prospective study assessed the impact of sleeve gastrectomy on circulating levels of CRP [64]. Over a 6-month follow-up, the number of patients with CRP values below 3 mg/dL increased from 3 out of 29 before surgery to 13 out of 29 postoperatively. In that study, decreases in CRP levels were directly proportional to decreases in BMI as well as to the initial BMI [64].

Regarding improvements in the lipid profile after SG, studies are not as discordant as observed for %EWL results and T2DM remission rates. RYGB and SG both lead to similar improvements in HDL-C level and TG levels [39, 58, 59•]. A study performed on 140 Spanish obese patients did not report significant differences in cardiovascular risk estimated using both 10-year Framingham risk score and the Registre Gironi del cor (REGICOR) model [40]. However, differences have been reported in all studies comparing both surgeries in regards to changes in LDL-C levels [39, 40, 58, 59•]. Indeed, significant decreases in LDL-C concentrations are observed after Roux-en-Y surgery, but not in patients who had a SG [39, 40, 58, 59•]. Total cholesterol was shown to increase after sleeve gastrectomy in two recent studies [40, 58]. Another study reported a persistently higher metabolic syndrome prevalence of 60 % following SG compared to 7 % after Roux-en-Y [39].

Biliopancreatic Diversion

Among the bariatric procedures, BPD-DS is known to offer some of the best long-term weight loss and resolution of

Table 1 Type 2 diabetes (T2DM) remission rates following sleeve gastrectomy in recent studies

Study	N	M/F	Average initial BMI (kg/m^2)	Average Initial age (yrs)	Initial % with T2DM	Design	Follow-up	Diabetes duration (years)	Diabetes medication	Remission rate (%)
Magee et al. [57]	68	39/29	68[a]	45[a]	32.35	Retrospective	12 mo	-	-	18.3
Chopra et al. [51]	174	25/149	48.97±8.25	39.6±10.7	25.86	Retrospective	Avg: 16±8.96 mo Range: 6-36 mo	-	-	33.0
Bobowicz et al. [53]	84	21/63	44.62	39	26.19	Retrospective Observational	Avg: 22±6.75 mo Range: 14-56 mo	-	-	41.0
Boza et al. [50]	51	10/41	38.5±3.7	18±1.45	3.9	Retrospective	Range: 6-24 mo	-	-	50.0
Gluck et al. [54•]	204	49/155	45.7	45	28.43	Retrospective Nonrandomized	Range: 3-36 mo	-	-	70.7
Behrens et al. [63]	34	1/33	50.3	48	56	Retrospective	Avg: 10 mo Range: 2-23 mo	-	-	74.0
Slater et al. [56]	22	17/5	46	55.3	100	Retrospective of prospective database	Avg: 7 mo	-	77 %: more than 1 medication 55 %: insulin	75.0
Casella et al. [61]	56	15/41	Group A: 42.7	Group A: 52.7	100	Retrospective	Avg group A: 11 mo	Group A: >10	Group A: 43.7 % HGO, 6.3 % insulin, 50 % HGO+insulin	Total: 80.3
			Group B: 44.9	Group B: 50.4			Avg group B: 10 mo	Avg: 14.8	Group B: 87.5 % HGO, 7.5 % insulin, 5 % diet	Group A: 31.0
							Range: 3-18 mo	Group B: <10 Avg: 2.8		Group B: 100
Alqahtani et al. [49]	108	53/55	47.4 [a]	13.9±4.3	14.81	Retrospective Observational	Range: 3-24 mo	-	-	93.8

a: median value; HGO: hypoglycemic oral agent; Avg: average; mo: months comorbidities for obese patients [15, 23]. Since its first description in the literature by Marceau et al. [22], the BPD-DS has been the standard surgical procedure of choice in our Center for most patients with severe obesity [22, 23]. In terms of %EWL, we reported a value 76±22 % in a sample of 810 obese individuals with a mean BMI of 44.2±3.6 kg/m^2 [23]. This study was performed over a long follow-up period of 8.6 years. Of the patients examined, 92 % reached a BMI below 35 kg/m^2 [23]. In another analysis with a follow-up of 7.9±4.2 years, a total of 1,271 patients experienced a 68.6±21.4 %EWL [65]. The number of individuals with a persistent BMI above 40 kg/m^2 was only 10 % eight years after surgery [65]. Initial BMI value was found to have a significant impact on %EWL, with a higher initial BMI being predictive of slightly lower %EWL values [65]. Recent studies from other groups reported %EWL values ranging from 61 to 78 % with mean follow-up durations of up to 11 years [66–69, 70••].

Mingrone et al. [28••] evaluated diabetes remission after BPD in a prospective randomized study, where remission was defined as a fasting glucose of <5.6 mmol/L and a glycated haemoglobin of <6.5 % in the absence of drug therapy. At 2 years, they observed remission in 95 % of patients who underwent BPD, a value which was far greater than that seen with the other two arms of the study. In another study comparing SG vs. biliopancreatic diversion with duodenal switch outcomes [60], no difference was reported between the procedures regarding improvements of anthropometrics, adiponectin, leptin and CRP levels [60]. Homeostasis model of assessment-insulin resistance (HOMA-IR) significantly decreased 3 months after both procedures, but this index worsened 15 days after the operation and later decreased in the SG subgroup [60]. This observation suggests that glucose and insulin may not be modulated through the same mechanism depending on the type of bariatric surgery [60]. Serum glucose, insulin, TG and free fatty acids were reduced after both surgeries, but changes were significant only in the case of BPD-DS [60]. BPD-DS seems to have a longer active weight loss phase than SG; even longer than the Roux-en-Y [19, 23, 32–34, 36–38, 40, 50, 54•, 56, 58, 59•, 60–62, 67, 68, 70••]. Indeed, weight loss has been reported to slow down approximately two to five years following BPD-DS [23, 60, 67, 68, 70••].

Our observational results show that diabetes remission is durable after many years of follow-up after BPD-DS surgery. In our patients, T2DM remission rates were in the magnitude of 92.5 % [23]. After a follow-up of 667 patients over 5.5 years (range 2 to 14 years), 96 % of diabetic patients could discontinue their medication [71]. Regarding other cardiometabolic risk factors, most studies support a significant improvement in several risk factors including hypertension, triglyceride concentrations and cholesterol levels [23, 66, 68, 71] which remained significantly improved on follow-up [68]. The results are particularly striking regarding dyslipidemia, with observed remission rates of 95 % to 100 % [68, 69]. The long-term follow-up data available after BPD-DS certainly supports its efficacy as a possible cure for morbid obesity and related metabolic comorbidities [23]; life-time nutritional follow-up remains, of course, an essential component of care for the bariatric patient after any malabsorptive procedure.

Conclusions

Bariatric surgery clearly improves the cardiometabolic risk profile and cardiovascular outcome in patients with severe obesity. The degree of initial obesity as well as the extent and durability of weight loss beyond a certain minimum only partly explain these effects, as suggested by the recent report from the SOS group. This rekindles the debate on the proper indications for bariatric surgery, particularly as it pertains to the role of BMI as a criterion for surgical eligibility or a predictor of benefit. In light of accumulating new evidence, a review and update of the 1991 NIH criteria for bariatric surgery may very well be in order [72]. There are significant variations with respect to the type of surgery as well as the patients' initial characteristics and the postoperative results, which should be considered, as additional evidence is collected overtime to better outline the health benefits of bariatric surgery. Body composition, fat distribution, metabolic dysfunction, insulin resistance and diabetes may in fact play a bigger role than BMI or the amount of weight loss in predicting response to bariatric surgery and postoperative changes in cardiometabolic risk. Currently, there is substantial evidence demonstrating the role of bariatric surgery in inducing significant and sustained weight loss over time as well as improvements in diabetes, dyslipidemia, hypertension and other comorbidities, as summarized in many systematic reviews on the topic. However, evidence from well-controlled prospective trials for the health benefits and cardiovascular risk reduction after bariatric surgery remains in its infancy. The SOS results have started to provide a glimpse of what that evidence may look like in the long-term. More research is clearly needed on the short and long-term cardiometabolic outcomes of some of the contemporary and newer procedures, such as the SG. In addition, weight dependent and independent mechanisms of bariatric procedures explaining the metabolic improvements seen in obese patients undergoing surgery remain of great clinical interest both in the early and late postoperative periods.

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- • Of importance
- •• Of major importance

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