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Beyond restrictive: Sleeve Gastrectomy and Single Anastomosis Duodeno-Ileostomy with Sleeve Gastrectomy as a spectrum of one sole surgical procedure

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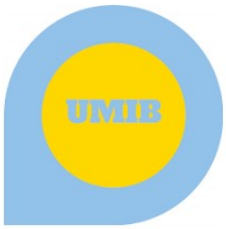

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« ὑγιέας μὲν γὰρ ποιέειν ἅπαντας τοὺς ἀσθενέοντας ἀδύνατον »

É realisticamente impossível conseguir curar todos os doentes

Hipócrates, *Prognosticon* 1. (tradução minha)

Resumo

Introdução: É frequente diferentes procedimentos bariátricos serem selecionados empiricamente para pacientes específicos, com base na gravidade da obesidade e na disfunção metabólica associada. A cirurgia SADI-S – Single-anastomosis duodeno-ileal bypass with sleeve gastrectomy – é uma das utilizadas para pacientes com obesidade classe III, por apresentar um mecanismo misto (restritivo e hipoabsortivo) de perda ponderal. De forma segura, ela pode ser dividida em dois procedimentos cirúrgicos desfasados no tempo, com o componente restritivo a ser inicialmente realizado – a gastrectomia em manga (SG). Contudo, é ainda desconhecido se pacientes com obesidade classe III submetidos a SADI-S num só procedimento, ou submetidos a SG, apresentam uma homeostasia endócrina pós-prandial diferente ao longo do pós-operatório.

Objetivo: Neste estudo, o nosso propósito foi avaliar, no pré e pós-operatório, a resposta hormonal pancreática pós-prandial em resposta a uma refeição padrão, em pacientes com obesidade classe III, submetidos a SADI-S ou a SG.

Metodologia: Indivíduos sem antecedentes cirúrgicos, submetidos a SADI-S num só procedimento (n = 7) ou a SG (n = 7), foram submetidos a uma prova de tolerância a refeição líquida (MMTT), no pré-operatório e 3, 6 e 12 meses após a cirurgia, para avaliar o seu perfil de glicemia e de hormonas pancreáticas, em jejum e após a ingestão.

Resultados: Os níveis de glicemia e das hormonas pancreáticas em jejum foram semelhantes entre a cirurgia SADI-S e SG. Após a MMTT, não se houve diferenças significativas nos perfis de glicemia, de insulina, de peptídeo-C, de taxa de secreção de insulina (ISR) nem na depuração de insulina.

Conclusão: Os perfis de glicemia e de hormonas pancreáticas após SADI-S num só procedimento e após SG são sobreponíveis, corroborando que o componente restritivo cirúrgico é o principal mediador das alterações metabólicas pós-operatórias. Assim, os cirurgiões poderão optar por uma cirurgia faseada, com um primeiro tempo de SG, para pacientes com obesidade grau III, adiando a introdução do componente hipoabsortivo sem comprometer resultados clínicos favoráveis.

Abstract

Introduction: Different bariatric techniques are often empirically selected for each patient, based on the severity of their obesity and metabolic dysfunction. Single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) is one of the chosen surgeries for patients with class III obesity, having a mixed weight loss mechanism (restrictive and hypoabsorptive). It can be safely split into two stages, with the restrictive component being performed first – the sleeve gastrectomy (SG). However, it is not known whether patients with class III obesity submitted to one-stage SADI-S or to SG have distinctive hormonal homeostasis after a mixed meal, at different time-points post-operatively.

Purpose: In this study, we intended to assess the postprandial pancreatic hormonal response to a standardized meal, in patients with class III obesity submitted to SADI-S or SG, both pre and post-operatively.

Methods: Subjects submitted to one-stage SADI-S (n = 7) or SG (n = 7), without previous abominal surgery, underwent a liquid mixed meal tolerance test (MMTT) pre-operatively and at 3, 6, and 12 months post-operatively, to assess the fasting and post-prandial profile of glucose and pancreatic hormones.

Results: Fasting homeostasis of glucose and pancreatic hormones were similar for SADI-S and SG patients. After the MMTT, no significant differences were observed neither in glycaemia, insulin, C-peptide, and insulin secretion rate (ISR) excursion, nor in insulin clearence.

Conclusion: Glucose and pancreatic hormone profiles after one-stage SADI-S and SG are altoghether similar, supporting the surgical restrictive component as the main driver of metabolic changes post-operatively. Therefore, surgeons could opt for a two-stage procedure, with SG as the first step, for patients with class III obesity, delaying the addition of the hypoabsorptive component without compromising favourable clinical results.

Abbreviation List

AUC	Area Under the Curve
BMI	Body Mass Index
BMS	Bariatric and Metabolic Surgery
BPD	Biliopancreatic Diversion
DS	Duodenal Switch
EBMIL	Excess Body Mass Index Loss
EEBMIL	Expected Excess Body Mass Index Loss
GLP-1	Glucagon-Like Peptide 1
HbA1c	Glycated Haemoglobin
HDL-c	High-density Lipoprotein cholesterol
HOMA-IR	Homeostasis Model Assessment for Insulin Resistance
HOMA-β	Homeostasis Model Assessment for β-cell function
ISR	Insulin Secretion Rate
LDL-c	Low-density Lipoprotein cholesterol
MMTT	Mixed Meal Tolerance Test
MS	Metabolic Syndrome
OSAS	Obstructive Sleep Apnoea Syndrome
RYGB	Roux-en-Y Gastric Bypass
SADI-S	Single Anastomosis Duodenal-Ileal bypass with Sleeve gastrectomy
SEM	Standard Error of Mean
SG	Sleeve Gastrectomy
T2D	Type 2 Diabetes Mellitus
TWL	Total Weight Loss

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Introduction

Obesity constitutes one large side of malnutrition worldwide, and the global incidence of people living with obesity keeps rising as the twenty first century goes on. In the most severe cases of the disease, people live with class III obesity, having a body mass index (BMI) of 40.0 kg/m^2 or greater (BMI ≥ 37.5 kg/m^2, if asian), with even worse quality of life as their BMI further increases. Despite optimal treatment for such cases, there is a poorer probability of them reaching a BMI of 25.0 kg/m^2 or lower, when compared to patients with a lower initial BMI[1, 2].

Bariatric and metabolic surgery (BMS) for patients with obesity is one of their best chances of remitting comorbidities and lowering disease risk[1, 3, 4]. The surgical approach has showed compelling results, not only in terms of weight loss, but also in the sustained improvement and even remission of type 2 diabetes mellitus (T2D) and its microvascular disease[1, 4]. Despite requiring a larger initial investment when compared to nonsurgical obesity treatments, BMS has been shown to be cost-effective in the long run, particularly if executed in highly experienced specialized centres, with low peri-operative morbidity and mortality rates[4, 5].

It must be highlighted that the most recent international recommendations for BMS have updated the criteria regarding patients eligibility, based on the highest quality evidence available so far. This means that, from now onwards, all patients with obesity classified as class II or higher (BMI ≥ 35 kg/m^2; or ≥ 32.5 kg/m^2 if asian) are eligible for BMS, whether or not they have comorbidities. Patients with class I obesity (30 ≤ BMI < 35 kg/m^2; or 27.5 ≤ BMI < 32.5 kg/m^2 if asian) should be considered for surgical intervention if they have T2D and/or other comorbidities poorly controlled with nonsurgical therapies, or even if they present with a considerable personal history of failed nonsurgical attemps of weight loss[6].

Bariatric procedures are traditionally classified into restrictive, hypoabsorptive, or mixed surgeries, depending on the anatomical rearrangements made. Current evidence shows that the best results in terms of sustained weight loss are obtained through procedures with a mixed and a hypoabsorptive mechanism[7, 8]. Although no formal guidelines have established how the surgeon and patient should pick the most appropriate procedure, techniques with greater hypoabsorptive component are commonly chosen for patients with class III obesity to optimize weight loss[8, 9]. Therefore, BPD-DS and SADI-S are often preferred for the most severe cases of obesity, even though they are technically complex and time-consuming surgeries[8].

SADI-S (Single Anastomosis Duodeno-Ileostomy with Sleeve gastrectomy) is a recent procedure that combines restrictive and hypoabsorptive weight loss mechanisms. It was introduced by Torres and Sánchez-Pernaute as a modification of the BPD, by discarding the Roux-en-Y reconstruction and introducing a Billroth II reconstruction. Through this simplification, one of the previously required anastomoses was eliminated, and operative time reduced up to 30% [10]. In terms of clinical results, SADI-S creates a sustained weight loss, with 95-100% of excess weight loss (EWL) up to 2 years after the procedure[11]. Comorbidity remission is noteworthy in patients with severe obesity, and it includes T2D, hypertension, dyslipidaemia and OSAS. Some technical variations, such as increasing the length of the efferent absorptive limb (> 200 cm), may reduce nutrient deficiencies after surgery[11]. Nevertheless, not only its complication rate is lower than BPD-DS[8], making it safer in the long therm, but SADI-S also seems to improve metabolic homeostasis[12, 13].

However, as stated before, both BPD-DS and SADI-S are time-consuming and technically challenging, since they are used in patients with super-obesity who present with increased anesthetic risks. Thereby, some studies have proposed these procedures as two-stage interventions[14, 15]. Regarding SADI-S, this means that the surgery is split into a 1st stage SG (the restrictive component), and a 2nd stage duodeno-ileostomy (the hypoabsorptive component). The 2nd stage is empirically conducted up to 18 months after the 1st stage as a planned intervention, or even later as a revisional procedure, usually after insufficient weight loss[14, 15]. This division might show the importance of each weight loss component behind the clinical success of the SADI-S surgery, something that has not yet been fully understood.

This fact makes us take a deeper look at the SG, the first step of a two-stage SADI-S. As a single surgery, the SG is traditionally classified as restrictive, being one of the most performed bariatric techniques worldwide. Between 2015 and 2018, almost 60% of all bariatric procedures performed worldwide were a SG, followed by the RYGB (approximately 30%)[16]. It should be highlighted that results of SG as a primary technique clearly surpass those expected of a merely restrictive procedure. It does indeed reduce the volume of the stomach, diminishing its capacity during food ingestion, but the volume of the ressected stomach is not directly associated with satisfactory excess BMI loss (EBMIL)[17]. Moreover, SG also modulates hormone metabolism: preprandial ghrelin peaks are reduced, due to stomach fundus ressection; and postprandial GLP-1 and PYY levels are elevated, through unclear molecular mechanisms[18]. Furthermore, SG appears to be more efficient in remitting T2D than hypertension, but this may be due to heterogeneous remission criteria used among different studies[19]. Lipidaemia is also affected, with improved control of hypertriglyceridaemia (mediated by weight loss) and hypoalphalipoproteinaemia (the best

evidence supports a short term HDL-c increase). Contrarily, SG shows a more neutral impact on LDL-c, whose reduction seems to be more associated with hypoabsorptive surgeries[18].

All things considered, we wonder whether the traditional classification of SG as a simply restrictive surgery may be misleading. Taking into account the two-stage SADI-S, its potential for carrying functional and hormonal changes starts right from the 1st stage: the SG alone[18, 20, 21]. Therefore, this goes against the premise that SG is solely a restrictive bariatric procedure, since the metabolic improvements are beyond the mere anatomical restriction of stomach volume. Furthermore, we also wonder whether both mechanisms associated with SADI-S metabolic behaviour – restriction and hypoabsorption – are balanced in the same scales or if the restriction plate is actually heavier. This would therefore position SG and SADI-S on a continuum of the same surgery, with more or less hypoabsorptive features, depending on the addition of a planned second-stage.

As we delved into this hypothesis of SG and SADI-S as a spectrum of one sole surgical procedure, our literature revision showed that this is a perspective neither commonly discussed nor tested. Some recent studies have examined the enteroendocrine physiological changes that SG induces, during an oral glucose tolerance test (OGTT), with promising results concerning insulin homeostasis, improvement of pancreatic β-cell function, and increased incretin levels[20, 22, 23]. However, the results were not assessed in a two-stage SADI-S protocol, and consequently SG patients were not compared to those submitted to one-stage SADI-S. Furthermore, no study so far has evaluated the hormonal modifications after a MMTT, both before surgery and at different time-points during follow-up.

Given all this, the primary goal of this study was to assess the fasting and postprandial hormonal response to a MMTT, pre-operatively and 3, 6 and 12 months after one-stage SADI-S and SG. Additionally, it was estimated how different hormonal profiles might relate to weight loss and to comorbidities remission between both groups.

Materials and methods

This is a prospective, interventional, randomized, and open label study. It is derived from the Surgical Innovation for Diabetes Treatment 2 (SURIDIAB2), having the ClinicalTrials.gov Identifier: NCT04712409. The Institutional Ethical Review Board approved of the study (CA-110/2020-0t_MP/AC) and written informed consents were obtained from all participants prior to any performed intervention.

Participants

In this study, participants with obesity (n=14) were submitted either to one-stage SADI-S (n=7) or to SG, as a first step of a two-stage SADI-S (n=7), performed between 2020 and 2021. They were selected from the patient referrals for multidisciplinary evaluation by the clinical team for surgical treatment of obesity at Centro Hospitalar Entre Douro e Vouga (CHEDV). Adults of any sex, aged 18 to 65 years old at surgery, and with a BMI between 45 and 55 kg/m^2, were considered to participate in the study. Any previous abdominal surgery constituted an exclusion criterion. Those patients found to be suitable and who accepted to participate were enrolled and randomized to one of the two study groups. Patients from both groups were paired regarding age, weight, BMI, and comorbidities (Table I). Prediabetes, T2D, and MS definitions were used as per international standard guidelines[24-26].

Study design

Participants were scheduled for study visits both before and at 3, 6 and 12 months after surgery, comprising several assessments.

The pre-operative clinical evaluation included a complete medical history, physical examination, and a fasting blood analysis. The parameters assessed were age, body weight, waist circumference, BMI, and comorbidities. Lab parameters, obtained in the pre-operative visit, consisted of a complete blood count, glycated haemoglobin (HbA1c), uric acid levels, renal function tests, lipid profile, total proteins and liver function tests. Obesity secondary to thyroid disfunction or adrenal glucocorticoid imbalance was excluded in every patient prior to surgery.

The post-operative clinical evaluation (at 3, 6 and 12 months after the surgical procedure) included a complete medical history, physical examination, and a fasting blood analysis. The parameters assessed were age, body weight, waist circumference, BMI, percentage of total weight loss (TWL), EBMIL, percentage of expected EBMIL (EEBMIL), and comorbidities (or their remission). Lab parameters consisted of a complete blood count, iron study, HbA1c, uric acid levels, renal

function tests, lipid profile, total proteins, liver function tests, and parathyroid function tests. Micronutrient analysis included zinc levels, and vitamins A, B1, B6, B9, B12, and D. Insulin and C-peptide were also obtained.

In each of the 4 visits (pre-operative; and 3, 6 and 12 months post-operatively), all subjects (n=7/group) underwent a MMTT, consisting of the ingestion of a standardized commercially available liquid meal (Fresubin Energy Drink, 200 mL, 300 kcal [50E% carbohydrate, 15E% protein and 35E% fat]; Fresenius Kabi Deutschland, Bad Homburg, Germany), over a maximum period of 15 minutes after a 12 hours overnight fast. Venous blood samples were collected to EDTA tubes (S-Monovette® 7.5 mL, K2 EDTA Gel, 1.6 mg/mL, Sarstedt), before the meal (-30 and 0 minutes) and at 15, 30, 45, 60, 90, and 120 minutes after ingestion. Venous sampling was performed through an indwelling antebrachial vein cannula with saline flushing of the catheter in between blood collections. Samples were centrifugated, and the plasma was separated and stored at – 20 ºC until assayed.

Surgical procedures

All patients in both groups had the sleeve gastrectomy performed with the same technique, which consisted of a vertical gastric section that was started 4 cm proximal to the pylorus, using a 36-French Boogie for calibration. Patients in the SG group had their procedure stopped after this step. For the one-stage SADI-S patients, surgery continued with right gastric artery dissection and ligation at its origin, to have the duodenum verticalized. The duodenum was then sectioned 2-3 cm distally to the pylorus. Small bowel was measured from the ileocecal valve in a proximal direction, counting 10 cm intervals with calibrated graspers. Then, the small intestine was marked with sutures at 300 cm proximally from the ileocecal valve. At this point, the marked small intestine loop was moved cranially to execute an end-to-side, 3-layer, hand-made duodenal-ileal anastomosis, creating the efferent absorptive limb of 300 cm running to the ileocecal valve (Fig. 1). Mesenteric defects were closed and methylene blue was used for testing anastomosis leaks.

All surgeries were performed laparoscopically by the same surgical team from the Department of General Surgery at CHEDV.

Biochemical measurements

Capillary blood glucose was measured during the blood samples collection, using a glucometer (Freestyle Precision Neo Glucose meter, Abott, USA), during the MMTT.

General haematological and biochemical profiles in each visit were obtained from the hospital laboratory. Insulin and C-peptide levels were measured by an electrochemiluminescence sandwich immunoassay (ECLIA) on Atellica® (Siemens).

Statistical analysis and calculations

BMI combines height (in meters) and weight (in kilograms) and was calculated as weight over square height (reported in kg/m^2). Waist-to-height ratio was obtained through waist circumference over height, and a ratio > 0.5 is associated to increased cardiovascular risk[27]. The other anthropometric parameters included were the percentage of EBMIL, calculated as [100 x (pre-operative BMI – post-operative BMI) / (pre-operative BMI – 25)]; the percentage of TWL, calculated as [100 x (pre-operative weight – post-operative weight) / (pre-operative weight)]. The EEBMIL was calculated using the formula [100 x (pre-operative BMI – post-operative BMI) / (pre-operative BMI – expected BMI)][19, 28].

Insulin resistance assessment was obtained through the HOMA-IR (homeostasis model assessment for insulin resistance) and calculated by means of the formula: [fasting glucose (mg/dL) x fasting insulin (mUI/L) / 405]. In addition, pancreatic β-cell function was measured by the HOMA-β (homeostasis model assessment for β-cell function), calculated through the formula [100 x (360 x insulin (mUI/L)) / (fasting glucose (mg/dL) – 63)].

The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), markers of systemic inflammatory response, were calculated by dividing the absolute neutrophil count by the absolute lymphocyte count and by dividing the platelet count by the absolute lymphocyte count, respectively. A NLR > 3.0 and a PLR > 150 were considered pathological[29, 30].

Total area under the curve (tAUC) was calculated through the trapezoidal rule, while incremental area under the curve (iAUC) was calculated subtracting the basal values to the tAUC. Prehepatic ISR was calculated from C-peptide plasmatic levels, using the ISEC software (ISEC, Version 3.4a, Hovorka, 1994)[31]. Insulin clearence was then obtained according to the formula: [$tAUC_{ISR}$ / $tAUC_{insulin}$].

Nominal variables are expressed as number of cases and percentage (%), and continuous variables are expressed as mean ± standard error of mean (SEM). Normality was evaluated using D'Agostinho and Pearson test. Given that no variable passed this test, the comparison of means was obtained through a Mann Whitney test. A Dunn's test was used to compare BMI, TWL and EBMIL changes from pre-operative time, within each of the two groups during follow-up. Comparisons between time-points during the MMTT were performed using a two-way analysis of

variance (ANOVA) with Šidák's *post hoc* test. Fisher's exact test was used to compare nominal variables. Statistical analysis was carried in the GraphPad Prism version 9.4.1 for Windows (GraphPad Software, La Jolla California USA). A p value < 0.05 was considered statistically significant.

Results

Anthropometric and metabolic data

No significant differences were found in any of the anthropometric and metabolic parameters between the two groups, either pre-operatively or at 3, 6 and 12 months after surgery (Table II).

For the one-stage SADI-S group (Fig. 2A), the BMI significantly decreased at 6 (34.1 ± 0.7 kg/m^2) and 12 months (28.2 ± 0.9 kg/m^2) when compared to the pre-operative time (48.6 ± 0.9 kg/m^2, $p < 0.01$). A significant difference was also observed between 3 and 12 months (39.5 ± 0.7 kg/m^2 *vs* 28.2 ± 0.9 kg/m^2, $p < 0.01$). The same was verified within the SG group (Fig.2A), since BMI only differed significantly from pre-operative time (47.1 ± 1.0 kg/m^2, $p < 0.01$) at 6 (32.3 ± 1.0 kg/m^2) and 12 months (28.6 ± 0.8 kg/m^2). BMI also decreased significantly between 3 and 12 months (36.7 ± 0.9 kg/m^2 *vs* 28.6 ± 0.8 kg/m^2, $p < 0.05$).

The same pattern was observed in the TWL during follow-up for both groups (Fig. 2B): in one-stage SADI-S patients, TWL increased significantly when compared to pre-operative time at 6 (29.5 ± 1.4 %, $p < 0.01$) and 12 months (41.6 ± 2.1 %, $p < 0.0001$). It also differed significantly between 3 and 12 months (18.4 ± 1.2 % *vs* 41.6 ± 2.1 %, $p < 0.01$). For the SG group, TWL differed significantly from pre-operative time at 6 (32.5 ± 2.2 %, $p < 0.01$) and 12 months (40.4 ± 1.7 %, $p < 0.0001$). A significant difference was also observed between 3 and 12 months (23.5 ± 1.7 % *vs* 40.4 ± 1.7 %, $p < 0.05$).

The EBMIL followed the same pattern as previously described (Fig. 2C). For the one-stage SADI-S, EBMIL was significantly different from pre-operative time at 6 (61.1 ± 2.8 %, $p < 0.01$) and 12 months (86.1 ± 3.9 %, $p < 0.0001$), and also between 3 and 12 months (38.1 ± 2.5 % *vs* 86.1 ± 3.9 %, $p < 0.01$). For the SG group, the EBMIL increased significantly from pre-operative time at 6 (68.0 ± 4.2 %, $p < 0.01$) and 12 months (84.6 ± 3.1 %, $p < 0.0001$), and also between 3 and 12 months (49.1 ± 3.4 % *vs* 84.6 ± 3.1 %; $p < 0.05$).

Post-operative complications

The mortality rate in this patient cohort was 0% for both procedures. In patients submitted to one-stage SADI-S, the complications' rate at 90 days after surgery was 14,3% (1/7) [thrombophlebitis (n=1, Clavien Dindo I)]. In patients within the SG group, the complications' rate at 90 days after surgery was 14,3% (1/7) [wound infection, with reintervention through percutaneous drainage (n=1, Clavien Dindo II)]. Morbidity rate after 90 days from surgery was 0%

in both groups. Patients of both groups did not report any regular dumping symptoms, in any visit post-operatively.

Analytical data

Almost all lab parameters evaluated pre-operatively and at 3, 6 and 12 months did not differ significantly between the two groups (Table III). Furthermore, the full blood count did not differ significantly between groups, both having normal levels of platelets, leucocytes, neutrophils and lymphocytes (data not shown). NLR and PLR also did not have any significant difference between groups, neither suggested ongoing systemic inflammation at any time point.

Micronutrients and nutritional deficiencies

There were no significant differences neither in the micronutrient levels nor in the rate of nutritional deficiencies during follow-up at 3, 6 and 12 months, between both patient groups (Table IV). Every case of anaemia reported in the two groups was normocytic and normochromic (data not shown). In addition, even though PTH levels did not differ significantly between both groups at any time point, secondary hyperparathyroidism occurred in the one-stage SADI-S group from 3 months forward until the 12 months visit, while the SG group maintained PTH levels in the normal range throughout follow-up (Fig. 3).

Comorbidities

The rate of comorbidities did not have any significant difference between the two groups at any time point (Table V). It should be noted that, at the end of follow-up (12 months), both groups had patients that symmetrically maintained hyperlipidaemia (n=2 in each group). All patients attained hypertension remission for the one-stage SADI-S, while the SG group maintained 2 patients with hypertension criteria. Almost all patients with prediabetes at recruitment in both groups achieved HbA1c < 5.7% from 3 months forward. The only exception belonged to the SG group (n=1): a patient who had an HbA1c in the range of 5.7 – 5.9 % at 3 and 12 months of follow-up.

Fasting glucose and pancreatic hormone homeostasis

Glycaemia and pancreatic hormone levels did not differ significantly in the fasting state (Table VI). Fasting ISR and insulin clearence were also not significantly different between groups.

Pancreatic hormone response to the mixed meal

No significant differences between the two groups were observed either in post-prandial glycaemia, insulin and C-peptide response, or in ISR and insulin clearence, at any time point of the pre and post-operative MMTT (Table VI and Fig. 4-5).

Patients in the SG group showed a tendency to reach the peak of glycaemia, insulin and C-peptide levels in the first 30 to 45 minutes after ingestion, at 3, 6 and 12 months post-operatively. The same applies to ISR, and it should be noted that, as follow-up time progressed (from 3 to 12 months), insulin levels and ISR reached greater proximity back to fasting levels at 120 minutes after ingestion. On the other hand, the one-stage SADI-S group showed a distinct tendency, reaching later the peak of glycaemia, insulin, C-peptide, and ISR: in the first 45 to 60 minutes after ingestion. Post-prandial insulin levels and ISR also reached greater proximity to the fasting baseline at 120 minutes, as follow-up time increased. Nevertheless, no differences between both groups were observed in none of those timepoints (Fig. 4 and 5).

Discussion

BMS creates anatomic rearrangements that translate into metabolic and enteropancreatic hormonal modifications, through restrictive and/or hypoabsorptive mechanisms. Different types of surgeries are often empirically chosen for each patient, based (among others) on the severity of their obesity and metabolic dysfunction[2, 6]. It was not known whether patients with class III obesity submitted to one-stage SADI-S or to a SG (as first step of a two-stage SADI-S) had distinctive hormonal homeostasis after a standardized meal, at different time-points post-operatively. In this study, we intended to assess the postprandial pancreatic hormonal response to a standardized meal, in patients with severe obesity submitted to two different surgical techniques, both pre and post-operatively. This was a leap forward in previous assessments with MMTT[12, 13, 32], as neither gathered this many different time-points post-operatively, nor included SG as one of the procedures studied.

After surgery, our patients showed significant weight loss, which was similar between groups. Even though mean BMI in both groups was above the overweight threshold at the end of 12 months, the EEBMIL exceeded 100% at the end of follow-up. Insulin resistance and pancreatic β-cell function, obtained through HOMA-IR and HOMA- β, also had similarly marked improvements. In fact, when compared to previous cohorts, our patients who underwent one-stage SADI-S had analogous findings[8]. However, although no formal comparisons were made concerning SG, our results are slightly better than in previous series[9, 19], which in our cohort may be due to the inclusion of more female patients, with fewer comorbidities, and to a shorter range of BMI in our selection criteria.

Looking now at the MMTT, our study revealed similar fasting profiles and similar postprandial glucose and pancreatic hormonal excursions, between both groups, pre-operatively and at 3, 6 and 12 months post-operatively. Overall, our results suggest that, although these surgeries result in different anatomical rearrangements, one-stage SADI-S and SG have identical post-prandial glucose and insulin excursions, during the first year after surgery. In the SG group, nutrients get in contact with biliary and pancreatic enzymes inside the duodenum, immediatly after leaving the stomach. Due to the preserved intestinal architecture, there is a larger absorption length, accelerating absorption and, therefore, increasing glycaemia slightly faster. On the other hand, SADI-S patients have a smaller absorption surface in the efferent absorptive limb. This means that, after gastric emptying, nutrients have less intestinal extension for mixing with biliary and

pancreatic enzymes, thus having a slower absorption and slightly later peaks of glycaemia and insulin secretion.

Despite adequate supplementation, one-stage SADI-S patients had below normal post-operative haemoglobin, serum iron, and hypoproteinaemia. It is clinically relevant, but even though these deficiencies are likely derived from the hypoabsorption component, they were not more likely to occur for one-stage SADI-S than for SG. It is also important to highlight the persistent hyperparathyroidism that was observed in the one-stage SADI-S group. This is not new evidence: surgeries with a hypoabsorptive mechanism are frequently associated with this change post-operatively, even without vitamin D3 or calcium deficiency, and sometimes accompanied by slight elevations in alkaline phosphatase[8, 11, 15, 33]. Nevertheless, we wonder whether this lasting hormonal imbalance in BMS patients might have clinical consequences for bone metabolism over time. Apart from this, the majority of other lab parameters did not have any relevant differences, corroborating the safety of SADI-S as in previous studies[11, 15].

One note concerning hyperlipidaemia: SADI-S had a numerical decrease in LDL-c, while SG a neutral effect (as expected), due to the absence of a hypoabsorptive component. Patients with obesity commonly fall into a moderate or high risk of cardiovascular disease, depending on comorbidities[34]. This fact should reinforce our goals of post-operative LDL-c to be < 100 mg/dL or even < 70 mg/dL, depending on the risk stratification[35]. In a chronic disease like obesity, the use of cholesterol lowering drugs after surgery should be thoroughly considered in patients who have minimal reductions in previously elevated LDL-c, aiming at established goals for CV protection.

In short, it became clear that the restrictive mechanism incorporated in SG and SADI-S is much more than a mere anatomical restriction. Weight loss and insulin resistance profile improvements after both procedures really seem more dependent on the restriction mechanism, at least in first year after surgery[11]. The same applies to physiological changes in pancreatic hormones. SG and SADI-S are positioned in the spectrum of one sole surgical procedure: whether performed as a one or two-stage intervention, obesity treatment goals are met both ways and non-inferiorly from one another, right from the primary surgery[15]. This is a valuable piece of information for the surgeon to have in their sleeve when faced with a patient with class III obesity. Instead of trying to pick between one-stage SADI-S or DS, we suggest starting with a procedure that will still have major metabolic gains – like the SG – setting aside surgical complexity. Not only the operating room is more available to treat other patients with obesity, but also the hospital stay can be reduced after surgery, as the risk of perioperative complications is smaller.

Even though these findings have great significance, the present study carries some limitations, since characterization of more hormone profiles are in order (namely glucagon, ghrelin, GLP-1, glucose-dependent insulinotropic polypeptide, peptide YY, and neurotensin), for results with stronger clinical relevance. Ideally, groups should have more patients and a greater follow-up up time, with MMTT performed post-operatively until weight loss stabilization. Comparing SG patients with others receiving the second-step of a SADI-S, at 24 months from the primary intervention, would really show us the full potential of the restrictive power on the hormone homeostasis. Also, including here re-sleeved patients, both with and without completion of a SADI-S would also add on that information. Moreover, doing all of these comparisions in cohorts of patients with and without prediabetes/T2D could show how far the restrictive effect will reach in normalizing glucose metabolism.

Conclusion

The fasting and post-prandial pancreatic hormone secretion profiles of patients submitted to one-stage SADI-S or SG are identical up to 1 year after surgery. Given that clinical results are similar between both procedures, these data support the restrictive component of the surgeries as the main driver behind metabolic changes in the post-operative period. Furthermore, this reinforces the hypothesis stating that the restriction mechanism originated with the SG goes beyond the anatomical ressection. In clinical practice, it means that the bariatric surgeon can safely and confidently opt for a first-step SG when faced with a patient with class III obesity, and leave the addition of a hypoabsorptive component for later, or as a revisional procedure.

Appendix

Table I Demographic, anthropometric and clinical features at recruitment of subjects submitted to one-stage SADI-S or SG

	One-stage SADI-S	**SG**	*p*-value
N (% of total)	7 (50%)	7 (50%)	-
Demographic and anthropometric data			
Sex (female/male)	6 / 1 (86%/14%)	5 / 2 (71%/29%)	1.00
Age (years)	44 ± 4	40 ± 5	0.74
Body weight at recruitment (kg)	127.6 ± 6.5	125.4 ± 5.0	1.00
BMI at recruitment (kg/m^2)	48.4 ± 0.7	48.1 ± 1.2	1.00
Comorbidities, N (% of group total)			
Hyperlipidaemia	4 (57%)	4 (57%)	1.00
Hypertension	3 (43%)	3 (43%)	1.00
Prediabetes	3 (43%)	2 (29%)	1.00
Type 2 diabetes mellitus	1 (14%)	1 (14%)	1.00
Metabolic syndrome	4 (57%)	6 (86%)	0.56

Note: Data are presented as mean ± SEM or number (%), as appropriate. *SADI-S* single-anastomosis duodeno-ileal bypass with sleeve gastrectomy; *SG* sleeve gastrectomy; *BMI* body mass index

Table II Anthropometric and metabolic characteristics of subjects submitted to one-stage SADI-S or SG, at pre-operative time and at 3, 6, and 12 months after surgery

		One-stage SADI-S	SG	*p*-value
Weight (kg)				
Pre-operative		127.7 ± 6.0	122.7 ± 4.2	0.97
3 months		103.7 ± 4.1	95.7 ± 3.0	0.55
6 months		89.6 ± 3.9	84.3 ± 2.9	0.83
12 months		73.7 ± 1.5	74.3 ± 1.4	1.00
BMI (kg/m²)				
Pre-operative		48.6 ± 0.9	47.1 ± 1.0	0.83
3 months		39.5 ± 0.7	36.7 ± 0.9	0.17
6 months		34.1 ± 0.7	32.3 ± 1.0	0.61
12 months		28.2 ± 0.9	28.6 ± 0.8	1.00
Waist (cm)				
Pre-operative	*Female*	140 ± 6	123 ± 1	0.34
	Male	158	150	-
3 months	*Female*	124 ± 6	105 ± 3	0.18
	Male	133	122 ± 4	-
6 months	*Female*	106 ± 3	96 ± 3	0.18
	Male	119	112 ± 1	-
12 months	*Female*	92 ± 4	84 ± 5	0.66
	Male	101	92	-
Waist-to-height ratio				
Pre-operative		0.88 ± 0.02	0.80 ± 0.03	0.40
3 months		0.76 ± 0.03	0.68 ± 0.02	0.10
6 months		0.66 ± 0.02	0.62 ± 0.02	0.51
12 months		0.58 ± 0.03	0.53 ± 0.03	0.63
TWL (%)				
3 months		18.4 ± 1.2	23.5 ± 1.7	0.14
6 months		29.5 ± 1.4	32.5 ± 2.2	0.73
12 months		41.6 ± 2.1	40.4 ± 1.7	0.99
EBMIL (%)				
3 months		38.1 ± 2.5	49.1 ± 3.4	0.09
6 months		61.1 ± 2.8	68.0 ± 4.2	0.59
12 months		86.1 ± 3.9	84.6 ± 3.1	1.00
EEBMIL (%)				
3 months		48.4 ± 3.2	62.1 ± 4.3	0.10
6 months		77.5 ± 3.6	86.0 ± 5.4	0.63
12 months		109.2 ± 5.1	107.0 ± 3.9	1.00
HOMA-IR				
Pre-operative		6.42 ± 1.04	4.81 ± 0.60	0.61
3 months		4.70 ± 1.13	2.41 ± 0.44	0.33
6 months		2.02 ± 0.50	1.27 ± 0.39	0.70
12 months		0.97 ± 0.20	1.02 ± 0.21	1.00
HOMA-β (%)				
Pre-operative		302.7 ± 60.6	179.4 ± 32.3	0.36

	One-stage SADI-S	SG	*p*-value
HOMA-β (%)			
3 months	423.0 ± 106.7	138.4 ± 15.3	0.14
6 months	289.7 ± 162.3	392.3 ± 286.8	1.00
12 months	62.4 ± 58.1	143.4 ± 383.8	1.00

Note: Data are presented as mean ± SEM. *SADI-S* single-anastomosis duodeno-ileal bypass with sleeve gastrectomy; *SG* sleeve gastrectomy; *BMI* body mass index; *TWL* total weight loss; *EBMIL* excess BMIL loss; *EEBMIL* expected excess BMI loss; *HOMA-IR* Homeostasis Model Assessment for Insulin Resistance (Reference values: < 1.85 for male and < 2.07 for female[36]); *HOMA*-β Homeostasis Model Assessment for β-cell function (Reference values: > 67.1% for male and > 86.2% for female[37])

Table III General haematological and biochemical laboratory data of subjects submitted to one-stage SADIS and SG, at pre-operative time and at 3, 6 and 12 months after surgery

			Pre-op	3 months	6 months	12 months
Hb (g/dL)	*Female*	One-stage SADI-S	13.3 ± 0.3	12.5 ± 0.4	12.3 ± 0.3	11.9 ± 0.2
		SG	13.7 ± 0.3	12.9 ± 0.4	12.6 ± 0.2	12.5 ± 0.2
		p-value	0.84	0.92	0.93	0.45
	Male	One-stage SADIS	15.3	13.7	13.4	12.7
		SG	15.2 ± 0.4	14.4 ± 1.2	13.8 ± 0.9	13.4 ± 0.5
		p-value	-	-	-	-
NLR		One-stage SADI-S	1.9 ± 0.2	2.6 ± 0.3	2.3 ± 0.2	1.8 ± 0.1
		SG	2.1 ± 0.3	2.7 ± 0.4	2.4 ± 0.4	2.0 ± 0.2
		p-value	0.93	1.00	1.00	0.97
PLR		One-stage SADI-S	33 ± 3	31 ± 2	36 ± 4	39 ± 5
		SG	30 ± 2	31 ± 2	31 ± 2	33 ± 2
		p-value	0.89	1.00	0.79	0.75
Serum iron (µg/dL)		One-stage SADI-S	-	49 ± 6	59 ± 8	92 ± 6
		SG	-	73 ± 10	91 ± 10	85 ± 15
		p-value	-	0.20	0.09	0.96
Ferritin (ng/mL)		One-stage SADI-S	-	160.6 ± 74.6	153.6 ± 77.7	153.4 ± 71.1
		SG	-	212.2 ± 92.1	206.3 ± 70.7	218.4 ± 88.9
		p-value	-	0.96	0.95	0.93
HbA1c (%)		One-stage SADI-S	5.7 ± 0.2	5.1 ± 0.1	5.1 ± 0.1	4.9 ± 0.1
		SG	5.8 ± 0.4	5.0 ± 0.2	5.1 ± 0.1	5.0 ± 0.2
		p-value	0.99	0.98	1.00	0.99
Uric acid (mg/dL)		One-stage SADI-S	6.0 ± 0.6	5.0 ± 0.4	4.4 ± 0.5	4.1 ± 0.4
		SG	6.5 ± 0.6	5.8 ± 0.7	5.0 ± 0.5	4.7 ± 0.5
		p-value	0.97	0.75	0.87	0.88
Creatinin (mg/dL)		One-stage SADI-S	0.69 ± 0.01	0.61 ± 0.01	0.60 ± 0.0	0.59 ± 0.03
		SG	0.76 ± 0.04	0.66 ± 0.02	0.69 ± 0.01	0.64 ± 0.02
		p-value	0.37	0.38	**0.03***	0.37
Blood urea (mg/dL)		One-stage SADI-S	32 ± 2	24 ± 2	22 ± 2	29 ± 2
		SG	25 ± 2	21 ± 2	26 ± 3	28 ± 3
		p-value	0.15	0.80	0.77	1.00
TC (mg/dL)		One-stage SADI-S	194 ± 11	157 ± 15	164 ± 17	160 ± 21
		SG	192 ± 14	173 ± 13	187 ± 16	192 ± 17
		p-value	1.00	0.89	0.83	0.72
LDL-c (mg/dL)		One-stage SADI-S	119 ± 11	95 ± 10	101 ± 12	94 ± 15
		SG	118 ± 10	117 ± 11	126 ± 13	122 ± 15
		p-value	1.00	0.51	0.52	0.63
HDL-c (mg/dL)	*Female*	One-stage SADI-S	52 ± 6	42 ± 4	47 ± 4	49 ± 6
		SG	45 ± 6	39 ± 2	41 ± 1	51 ± 3
		p-value	0.86	0.93	0.66	1.00
	Male	One-stage SADI-S	48	29	32	46
		SG	49 ± 1	38 ± 7	48 ± 9	59 ± 10
		p-value	-	-	-	-

			Pre-op	3 months	6 months	12 months
Triglycerides (mg/dL)		One-stage SADI-S	118 ± 21	107 ± 14	90 ± 12	85 ± 16
		SG	140 ± 26	89 ± 10	87 ± 14	84 ± 15
		p-value	0.95	0.77	1.00	1.00
Total proteins (g/dL)		One-stage SADI-S	7.1 ± 0.1	6.4 ± 0.1	6.3 ± 0.1	6.3 ± 0.1
		SG	7.2 ± 0.2	6.6 ± 0.2	6.6 ± 0.1	6.6 ± 0.2
		p-value	0.95	0.85	0.15	0.52
Albumin (g/dL)		One-stage SADI-S	-	3.8 ± 0.1	3.6 ± 0.1	3.8 ± 0.1
		SG	-	3.9 ± 0.1	3.9 ± 0.1	4.0 ± 0.1
		p-value	-	0.50	0.13	0.12
AST (U/L)		One-stage SADI-S	21 ± 2	23 ± 4	17 ± 1	27 ± 7
		SG	24 ± 3	17 ± 2	16 ± 1	17 ± 1
		p-value	0.87	0.59	0.99	0.60
ALT (U/L)		One-stage SADI-S	-	37 ± 8	23 ± 3	44 ± 12
		SG	-	15 ± 2	12 ± 2	17 ± 1
		p-value	-	0.09	**0.02***	0.19
γ-GT(U/L)	*Female*	One-stage SADI-S	33 ± 4	18 ± 3	20 ± 7	25 ± 9
		SG	34 ± 9	15 ± 2	12 ± 2	16 ± 2
		p-value	1.00	0.93	0.76	0.86
	Male	One-stage SADI-S	29	22	21	64
		SG	87 ± 23	38 ± 8	31 ± 6	54 ± 15
		p-value	-	-	-	-
AP (U/L)		One-stage SADI-S	79 ± 6	79 ± 6	85 ± 5	81 ± 8
		SG	61 ± 6	59 ± 4	59 ± 3	57 ± 5
		p-value	0.21	0.052	**0.006****	0.13

Note: Data are presented as mean ± SEM. *SADI-S* single-anastomosis duodeno-ileal bypass with sleeve gastrectomy; *SG* sleeve gastrectomy; *Hb* haemoglobin; *NLR* neutrophile-to-lymphocyte ratio; *PLR* platelet-to-lymphocyte ratio; *HbA1c* glycated haemoglobin; *TC* total cholesterol; *LDL-c* low-density lipoprotein-cholesterol; *HDL-c* high-density lipoprotein-cholesterol; *AST* aspartate aminotransferase; *ALT* alanine transaminase; *γ-GT* gamma-glutamyl transferase; *AP* alkaline phosphatase. *$p < 0.05$ and **$p < 0.01$: one-stage SADI-S *vs* SG; Statistically significant differences are highlighted in bold

Table IV Micronutrient levels and nutritional deficiencies from 3 to 12 months post-operatively for one-stage SADI-S and SG subjects

			One-stage SADI-S	SG	*p*-value
Micronutrients					
Vitamin A (µg/dL)		3 months	38 ± 3	37 ± 3	0.99
		6 months	42 ± 4	45 ± 5	0.94
		12 months	49 ± 6	59 ± 8	0.73
Vitamin B1 (µg/dL)		3 months	4.4 ± 0.4	4.3 ± 0.3	1.00
		6 months	4.6 ± 0.5	4.9 ± 0.3	0.93
		12 months	5.2 ± 0.4	5.5 ± 0.4	0.97
Vitamin B6 (nmol/L)		3 months	28.5 ± 8.3	25.7 ± 3.2	0.99
		6 months	21.1 ± 6.4	25.1 ± 6.0	0.96
		12 months	23.0 ± 6.4	40.5 ± 10.0	0.41
Vitamin B9 (ng/mL)		3 months	6.5 ± 1.2	6.3 ± 1.9	1.00
		6 months	5.0 ± 1.0	6.3 ± 1.4	0.85
		12 months	7.8 ± 2.1	6.6 ± 1.5	0.96
Vitamin B12 (pg/mL)		3 months	549 ± 72	394 ± 51	0.28
		6 months	587 ± 88	374 ± 39	0.16
		12 months	582 ± 83	399 ± 42	0.22
Vitamin D (ng/mL)		3 months	18.7 ± 3.7	23.8 ± 4.4	0.78
		6 months	21.3 ± 4.2	28.0 ± 4.0	0.61
		12 months	24.7 ± 3.1	36.1 ± 4.2	0.14
Zinc (µg/dL)	*Female*	3 months	86.9 ± 4.8	80.7 ± 3.5	0.69
		6 months	75.1 ± 2.7	88.3 ± 9.8	0.59
		12 months	78.8 ± 7.1	82.2 ± 6.2	0.98
	Male	3 months	94.7	67.4 ± 5.9	-
		6 months	78.3	74.9 ± 1.6	-
		12 months	70.9	68.7 ± 0.8	-
Nutritional deficiencies, N (% of group total)					
Iron deficiency		3 months	5 (71%)	3 (43%)	0.59
		6 months	5 (71%)	1 (14%)	0.10
		12 months	0 (0%)	2 (29%)	0.46
Anaemia		3 months	2 (29%)	1 (14%)	1.00
		6 months	2 (29%)	2 (29%)	1.00
		12 months	5 (71%)	3 (43%)	0.59
Hypoproteinaemia		3 months	2 (29%)	2 (29%)	1.00
		6 months	4 (57%)	1 (14%)	0.27
		12 months	4 (57%)	3 (43%)	1.00
Vitamin A deficiency		3 months	1 (14%)	2 (29%)	1.00
		6 months	1 (14%)	1 (14%)	1.00
		12 months	1 (14%)	0 (0%)	1.00
Vitamin B1 deficiency		*No deficiency (0%/group) at any time point*			

		One-stage SADI-S	SG	*p*-value
Vitamin B6 deficiency	3 months	4 (57%)	3 (43%)	1.00
	6 months	5 (71%)	4 (57%)	1.00
	12 months	5 (71%)	2 (29%)	0.29
Vitamin B9 deficiency	3 months	0 (0%)	2 (33%)	0.46
	6 months	2 (29%)	1 (14%)	1.00
	12 months	0 (0%)	1 (14%)	1.00
Vitamin B12 deficiency	3 months	0 (0%)	1 (14%)	1.00
	6 months	0 (0%)	1 (14%)	1.00
	No deficiency (0%/group) at 12 months			
Vitamin D deficiency	6 months	1 (14%)	0 (0%)	1.00
	No deficiency (0%/group) at 3 and 12 months			
Hypocalcaemia	3 months	1 (14%)	0 (0%)	1.00
	No deficiency (0%/group) at 6 and 12 months			

Note: Data are presented as mean ± SEM or number (%), as appropriate. *SADI-S* single-anastomosis duodeno-ileal bypass with sleeve gastrectomy; *SG* sleeve gastrectomy

Table V Comorbidities of subjects submitted to one-stage SADI-S and SG at pre-operative time and at post-operative visits (3, 6 and 12 months)

	Pre-op	3 months	6 months	12 months
Hyperlipidaemia				
One-stage SADI-S	4 (57%)	2 (29%)	2 (29%)	2 (33%)
SG	4 (57%)	2 (29%)	2 (29%)	2 (29%)
p-value	1.00	1.00	1.00	1.00
Hypertension				
One-stage SADI-S	3 (43%)	0 (0%)	0 (0%)	0 (0%)
SG	3 (43%)	2 (29%)	2 (29%)	2 (29%)
p-value	1.00	0.46	0.46	0.46
T2D				
One-stage SADI-S	1 (14%)	0 (0%)	0 (0%)	0 (0%)
SG	1 (14%)	0 (0%)	0 (0%)	0 (0%)
p-value	1.00	-	-	-
MS				
One-stage SADI-S	4 (57%)	4 (57%)	0 (0%)	0 (0%)
SG	6 (86%)	4 (57%)	1 (14%)	0 (0%)
p-value	0.56	1.00	1.00	-

Note: Data are presented as number (%). *SADI-S* single-anastomosis duodeno-ileal bypass with sleeve gastrectomy; *SG* sleeve gastrectomy; *T2D* type 2 diabetes mellitus; *MS* metabolic syndrome

Table VI Glycaemia and pancreatic hormones levels in fasting state and respective post-prandial increment and total areas under the curve for one-stage SADI-S and SG subjects, both at pre-operative and post-operative visits (3, 6 and 12 months)

		Pre-op	3 months	6 months	12 months
Glycaemia					
Fasting (mg/dL)	One-stage	101 ± 4	86 ± 3	87 ± 1	88 ± 4
	SG	116 ± 16	84 ± 3	83 ± 4	90 ± 3
	p-value	0.97	0.99	0.96	1.00
iAUC (mg/dL x min)	One-stage	3279 ± 522	3447 ± 807	1983 ± 299	2574 ± 298
	SG	2422 ± 592	3833 ± 402	2294 ± 359	2752 ± 522
	p-value	0.76	0.99	0.95	1.00
tAUC (mg/dL x min)	One-stage	15385 ± 856	13577 ± 895	11518 ± 227	11186 ± 477
	SG	16181 ± 2479	13824 ± 551	11169 ± 611	12414 ± 819
	p-value	1.00	1.00	0.98	0.64
Insulin					
Fasting (pmol/L)	One-stage	182.7 ± 26.8	75.3 ± 10.9	52.6 ± 5.4	40.0 ± 7.2
	SG	129.0 ± 16.3	47.6 ± 5.8	49.5 ± 8.8	38.9 ± 4.5
	p-value	0.59	0.31	1.00	1.00
iAUC (pmol/L x min)	One-stage	66902 ± 11793	81248 ± 12018	71658 ± 10510	53512 ± 8661
	SG	61885 ± 10436	59235 ± 6986	49379 ± 6940	43502 ± 7001
	p-value	1.00	0.47	0.36	0.86
tAUC (pmol/L x min)	One-stage	88762 ± 11586	90278 ± 12494	77945 ± 10808	58257 ± 8935
	SG	77314 ± 11939	64952 ± 6989	55302 ± 7322	48034 ± 7216
	p-value	0.94	0.37	0.38	0.86
C-peptide					
Fasting (pmol/L)	One-stage	715.9 ± 113.6	523.1 ± 75.8	377.9 ± 51.5	329.1 ± 20.9
	SG	589.4 ± 44.6	406.4 ± 63.0	383.3 ± 45.6	360.0 ± 33.7
	p-value	0.94	0.88	1.00	0.99
iAUC (pmol/L x min)	One-stage	57250 ± 6387	136463 ± 28202	121589 ± 26389	119927 ± 14039
	SG	73863 ± 12275	139186 ± 13841	103428 ± 21702	112166 ± 7846
	p-value	0.70	1.00	0.98	0.98
tAUC (pmol/L x min)	One-stage	137830 ± 11821	199236 ± 34831	166314 ± 29042	159417 ± 15479
	SG	144583 ± 15063	187974 ± 10366	149428 ± 23598	155358 ± 9541
	p-value	0.99	1.00	0.99	1.00
ISR					
Fasting (pmol.kg^{-1}min^{-1})	One-stage	1.7 ± 0.3	1.4 ± 0.2	1.1 ± 0.1	1.0 ± 0.1
	SG	1.4 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1
	p-value	0.82	0.72	1.00	0.94
iAUC (pmol.kg^{-1}min^{-1} x min)	One-stage	202.7 ± 11.7	472.0 ± 101.6	442.9 ± 87.2	468.8 ± 53.0
	SG	225.7 ± 37.2	474.6 ± 49.5	371.1 ± 77.9	429.4 ± 37.2
	p-value	0.97	1.00	0.96	0.96
tAUC (pmol.kg^{-1}min^{-1} x min)	One-stage	369.0 ± 22.1	621.0 ± 121.1	545.0 ± 100.2	560.0 ± 54.1
	SG	386.9 ± 48.7	587.1 ± 38.0	489.5 ± 84.6	535.5 ± 31.8
	p-value	1.00	1.00	0.99	0.99
Insulin clearence					
Fasting	One-stage	0.010 ± 0.001	0.020 ± 0.003	0.022 ± 0.003	0.032 ± 0.005
	SG	0.011 ± 0.001	0.024 ± 0.003	0.026 ± 0.004	0.030 ± 0.002
	p-value	0.66	0.73	0.91	1.00

		Pre-op	3 months	6 months	12 months
Insulin clearence					
Post-prandial $_{0\text{-}120\ min}$	One-stage	0.005 ± 0.001	0.007 ± 0.001	0.008 ± 0.002	0.011 ± 0.002
	SG	0.005 ± 0.001	0.009 ± 0.001	0.010 ± 0.002	0.012 ± 0.002
	p-value	0.90	0.10	0.87	0.99

Note: Data are presented as mean ± SEM. *SADI-S* single-anastomosis duodeno-ileal bypass with sleeve gastrectomy; *SG* sleeve gastrectomy; *iAUC* incremental area under the curve; *tAUC* total area under the curve; *ISR* insulin secretion rate

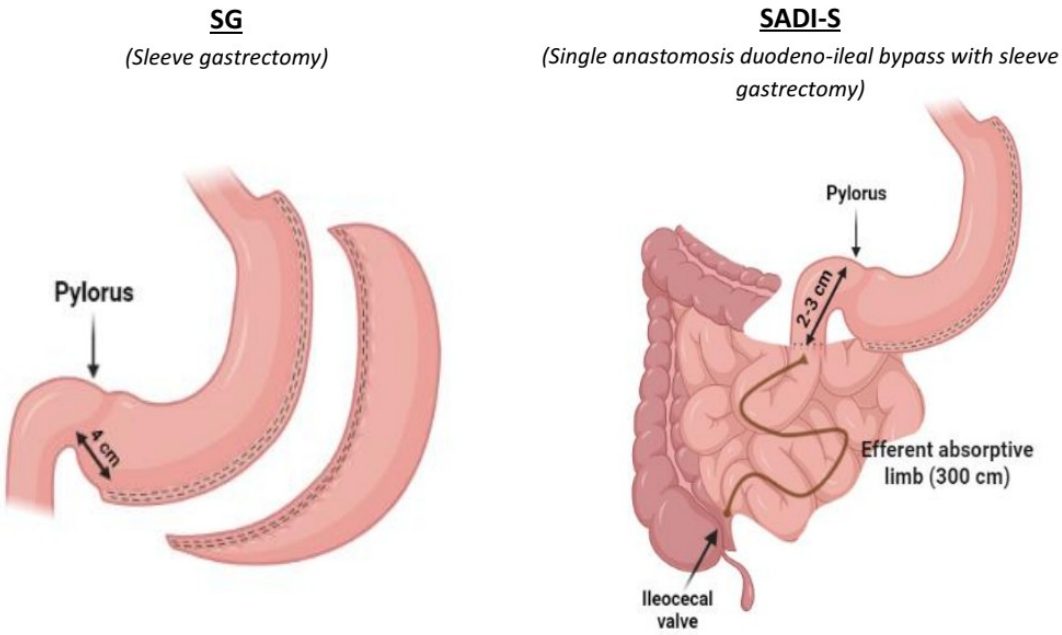


Figure 1 Schematic representation of the digestive anatomy after the sleeve gastrectomy (SG) and single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) surgeries. Created with BioRender.com

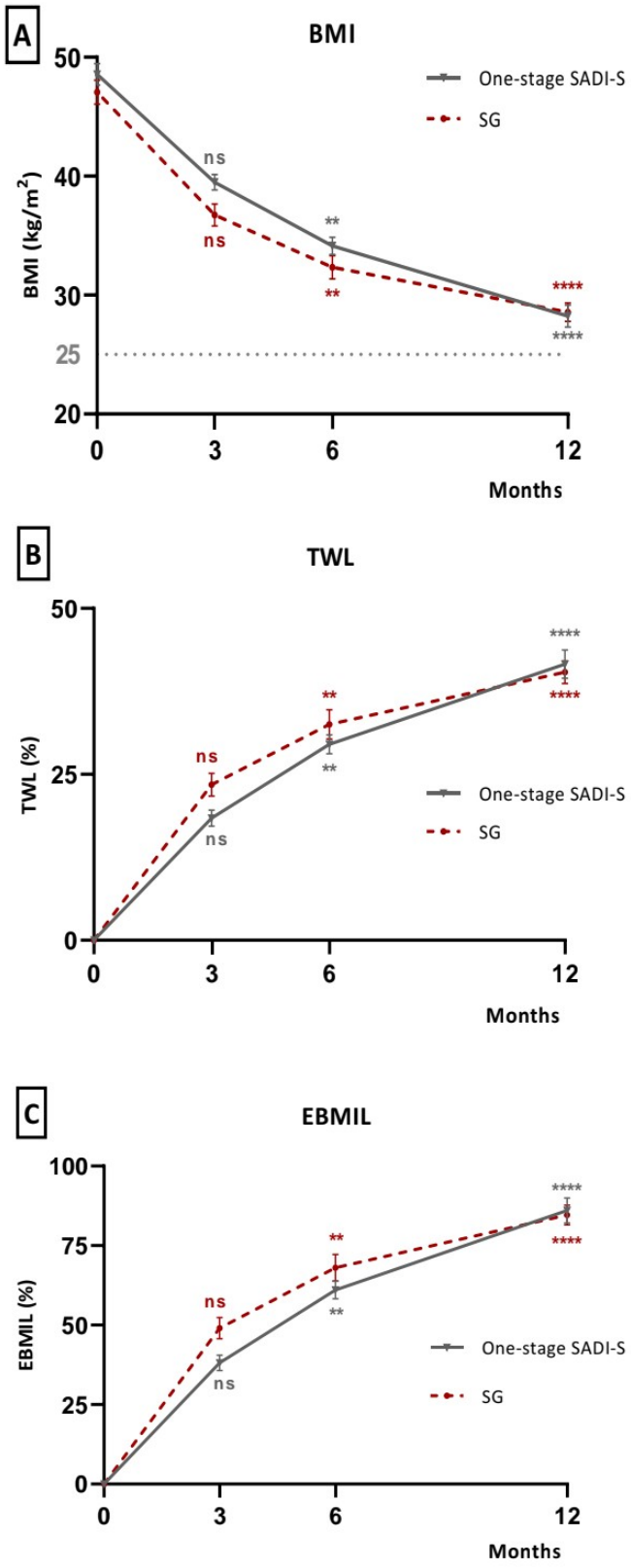


Figure 2 Graphic representation of (**A**) BMI, (**B**) %TWL, and (**C**) %EBMIL of patients submitted to one-stage SADI-S and SG during the follow-up of 12 months. Data are presented as mean ± SEM. *SADI-S* single-anastomosis duodeno-ileal bypass with sleeve gastrectomy; *SG* sleeve gastrectomy; *BMI* body mass index; *TWL* total weight loss; *EBMIL* excess BMIL loss. Statistically significant differences in measures compared to pre-operative time for each group are represented as: ns (not significant); ** $p < 0.01$; ****$p < 0.0001$

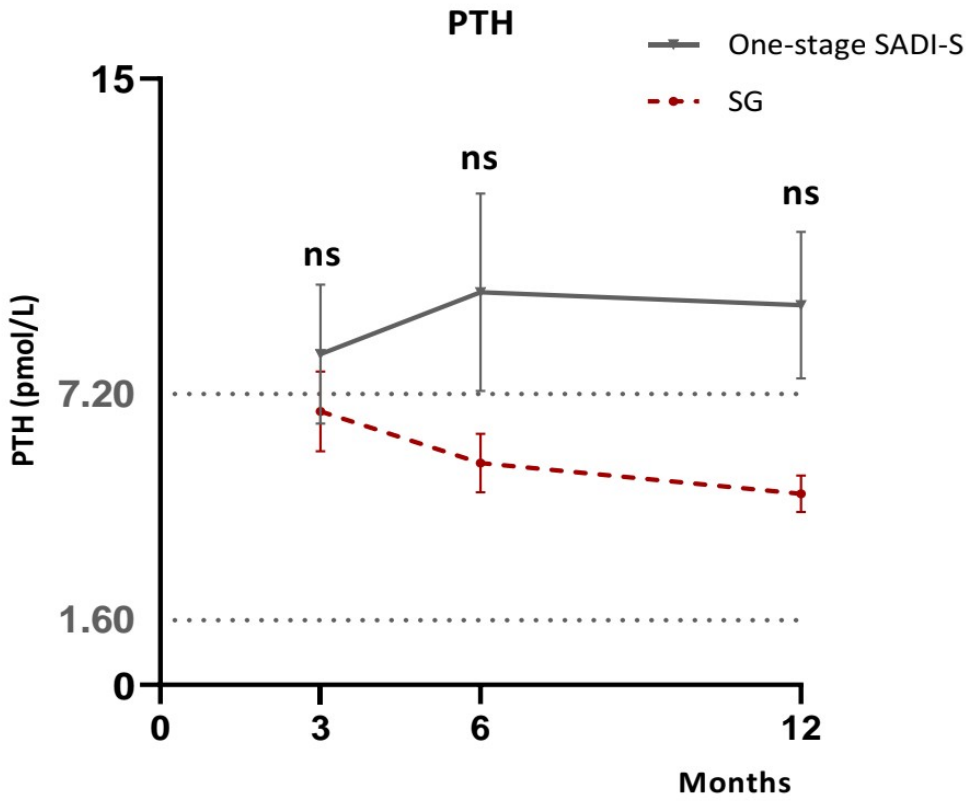
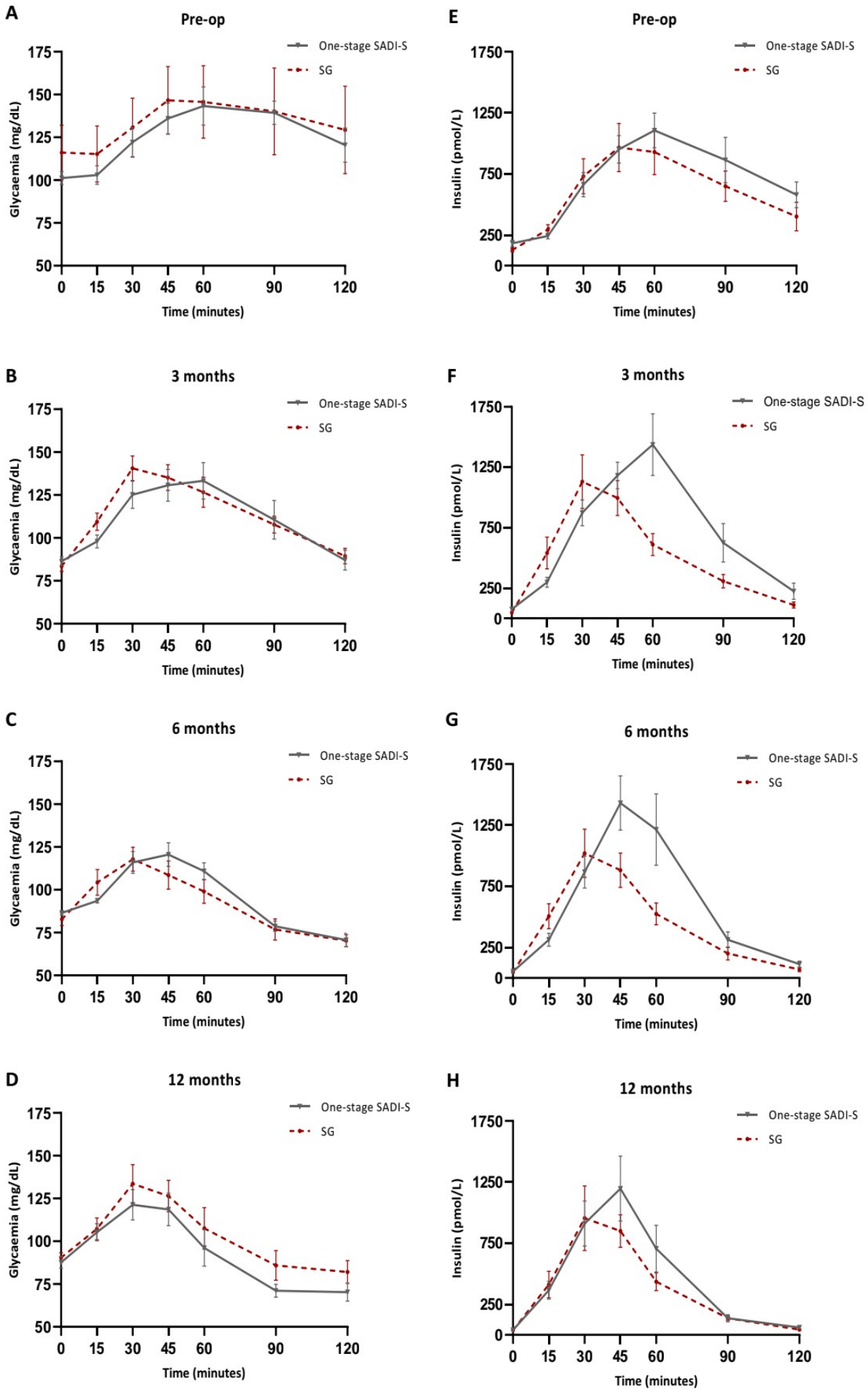
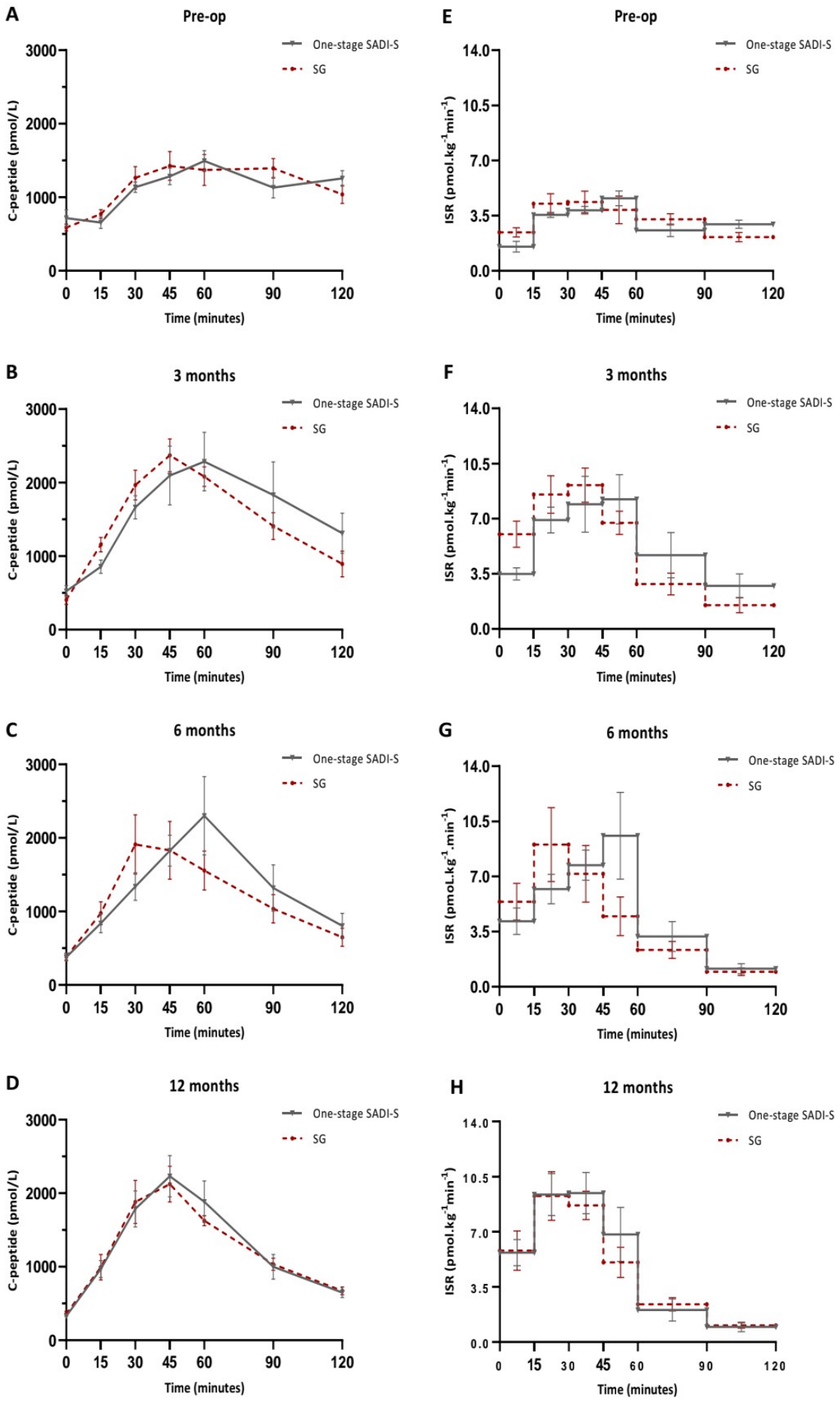


Figure 3 Graphic representation of PTH levels of patients submitted to one-stage SADI-S and SG from 3 to 12 months of follow-up. Data are presented as mean ± SEM. *SADI-S* single-anastomosis duodeno-ileal bypass with sleeve gastrectomy; *SG* sleeve gastrectomy; *PTH* parathyroid hormone (Reference values: 1.60 - 7.20 pmol/L). No statistically significant differences were found between groups (*ns*: not significant)


A
Pre-op
One-stage SADI-S
SG
Glycaemia (mg/dL)
175
150
125
100
75
50
0 15 30 45 60 90 120
Time (minutes)
E
Pre-op
One-stage SADI-S
SG
Insulin (pmol/L)
1750
1250
750
250
0
0 15 30 45 60 90 120
Time (minutes)
B
3 months
One-stage SADI-S
SG
Glycaemia (mg/dL)
175
150
125
100
75
50
0 15 30 45 60 90 120
Time (minutes)
F
3 months
One-stage SADI-S
SG
Insulin (pmol/L)
1750
1250
750
250
0
0 15 30 45 60 90 120
Time (minutes)
C
6 months
One-stage SADI-S
SG
Glycaemia (mg/dL)
175
150
125
100
75
50
0 15 30 45 60 90 120
Time (minutes)
G
6 months
One-stage SADI-S
SG
Insulin (pmol/L)
1750
1250
750
250
0
0 15 30 45 60 90 120
Time (minutes)
D
12 months
One-stage SADI-S
SG
Glycaemia (mg/dL)
175
150
125
100
75
50
0 15 30 45 60 90 120
Time (minutes)
H
12 months
One-stage SADI-S
SG
Insulin (pmol/L)
1750
1250
750
250
0
0 15 30 45 60 90 120
Time (minutes)

↑

Figure 4 Capillary blood glucose and peripheral levels of insulin at pre-op (**A** and **E**), and at 3 (**B** and **F**), 6 (**C** and **G**) and 12 months (**D** and **H**) post-operatively, in subjects submitted to one-stage SADI-S (n=7) or SG (n=7) after ingestion of a standardized mixed meal served at t=0 min. Data are presented as mean ± SEM. *SADI-S* single-anastomosis duodeno-ileal bypass with sleeve gastrectomy; *SG* sleeve gastrectomy. No statistically significant differences were found between groups at any time point


A
Pre-op
One-stage SADI-S
SG
C-peptide (pmol/L)
3000
2000
1000
0
0 15 30 45 60 90 120
Time (minutes)
E
Pre-op
One-stage SADI-S
SG
ISR (pmol.kg-1min-1)
14.0
10.5
7.0
3.5
0.0
0 15 30 45 60 90 120
Time (minutes)
B
3 months
One-stage SADI-S
SG
C-peptide (pmol/L)
3000
2000
1000
0
0 15 30 45 60 90 120
Time (minutes)
F
3 months
One-stage SADI-S
SG
ISR (pmol.kg-1min-1)
14.0
10.5
7.0
3.5
0.0
0 15 30 45 60 90 120
Time (minutes)
C
6 months
One-stage SADI-S
SG
C-peptide (pmol/L)
3000
2000
1000
0
0 15 30 45 60 90 120
Time (minutes)
G
6 months
One-stage SADI-S
SG
ISR (pmoL.kg-1.min-1)
14.0
10.5
7.0
3.5
0.0
0 15 30 45 60 90 120
Time (minutes)
D
12 months
One-stage SADI-S
SG
C-peptide (pmol/L)
3000
2000
1000
0
0 15 30 45 60 90 120
Time (minutes)
H
12 months
One-stage SADI-S
SG
ISR (pmol.kg-1min-1)
14.0
10.5
7.0
3.5
0.0
0 15 30 45 60 90 120
Time (minutes)

↑

Figure 5 Peripheral levels of C-peptide and ISR at pre-op (**A** and **E**), and at 3 (**B** and **F**), 6 (**C** and **G**) and 12 months (**D** and **H**) post-operatively, in subjects submitted to one-stage SADI-S (n=7) or SG (n=7) after ingestion of a standardized mixed meal served at t=0 min. Data are presented as mean ± SEM. *SADI-S* single-anastomosis duodeno-ileal bypass with sleeve gastrectomy; *SG* sleeve gastrectomy; *ISR* insulin secretion rate. No statistically significant differences were found between groups at any time point

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