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Laparoscopic sleeve gastrectomy for morbid obesity and glucose metabolism: a new perspective

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Abstract
Background Global rise in the incidence of obesity and type 2 diabetes mellitus is widely recognized as one of the most challenging contemporary threats to public health. Weight loss surgery has proven to be an effective and durable solution for morbidly obese adults. Laparoscopic sleeve gastrectomy (LSG) was introduced as a restrictive procedure for obese patients, initially described as a possible first-stage operation, but now commonly performed as a stand-alone bariatric operation for both high-risk and super-morbid-obese patients, as well as for patients with lower body mass index. This study aims to evaluate the progression of glucose metabolism in patients undergoing LSG.
Methods This prospective study investigated 62 patients who underwent LSG by the same surgical team in an 18-month period. Preoperative evaluation included demographic information, complete medical history including comorbidities and medication, clinical examination, evaluation of cardiopulmonary function, measurement of weight and height on a standard electronic scale, upper gastrointestinal endoscopy and upper abdominal ultrasound, as well as interviews with a psychologist and nutritionist. Glucose metabolism was evaluated by oral glucose tolerance test (OGTT), preoperatively and at 3, 6, and 12 months after surgery.
Results The OGTT was significantly ameliorated in all groups during follow-up. Nine of 12 diabetic patients (75 %) ceased drug treatment at 3 months postoperatively ($p = 0.004$), increasing to 100 % at 1-year follow-up ($p < 0.001$). Normoglycemic patients and patients with borderline OGTT experienced mild or severe hypoglycemia during the glucose tolerance test at 3, 6, and 12 months' follow-up.
Conclusions LSG offers excellent results to morbidly obese patients with regard to type 2 diabetes mellitus. Implementation of OGTT in these patients can be a valuable tool in their postoperative management. Bariatric teams performing LSG for morbid obesity should heighten their sensitivity to postoperative hypoglycemia, even in patients with type 2 diabetes mellitus.

Keywords Obesity · LSG · Diabetes · Metabolism · Oral glucose tolerance test

Global rise in the incidence of obesity and type 2 diabetes mellitus is widely recognized as one of the most challenging contemporary threats to public health [1]. Weight loss surgery has proven to be an effective and durable solution for morbidly obese adults.

Laparoscopic sleeve gastrectomy (LSG) was introduced as a restrictive procedure for obese patients, initially described as a possible first-stage operation in super-obese patients with a body mass index (BMI) of over 60 kg/m^2, as well as in high-risk patients, to a more complex definitive procedure [2]. In addition to its use in staged approaches in high-risk, high-BMI patients, LSG is now commonly performed as a stand-alone bariatric operation for both high-risk and super-morbid-obese patients, as well as for patients with lower BMI [3]. Although it has been classified among the restrictive procedures, there is increasing evidence in the literature that LSG acts with

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Table 1 Exclusion criteria

Exclusion criteria	*n*	%
Type 1 diabetes mellitus	8	2.78
β-Blocker treatment	81	28.13
Corticosteroid treatment	19	6.60
Thiazide diuretic treatment	40	13.89
Psychiatric medicinal treatment	32	11.11
Refusal to enroll	22	7.64
Major surgical complications	2	0.69
Total number of LSG patients	288	
Eligible for enrollment	86	
Refused to enroll	22	
Late exclusion (major complication)	2	
Total number of patients in the study	62	

more than one mechanism [4]. Studies have shown weight loss and diabetes resolution similar to Roux en Y gastric bypass (RYGB) [5].

While there has been considerable focus on the resolution of type 2 diabetes, other aspects of glucose regulation have been less actively investigated. It is important to recognize that the majority of patients undergoing bariatric surgery are not diabetic. Furthermore, after RYGB an increasing number of patients have been diagnosed with hyperinsulinemic hypoglycemia. Some have had endocrine symptoms requiring reoperations that have even extended to total pancreatectomy [6].

This study aims to evaluate the progression of glucose metabolism in patients undergoing LSG.

Materials and methods

Patient selection and assessment

This prospective study investigated 62 patients who underwent LSG by the same surgical team in our department in an 18-month period.

Preoperative evaluation included demographic information, complete medical history including comorbidities and medication, clinical examination, evaluation of cardiopulmonary function, measurement of weight and height on a standard electronic scale, upper gastrointestinal endoscopy and upper abdominal ultrasound, as well as interviews with a psychologist and nutritionist. Glucose metabolism was evaluated by oral glucose tolerance test (OGTT), preoperatively and at 3, 6, and 12 months after surgery.

The Ethics Committee of our hospital approved the study, and informed consent was signed preoperatively by all patients. The inclusion criteria specified a BMI greater than 40 kg/m^2, or a BMI greater than 35 kg/m^2 accompanied with relevant comorbidities. The exclusion criteria specified patients who suffered from type 1 diabetes mellitus, and patients who had previous bariatric surgery. The study also excluded patients under treatment with β-blockers, corticosteroids, thiazide diuretics, and psychiatric medication on the basis that said agents affect glucose metabolism, patients who presented significant postoperative complications and patients who refused to be enrolled. A total of 288 patients were initially evaluated, with 62 patients fulfilling the inclusion criteria (Table 1). Patients were assigned to one of three groups based on their preoperative OGTT performance (Table 2).

Table 2 Preoperative demographic characteristics between morbidly obese patients

	Group		
	Normoglycemic	Borderline	DM II
Age (years)	39.13 ± 2.42	42.10 ± 2.58	44.67 ± 2.43
Gender			
Male, *n* (%)	19 (50)	14 (36.8)	5 (13.2)
Female, *n* (%)	11 (45.8)	6 (25)	7 (29.2)
BMI	51.8 ± 4.77	48.08 ± 1.4	53.38 ± 3.5

DMII type 2 diabetes mellitus, *BMI* body mass index

Operative technique

An optical trocar is used for entering the peritoneal cavity. The pylorus is identified and dissection of the greater omentum begins 5–7 cm cephalad. The lesser sac is entered and all the branches of the gastroepiploic vessels are ligated at their point of entrance into the greater curvature. Dissection is continued until the gastric fundus is completely mobilized. Mobilization of the fundus is considered complete when the entire angle of Hiss is visualized along with the left crura. After insertion of a 38 Fr bougie, the stomach is divided along the lesser curvature with the use of a stapling device.

A low-suction silicon drain was routinely left along the stapling line for 48 h. Then on the second postoperative day, a per os test for staple-line leak with methylene blue was performed and the drain was removed. The patients were subsequently advanced to clear liquid diets if the results were normal, and were discharged on postoperative day 3 if no complications were present.

Follow-up

After LSG, all patients were evaluated by a multidisciplinary team that included a bariatric surgeon, a psychologist, and a dietician at months 1, 3, 6, 9, and 12, and then

annually. We reported body weight, blood pressure, use of medication, and laboratory values.

Each comorbidity was assessed to determine whether it was aggravated, unchanged, improved, or in remission compared with preoperative status, and this assessment was based on a change in severity of the condition or a change in quantity, dose, or frequency of medical treatment. Remission was defined as clinical resolution without medical treatment. For example, hypertension was considered in remission if the patient was normotensive without medication, or improved if the patient was normotensive with medication or had a decrease in antihypertensive agent usage or dosage

Oral glucose tolerance test

Patients' blood glucose levels were measured immediately prior to, and at 30, 60, 90 and 120 min after, oral administration of 75 g of glucose, after at least 8 h fasting. Fasting blood glucose of 110 mg/dl or less is considered normal, 110–125 mg/dl indicates impaired glucose tolerance (commonly referred to as 'pre-diabetes'), while values over 125 mg/dl suggest diabetes and, if confirmed in three or more tests, are diagnostic. Blood glucose levels of 140 and 200 mg/dl after 2 h of glucose administration suggest impaired glucose tolerance, as is the case with levels over 200 mg/dl after 1 h. Levels over 200 mg/dl after 2 h are diagnostic of diabetes. Hypoglycemia was diagnosed if blood glucose was <90 mg/dl. Hypoglycemia was considered mild when glucose levels were between 60 and 90 mg/dl, and severe when plasma glucose was <60 mg/dl.

Statistical analysis

Data are presented as mean ± standard error of the mean for quantitative variables, and as number (%) for quantitative patients. Normality assumption was tested using the Shapiro-Wilk and Kolmogorov Smirnoff test along with graphical methods. Parametric statistics were used when normality assumption was satisfied for qualitative data. In cases when normality was not the case, mathematical transformation was used. The area under the curve (AUC) was calculated using the trapezoidal rule, with a y-axis baseline at zero. In determining within and between group differences, the ANOVA for repeated test was used with Bonferroni correction adjusted for multiple comparisons. Categorical data were analyzed with Chi-square with Fisher's exact test when applicable, or with Kendall tau-b for ordinal to ordinal data. The McNemar test was performed for changes of categorical values within the same subjects. Tests were consider statistically significant if $p < 0.05$.

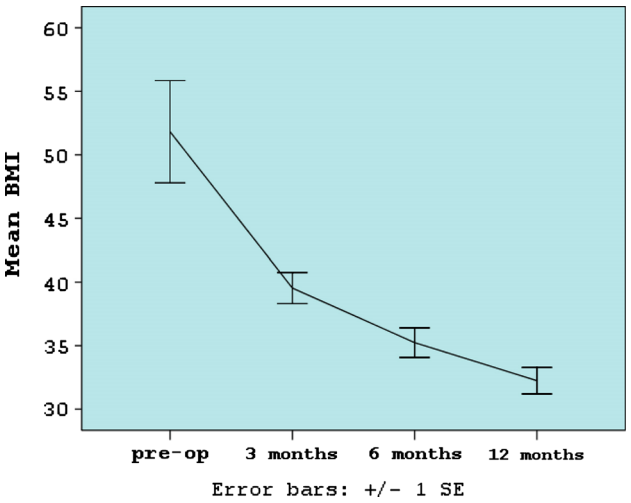

Fig. 1 BMI in severely obese patients following laparoscopic sleeve gastrectomy at 3, 6, and 12 months postoperatively. *BMI* body mass index

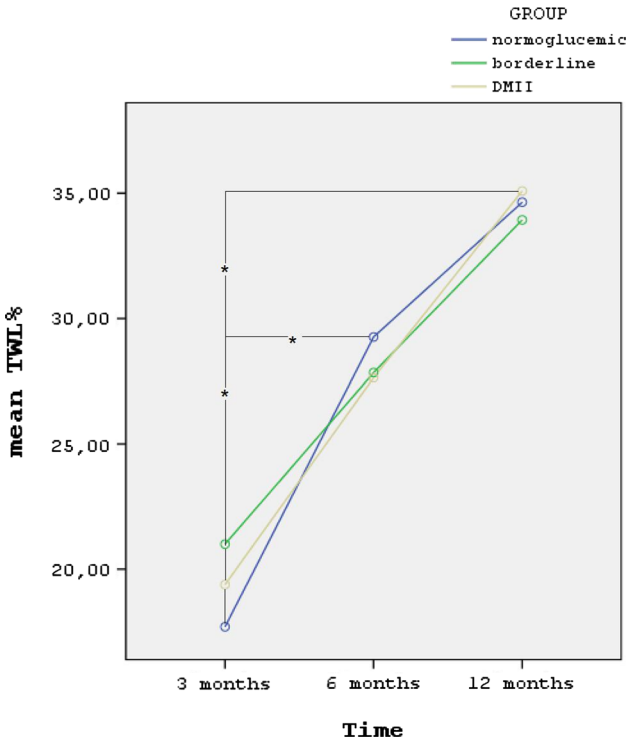

Fig. 2 %TWL during 1-year follow-up after laparoscopic sleeve gastrectomy in normoglycemic, borderline and DMII patients. *Astreisks* denotes $p < 0.05$. *%TWL* percentage of total weight loss, *DMII* type 2 diabetes mellitus

Results

Sixty-two obese patients were divided into three groups according to their glycemic profile preoperatively. Patients with normal OGTT were included in the first group as normoglycemic patients ($n = 30$). Patients with abnormal

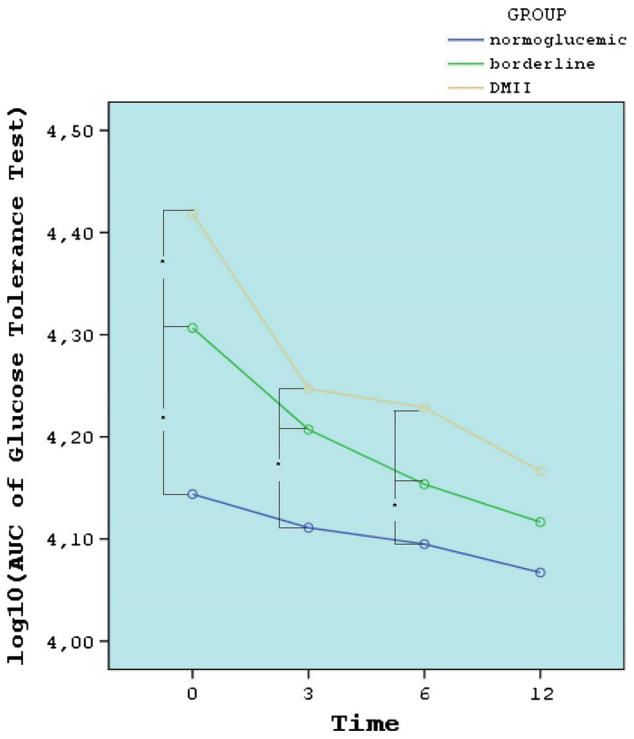

Fig. 3 Logarithmic transformation of AUC of blood glucose tolerance test results in normoglycemic, borderline and diabetic obese patients undergoing laparoscopic sleeve gastrectomy. *AUC* area under the curve, *DMII* type 2 diabetes mellitus

OGTT were divided into those who were undiagnosed (borderline, $n = 20$), and those who were diagnosed and treated as type 2 diabetes mellitus patients ($n = 12$). Preoperative characteristics of the patients in each group are shown in Table 2. There was no postoperative mortality.

All patients underwent LSG. BMI was significantly reduced in all patients during the 1-year follow-up ($p < 0.001$; Fig. 1). The percentage of total weight loss (%TWL) was significantly reduced during the 1-year follow-up within groups ($p < 0.001$ for each group). Almost all patients had a 35 % TWL at 1-year after sleeve gastrectomy; however, no significant change was observed between groups (Fig. 2).

The OGTT was significantly ameliorated in all groups during follow-up, and the AUC was significantly reduced in all groups ($p < 0.001$; Fig. 3). Significant changes have been observed between groups until 6 months postoperatively, with diabetic patients always having increased AUC values compared with borderline patients and patients with normal OGTT, as expected. However, these changes lost their statistical significance at 1-year postoperatively.

Nine of 12 of diabetic patients (75 %) ceased drug treatment at 3 months postoperatively ($p = 0.004$), increasing to 11 (91.5 %) at 6 months ($p = 0.001$) and 100 % at 1-year follow-up ($p < 0.001$). Sleeve gastrectomy changed the glycemic status of borderline and normoglycemic obese patients also. Hence, normoglycemic patients and patients with borderline OGTT experienced mild (90 mg/dl < glu < 60 mg/dl) or severe (glu <60 mg/dl) hypoglycemia during the glucose tolerance test at 3, 6, and 12 months' follow-up (Table 3). Hypoglycemic events were experienced more frequently at 2-hourly measurements. Indeed, the mean values of glucose in normoglycemic patients at 120 min was 100 ± 3.8 mg/dl preoperatively, and dropped to 65.81 ± 4.6 mg/dl at 1-year follow-up ($p = 0.001$). Borderline patients showed a similar pattern with blood glucose levels of 151.1 ± 10 mg/dl 2 h after glucose ingestion preoperatively, which decreased to hypoglycemic levels of 67.9 ± 3.1 mg/dl 1-year post operatively ($p < 0.001$). Diabetic patients showed normoglycemic levels at 2 h post-glucose ingestion 1 year postoperatively compared with preoperative levels (231.57 ± 21 vs 94.4 ± 12 mg/dl; $p = 0.006$).

Discussion

It has been shown that sleeve gastrectomy offers adequate improvement to obesity-related type 2 diabetes [3, 7]. Indeed, in this study all patients were reclassified as normal at the 12-month follow-up, as measured by the AUC of the OGTT, and after discontinuation of diabetic medication. This is true for all patients, regardless of preoperative OGTT classification. Observational studies have suggested that bariatric or metabolic surgery can rapidly improve glycemic control and cardiovascular risk factors in severely obese patients with type 2 diabetes [8–10]. Vidal et al. [11] showed a comparable remission of type 2 diabetes with patients undergoing laparoscopic RYGB, which is thought to be the gold standard for metabolic surgery. Schauer et al. [1] showed a 37 % complete remission in diabetic patients 1 year after LSG. Furthermore, Abbatini et al. [12] confirmed the metabolic amelioration in type 2 diabetic patients that was sustained 5 years post-LSG, with 77 % of the patients having normal fasting plasma glucose and HbA1c values without antidiabetic therapy. The underlined pathophysiology implicates glucagon-like peptide-1 (GLP-1) and peptide YY, which are released postprandially from the L-cells of the gut [13]. Indeed, Tsoli et al. [14] showed markedly enhanced postprandial peptide YY and GLP-1 response, and reduced ghrelin levels. Papamargaritis et al. [15] showed that peptide YY AUC along with GLP-1 AUC remained elevated 1-year postoperatively. Insulin and glucose AUC following OGTT was significantly decreased 1 year after sleeve gastrectomy. along with ameliorated insulin resistance. Lee et al. [16] also showed that LSG resulted in remission of poorly controlled diabetic mellitus patients mainly due to decreased insulin resistance.

Table 3 Mild or severe hypoglycemia experienced in normoglycemic, borderline, and diabetic patients undergoing laparoscopic sleeve gastrectomy

		Group, *n* (%)			
		Normoglycemic	Borderline	DM II	*p*-Value
Preoperatively	Mild hypoglycemia	3 (10)	1 (5)	0 (0)	NS
	Severe hypoglycemia	0 (0)	0 (0)	0 (0)	
3 months	Mild hypoglycemia	10 (38.5)	1 (8.3)	0 (0)	0.001[a]
	Severe hypoglycemia	6 (23.1)	1 (8.3)	1 (8.3)	
6 months	Mild hypoglycemia	12 (57.1)	6 (35.3)	3 (25)	0.004[a]
	Severe hypoglycemia	5 (23.8)	3 (17.6)	1 (8.3)	
12 months	Mild hypoglycemia	7 (43.8)	6 (54.5)	3 (42.9)	0.03[a]
	Severe hypoglycemia	6 (37.5)	3 (27.3)	0 (0)	

NS not significant

[a] Kendall tau-b

OGTT implementation has offered significant insight into the characteristics of morbidly obese patients. We have seen a large number of patients who were classified as borderline preoperatively. These individuals were neither diagnosed nor treated for this condition, and would have remained unaware of their pre-diabetic state if screened by conventional fasting glucose testing. This is particularly interesting with regard to our view of morbidly obese patients. Whereas, by usual standards, in this series we would have had 80 % of patients classified as normoglycemic prior to surgery, OGTT testing has shrunk this group to 48 % of patients. This observation is an indication that morbid obesity has a profound impact on glucose metabolism in a larger number of patients than previously estimated. This is a factor to be taken into account when approaching morbidly obese individuals, and suggests that OGTT screening for impaired glucose intolerance should be considered in this population. The prevalence of cryptogenic diabetes in morbidly obese patients is not formerly documented. In one study, screening in 433 consecutive morbidly obese patients revealed impaired glucose intolerance in 23.7 % of patients [17], 19 % of whom were newly diagnosed. In another cross-sectional study recruiting 1,329 morbidly obese patients, 16 % had impaired OGGT and 31 % had not known diabetes [18]. Finally, in a retrospective study by de la Cruz-Muñoz et al. [19] 17 % of patients were pre-diabetic with borderline fasting glucose plasma levels.

With regard to weight loss, no significant difference is recorded between diabetic, borderline and healthy patients, leading to the conclusion that LSG is a valid option for these patients regardless of diabetic state. On the contrary, in the retrospective study of de la Cruz-Muñoz et al. [19] pre-diabetic patients had the most dramatic loss in weight, followed closely by undiagnosed type 2 diabetes mellitus (46.62 kg), normal IFG, and type 2 diabetes mellitus at 3 years after RYGB. The observed discrepancy may be due to differences in surgical technique.

Perhaps the most interesting observation that OGTT has offered is the manner in which LSG affects glucose metabolism. We have found that blood glucose levels are decreased after LSG in all patients. While this effect translates into medicinal reduction and eventual resolution of diabetes in the type 2 diabetes mellitus group, it also affects all other patient groups. In the borderline group there is a succession from normalization of the OGTT to hypoglycemia. This happens in 16.6 % of borderline patients at 3 months after surgery ($p = 0.001$), and escalates to 50.9 % at 6 months ($p = 0.004$). At 12 months after surgery, incidence of hypoglycemia in borderline patients tends to equalize with that in normoglycemic patients at 81.8 % (normoglycemic patients' hypoglycemia at 12 months is 81.3 %). There is a difference, however, and that lies in the severity of the observed hypoglycemia. In normoglycemic patients, hypoglycemia is severe in 37.5 % and mild in 43.8 % of cases, while in the borderline group these percentages are 27.3 and 54.5 %, respectively ($p = 0.03$). Even patients with type 2 diabetes mellitus experience mild hypoglycemia at this point (42.9 %; $p = 0.03$). Hypoglycemia is a well-documented complication in bariatric patients [20]. In 2005, Service et al [21] reported six patients experiencing severe hypoglycemia, recognizing it for the first time as a complication of bariatric surgery. Since then there have been numerous studies trying to evaluate the incidence and severity of hypoglycemia in patients undergoing bariatric surgery [22–24]. The incidence of mild hypoglycemia is estimated at about 30 % in this population; however, there are some issues still under consideration. One issue is the complication regarding the characterization of postprandial hypoglycemia, since many patients who have undergone bariatric

surgery typically experience numerous postprandial symptoms, including dumping syndrome, which may be part of the postprandial hypoglycemia. Furthermore, there is a lack of a simple diagnostic test that may distinguish hypoglycemia from dumping syndrome since the Whipple triad is difficult to perform in an outpatient base. Hyperinsulinemic hypoglycemia is another term used in order to characterize this phenomenon [25]. Suggested mechanisms proposed for the pathophysiology of hyperinsulinemic hypoglycemia range from expansion of beta-cell mass to alterations in beta-cell function, and non-beta-cell-related factors, or possibly a combination of mechanisms [26–28].

The incidence of postprandial hypoglycemia in bariatric procedures not altering gastrointestinal anatomy is not well documented. In one study the incidence of asymptomatic hypoglycemia in patients with gastric band was estimated at 3–4 % [29]. Papamargaritis et al. found that 33 % of patients experienced hypoglycemia provoked by OGGT at 6 and 12 months following LSG, while Tzovaras et al. documented only one patient (3.3 %) with late hypoglycemia after oral glucose challenge 6 weeks after the same procedure [4, 30]. Hence this information is useful in managing LSG patients after surgery. The incidence of hypoglycemic events may significantly influence these patients' quality of life, and may be misconstrued as fatigue, anemia, or psychological distress. OGTT follow-up may be a helpful tool in the management of morbidly obese patients undergoing LSG. In addition, asymptomatic hypoglycemia may unconsciously divert the diet of these patients towards high-caloric substance, becoming the so-called sweet eaters. This condition may be associated with weight regain or failure to achieve the desired weight loss.

Conclusions

LSG offers excellent results to morbidly obese patients regarding type 2 diabetes mellitus. Implementation of OGTT assessment of glucose metabolism in these patients can reveal useful information about these individuals' glucose metabolism status and can be a valuable tool in their postoperative management. Bariatric teams performing LSG for morbid obesity should heighten their sensitivity to postoperative hypoglycemia, even in patients with type 2 diabetes mellitus. The incidence of hypoglycemic events escalates to over 80 % of non-diabetic LSG patients 1 year after surgery, and almost half are severe. At this time point, even diabetic patients will develop mild hypoglycemia in up to 43 % of cases.

It is intriguing to monitor the progression of this phenomenon in LSG patients, and evaluate the incidence and severity of hypoglycemia with longer follow-up.

Disclosures Dr. Maria Natoudi, Dr. Sotirios George Panousopoulos, Dr. Nikolaos Memos, Dr. Menenakos Evangelos, Prof. George Zografos, Prof. Emmanuel Leandros, and Dr. Kostandinos Albanopoulos have no conflicts of interest or financial ties to disclose.

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