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Dynamics Changes of Solids Gastric Emptying Post -Pancreaticoduodenectomy

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Abstract

BACKGROUND: Gastric emptying (GE) is one of the common post-operative complications after pancreaticoduodenectomy (PD). Multiple factors have been involved in this complication. Dynamic studies such as GE scintigraphy (GES) have informed us about changes in the behavior of the stomach before and after the operation.

AIM: The objective of this study is a short-term scintigraphic evaluation of GE in post-PD patients for solid food before (baseline) and after the operation for 30 days.

METHODS: Between April 2016 and September 2019, 30 patients who underwent PD were investigated for the effect on GE of solids. GE scan GES was performed for the evaluation of solids in GE on pre-operative and post-operative day 30. The operative time, blood loss, the specimens' pathology and resection margins, the interpretation of the GES study, and finally the hospital course data were all gathered and subjected to statistical analysis.

RESULTS: Nineteen patients developed delayed GE (DGE) while four developed rapid GE or dumping. The type of pancreatic reconstruction affected the GE dynamics. DGE was evident in all cases with pancreaticogastrostomy (PG), while it was observed only in 4 patients of 15 with pancreaticojejunostomy (PJ). Seven cases developed a post-operative pancreatic fistula (POPF), 3 after PG versus 4 after PJ, and were all successfully managed conservatively.

CONCLUSION: The reconstruction method of the remnant pancreas could affect the dynamics of GE. The DGE to solids was witnessed more in cases reconstructed by PG and less in cases with PJ. Post-operative complications associated, such as POPF, are factors associated with DGE.

Introduction

Normally, the half-time of solid gastric emptying (GE) is <2 h. Liquids show an initial rapid phase succeeded by a linear phase of emptying, which is slower. Unlike liquids, solids have an initial 30-min lag phase, during which grinding, and mixing occur, but little solids are empty. It is called receptive relaxation and gastric accommodation. After the receptive relaxation phase, the linear emptying phase occurs. Smaller particles pass through the duodenum. The solid GE time changes according to the size of the meals, the caloric content and the macros composition (especially fat) [1].

Pancreaticoduodenectomy (PD) remains the only curative option for the resectable pancreatic head, ampullary, duodenal, and distal common bile duct tumors. Morbidity related to this operation remains remarkably high. Around 75% of patients suffer from at least one complication related to PD. It is associated with a perioperative mortality rate of <4%. However, morbidity rates due to long-term postoperative complications have not proportionally improved and remain high at 40–50%. The most common sources of postoperative morbidity include post-operative pancreatic fistula (POPF), pancreatic insufficiency, delayed GE (DGE), biliary fistula, and wound infection. These are associated with increased mortality, prolonged hospital stays, and markedly increased health-care costs. Therefore, the best surgical techniques are required to reduce the risk of complications [2].

Pancreaticogastrostomy (PG) and pancreaticojejunostomy (PJ) are two widely applied reconstruction techniques after PD. Early systematic reviews and meta-analyzes did not provide adequate evidence to prove the superiority of PG over PJ or vice versa. While some other studies found a higher significant incidence of DGE in the PG group. This reflects the trauma and disruption of the design of a PG in the posterior wall and an 'access' gastrostomy in the anterior wall. For example, Shahzad *et al*. [3] found that DGE post-PG is 21.7% of patients and post-PJ is 19.7% of patients. Recently, several high-quality randomized controlled trials have compared PG and PJ. However, even with a meta-analysis of the RCTs, it remains debatable which is the better reconstruction method after PD [3].

DGE is of particular importance with incidence rates as high as 59% after PD. DGE is defined by symptoms of early satiety, nausea, and vomiting, without evidence of mechanical obstruction. Although DGE is not acutely life-threatening, chronic DGE can lead to nutritional difficulties, prolonged length of stay, readmissions, significant morbidity, and decreased quality of life [4], [5], [6].

The exact etiology and pathogenesis of DGE are unclear. Many potential mechanisms for DGE after PD have been identified, including gastric dysrhythmias due to post-operative intra-abdominal complications, such as POPF, and the presence of local inflammation may be one of the possible etiologies, hemorrhage, ileus, infection and anastomotic leakage, gastric atony due to the absence of motilin stimulation after duodenal resection; pylorospasm secondary to vagotomy; pyloric or antral ischemia; and denervation of the stomach and duodenum or jejunum, Roux stasis syndrome, transient pancreatitis, and torsion or angulation of the intestines. The most significant predictor of DGE is the presence of a POPF, but it has also been associated with increased operative time, post-operative sepsis, and reoperation [7], [8], [9]. However, DGE can develop in the absence of POPF as well. Without any evidence of intra-abdominal infection or local inflammation, an "isolated DGE" can develop pointing at unique pathophysiology that cannot be subtracted from POPF by simple multivariable statistical analysis. Yet, risk factors for DGE in the absence of pancreatic fistula are poorly characterized [4].

The consensus definition of DGE after pancreatic surgery has been established in 2007. To evaluate the occurrence of DGE, it is necessary to prove the patency of the intestinal tract by upper gastrointestinal contrast series or endoscopy and to exclude a small bowel obstruction (e.g., stenosis or kicking). Table 1 shows the grade of DGE as defined by the consensus meeting [10].

The most cost-effective, objective, simple, and widely available technique for confirming the presence of DGE is scintigraphy. Documenting the presence of DGE and assessing the severity is best achieved by evaluating the GE of solids. Since liquids often empty from the stomach normally even when solids are abnormally retained, the assessment of liquid emptying is unnecessary unless dumping syndrome is suspected [11].

The consensus guidelines released in 2008 standardized imaging and interpretation, supporting a protocol developed in 2000 by Tougas *et al*. This simplified methodology for solid GE scintigraphy (GES) requires 1-min images to be acquired at only 4-time points: immediately after meal ingestion and at 1, 2, and 4 h with an optional 5th-time point at 30-min which can be helpful in the assessment of rapid GE (RGE) [12]. Recent investigations also suggest that rapid emptying is detected 15–60 min after meal ingestion. Table 2 shows the lower limit and upper limit values for the interpretation of GES [13].

Table 2: Normal solid gastric emptying (percentage of retention values) [13]

Imaging Time	Lower normal limita (%)	Upper normal limitb (%)
0 min		
0.5 h	70	
1 h	30	90
2 h		60
3 h		30
4 h		10

[a]For the lower normal limit, lower values suggest rapid gastric emptying. [b]For upper normal limit values, a higher value suggests delayed gastric emptying.

Grading for the severity of DGE based on the 4-h value in groups related to the standard deviation (SD) of the normal results is: Grade 1 (mild): 11–20%retention at 4 h; Grade 2 (moderate): 21–35% retention at 4 h; Grade 3 (severe): 36–50% retention at 4 h; and Grade 4 (very severe): 50% retention at 4 h. On the other hand, a combination of the degree of delay in GE and the nutritional needs or approaches necessary to support patient hydration and nutrition provides a better severity assessment and facilitates the approach to treatment. In a recent review, mild delay was designated as 11–15%, moderate 16–35%, and severe retention of.35% at 4 h [13].

The objective of this study is a short-term scintigraphic evaluation of GE in post-PD patients for solid food before (baseline) and after the operation for 30 days. We aim to study the dynamics of GE for solids post PD and identify risk factors for the development of DGE following PD, including method of pancreatic stump reconstruction either PG or PJ, POPF, amount of blood loss, required blood replacement, operation time, post-operative complications, and presence of intra-abdominal post-operative sepsis.

Methods

This prospective randomized controlled study was conducted in Cairo University hospitals in the period between April 2016 and September 2019 after approval of the institutional review board and obtaining informed consent from all patients, including approval of

Table 1: DGE grading (after the mechanical obstruction is excluded) [10]

DGE grade	NGT required	Unable to tolerate solid oral intake by POD	Vomiting/gastric distension	Use of prokinetics
A	4–7 days or reinsertion > POD 3	7	±	±
B	8–14 days or reinsertion > POD 7	14	+	+
C	>14 days or reinsertion > POD 14	21	+	+

DGE: Delayed gastric emptying, POD: Post-operative day, NGT: Nasogastric tube.

the treatment protocol. The study comprises 30 patients indicated for PD. The reconstruction of the pancreas was done in one of two ways, either PJ or PG, dividing the total number of patients into twwwooo equal groups each consisting of 15 patients (by block randomization each block 3 patients). Patients with gastric outlet obstruction before PD, detected by CT abdomen with oral and intravenous contrast and/or upper GI, were excluded from the study. Patients with gastroparesis on the baseline GES for solids or on medical treatment for diagnosed DGE before surgery were excluded to avoid other confounding variables affecting DGE.

In terms of pre-operative preparation, a clinical evaluation was performed to assess the comorbidities of the patients, including diabetes mellitus (DM) and the nutritional status of the patients. Proper routine pre-operative preparation for PD and metastatic workup. Each patient performed a scintigraphic assessment of GE before the operation (Figure 1) ^{99m}Tc di-ethylene-triamine-penta-acetic acid (DTPA) GES with quantitation “T½ and percentage of retention” as a “baseline”, for solid, to compare it with the postoperative outcome and to assess if there is any preoperative gastroparesis. If gastroparesis is encountered preoperatively, the patient is excluded from the study.

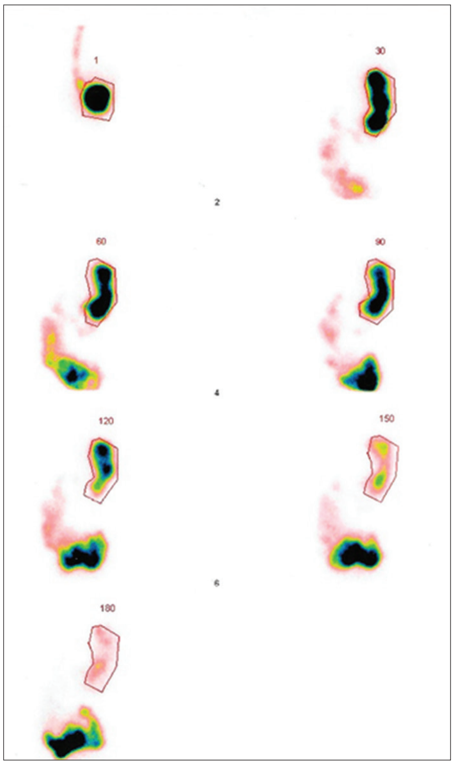

Figure 1: Solid GES for one of our patients preoperatively as a baseline for the evaluation of the gastric emptying function of the patient

All patients underwent PD with antral resection and the gastrojejunostomy pathway was ante colic after performing a Roux-en-Y jejunal loop. We did not perform a decompression gastrostomy or feeding jejunostomy in any of our patients. The type of pancreatic anastomosis defined each group: Half of the patients with PG (using invagination method) as one group (PG). The other half ended with PJ (using the dunking method) as the other group PJ.

In addition to the routine post-operative follow-up, abdominal ultrasound and abdominal CT with oral and IV contrast were done when the collection was suspected and amylase in the drain was measured when POPF was suspected to confirm the diagnosis. Assessment of GE by scintigraphic assessment. DTPA ^{99mTc} DTPA GES after solid surgery, with quantitation (T½ and percentage of retention after meal ingestion at 30, 60, 120, and 180 min) at POD 30 (most cases after discharge from the hospital). The effect of each group on the length of post-operative hospital stay was observed and recorded for analysis. In uneventful cases, we aim to discharge 1 week after surgery.

Preparing the patient for GES, we instructed the patient to take nothing by mouth starting at midnight and then undergo the exam in the morning “Nothing per oral for at least 4 h”. Medications such as prokinetic agents, or that delay GE if any were prescribed for the patient, were discontinued for 2 days before the study. Laxatives were not taken the day before the test. In the case of insulin-dependent diabetic patients, their blood sugar was <200 mg/dL. The morning dose of insulin is adjusted according to the prescribed meal.

Solid meal preparation

For the baseline study and the 30 days post-operative study, patients ingested the prepared standard meal. A sequential static acquisition was started immediately after the patient completed the meal, obtaining a 1-min frame at 0, 30-, 60-, 120-, and 180-min. The region of interest (ROI) was the fundus of the stomach.

Taking into account the early performance of the GE study preoperatively and 30 days after PD, we practiced the standardized egg white meal labeled ^{99m}Tc-DTPA (total activity of 1 mCi). This meal is recommended by the American Society of Neurogastroenterology and Motility and SNM [14].

Imaging was performed in a supine position on a dual-head gamma camera equipped with an all-purpose, low-energy, parallel hole collimator covering a NaI (Tl) crystal of 3/8 inch thickness, set at 140 keV, with a 20% window, zoom 1.0 using a matrix size of 64 × 64 for dynamic acquisition and 128 × 128 for static acquisition at different time intervals obtaining 1 min frame as a percentage of retention at 0, 30, 60, 120, and 180 min after meal ingestion (1 frame per min). The ROI was the fundus of the stomach. In the solid study, patients were allowed to be in the sitting position between each measurement.

Visual assessment of the activity in the entire stomach or the remaining stomach post PD to draw

ROIs including the stomach fundus with care to adjust the ROI to avoid activity from adjacent small bowel in anterior and posterior views of the composite image.

Calculation of a geometric mean (the square root of the product of counts in the anterior and posterior ROIs) obtained simultaneously during the acquisition of anterior and posterior views. Time activity curve obtained from the geometric mean of gastric counts displayed for all time points was constructed and gastric retention at 30-, 60-, 120-, and 180-min post-meal ingestion was calculated as a percentage of the counts obtained at the first image (0 times, 100%). The emptying time T12 for solid meal was calculated by interpolation from the observed data during the study (Figure 2).

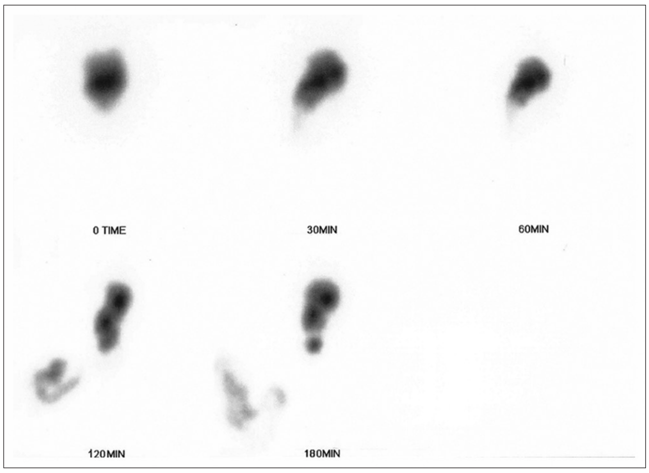

Figure 2: Solid GES post-PD with PG method of reconstruction, frames displayed at 0, 30, 60, 120, and 180 min showing severe delayed gastric emptying

Statistical analysis

Data are presented as mean ± SD, mean ± standard error of means, and/or as percentages as convenient. The characteristics of the patients and the perioperative and postoperative factors associated with DGE were compared using the Chi-square test or the Fisher exact test. Differences between continuous variables were evaluated using the Student t-test or the Mann–Whitney U test, where appropriate. $p < 0.05$ was considered statistically significant. Univariate analysis between predictive factors and results was performed using a logistic regression model. All variables with $p < 0.05$ in the univariate analysis were entered into a multivariate analysis to determine independent risk factors associated with the development of DGE, and results were expressed as an odds ratio (OR) with their 95% confidence interval (CI) or relative risk (RR). We use the OR or RR as an estimate of the risk of development of DGE. Statistical significance was defined as $p < 0.05$. All statistical analysis was performed using the SPSS software package (version 22.0; SPSS Inc., Chicago, IL, USA) for Microsoft Windows.

Results

Between April 2016 and September 2019, we encountered 83 PD candidates, only 30 fit the study and met the inclusion and exclusion criteria. 19 patients developed DGE while only 4 had RGE. We evaluated the two entities to evaluate the risk factors for DGE, the univariate analysis (Table 3) showed that the pancreatic type of anastomosis, PG or PJ ($p = 0.018$), the number of lymph nodes resected ($p = 0.042$), POPF ($p = 0.025$), intra-abdominal collection ($p = 0.021$), and wound infection ($p = 0.013$), showed statistically significant difference. We compared the patients with PG versus PJ (Table 4 and Figure 3), the only difference between the two groups was in the post-operative solid GE. Although tolerance to a solid diet was found later in the PG group (after 12 ± 6 days) than in the PJ group (after 10.4 ± 7.5 days), this difference was insignificant ($p = 0.5331$). According to the International Study Group of Pancreatic Surgery (ISGPS) definition for DGE, we had 16 patients with DGE of different grades (56.6%), the PG group included nine patients (66.6%), while the PJ group of patients showed seven patients (46.7%). This reflects that the clinical interpretation of DGE was statistically insignificantly different between both groups ($p = 0.3035$). Curve analysis of the results (Figure 3) showed that the type of anastomosis significantly affects GE. The patient tolerance for a solid diet (as well as the clinical grading of DGE) was not reflected in the objective assessment of GE by GES. In the PG group of patients, all patients showed DGE, which means that seven cases were clinically asymptomatic within the group (46.7%). While only four patients (26.6%) showed DGE in the PJ group by GES, which might reflect those three patients within the group (20%) were falsely clinically diagnosed with DGE, and intolerance to solids might be due to other reasons other than DGE. Multivariate analysis (Table 5) of the significant factors in univariate analysis using regression analysis with the post-operative solid GES T½ of the linear fit curve revealed that none of the factors is a statistically independent significant factor for DGE except for the pancreatic anastomosis type ($p < 0.001$) and the POPF ($p = 0.002$). Regarding the Effect of DGE on tolerance to solid and length of hospital stay, the tolerance to solid among the DGE group (n = 19) was after 14 ± 7.5 days compared to the no-DGE group (n = 11), as it was 6 ± 1.5 days, with significant difference ($p = 0.006$). The length of hospital stay was also significantly different ($p < 0.0001$) and was 19 ± 6 days for the DGE group and 11 ± 2 days for the non-DGE group of patients. All patients with clinically manifesting DGE were instructed to ingest small-sized meals with low-fat content. The number of meals varies from 5 to 6 meals per day. Fluid intake is encouraged. When the symptoms persist, we prescribed metoclopramide 10 mg daily for our patients. Some patients needed liquid protein formulas for nutritional support. All of our cases responded

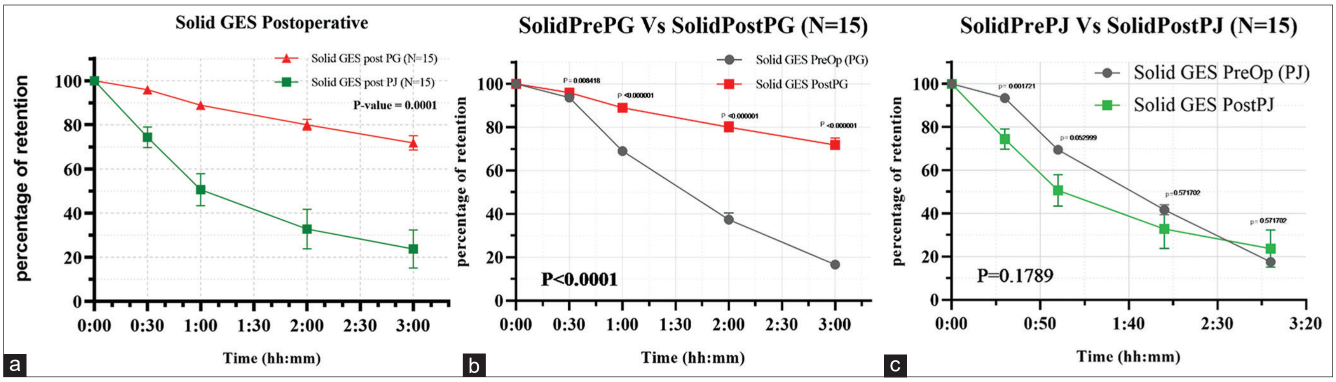

Figure 3: (a) Post-operative solid gastric emptying for both groups. (b) and (c) Solid GES, pre-and post-operative, (b) in PG group, (c) in PJ group. Values are expressed in mean ± SEM. PG, Pancreaticogastrostomy group; PJ, pancreaticojejunostomy group; PreOP, preoperative; PostPG, post-pancreaticogastrostomy; PostPJ, post-pancreaticojejunostomy

to treatment regimens and there were no additional complaints in terms of nausea, the sensation of fullness, and/or vomiting.

Discussion

DGE and pancreatic fistula are the most frequently reported complications after PD in many series, yet the latter complication has been much more widely studied in the literature. Nevertheless, DGE after PD poses a substantial financial and emotional burden to patients, hospitals, and society at large [9]. Our study targeted DGE as the main outcome study, comparing pancreaticogastrostomy and pancreaticojejunostomy as two methods for reconstruction of the pancreas after head resection in Whipple's operation. Until now, a few large consecutive series of pancreaticoduodenectomies have applied the consensus definition of DGE of ISPGS [10], [15]. Although significant efforts have been made in different studies to search for reasonable mechanisms as well as technical modifications to reduce the incidence of DGE, little has been carried out in terms of using objective diagnostic investigations for detecting this complication. The ISGPS definition of diagnostic criteria and stratification of severity of DGE are based on the clinical criteria of removal of NGT as well as tolerance to oral feeding and does truly little to clarify the uncertainty. However, the assessment of

Table 3: Univariate analysis of variances affecting GE

Variant	DGE (n = 19)	No-DGE (n = 11)	"OR" or "RR" (95% CI)	p-value
Age (Mean ± SD)	56.61 ± 4.7	52.64 ± 9.3	OR: 0.924 (0.82 1.039)	0.186
Gender (n [%])				
Male	11 (57.9)	4 (36.4)	OR: 2.406 (0.521–11.1)	0.256
Female	8 (42.1)	7 (63.6)	OR: 0.416 (0.09–1.918)	
BMI (Mean ± SD)	23.9 ± 3	22.3 ± 2.7	OR: 0.823 (0.626–1.083)	0.164
DM (n[%])	2 (10.5)	0 (0)	RR: 1.647 (1.223–2.219)	0.265
Smoking (n [%])	6 (31.6)	1 (9.1)	OR: 4.615 (0.476–44.76)	0.187
ASA (n [%])				
ASA class II	14 (73.7)	11 (100)	RR: 0.56 (0.396–0.793)	0.062
ASA class III	5 (26.3)	0 (0)	RR: 1.786 (1.26–2.53)	
Operation duration (Mean ± SD) (min)	393.4 ± 128	384 ± 94	OR: 0.999 (0.993–1.006)	0.829
Blood loss (Mean ± SD) (cc)	423 ± 282	409 ± 163	OR: 1 (0.997–1.003)	0.871
Blood transfusion (n [%])	5 (26.3)	4 (36.4)	OR: 0.836 (0.314–2.224)	0.719
Lesion site (n [%])				
Ampulla of Vater	8 (42.1)	6 (54.5)	OR: 0.606 (0.136–2.705)	0.510
Head of the pancreas	11 (57.9)	5 (45.5)	OR: 1.650 (0.37–7.365)	
Lesion size (Mean ± SD)	150 ± 265.7	37.9 ± 62	OR: 0.996 (0.990–1.003)	0.246
Lesion pathology (n [%])				
Invasive adenocarcinoma	17 (89.5)	11 (100)	OR: 0.304 (0.013–6.94)	0.538
Solid pseudopapillary tumor	1 (5.3)	0 (0)		
Serous cystadenocarcinoma	1 (5.3)	0 (0)		
Tumor differentiation: (n [%])				
Well-differentiated	3 (15.8)	0 (0)	-	0.195
Moderately differentiated	12 (63.2)	6 (54.5)		
Poorly differentiated	3 (15.8)	5 (45.5)		
Undifferentiated	1 (5.3)	0 (0)		
LNs resected (range)	4–23	4–15	OR: 0.791 (0.631–0.991)	0.042
LNs positive (range)	0–7	0–1	OR: 0.428 (0.157–1.162)	0.096
Perineural invasion	6 (31.6)	3 (27.3)	OR: 1.231 (0.238–6.358)	0.804
Pancreatic anastomosis				
PG	15 (78.9)	0	RR: 3.75 (1.62–8.679)	0.018
PJ	4 (21.1)	11 (100)		
POPF	7 (36.6)	0 (0)	RR: 1.917 (1.296–2.835)	0.025
Biochemical leak	2 (10.5)	0 (0)		
POPF B	5 (26.3)	0 (0)		
Intra-abdominal collection	7 (36.6)	0 (0)	RR: 1.917 (1.296–2.835)	0.021
Wound infection	7 (36.6)	0 (0)	RR: 1.917 (1.296–2.835)	0.013
Superficial infection	6 (31.6)	0 (0)		
Deep infection	1 (5.3)	0 (0)		

RR: Relative risk, OR: Odd ratios, POPF: Postoperative pancreatic fistula, PG: Pancreaticogastrostomy, PJ: Pancreaticojejunostomy, DM: Diabetes mellitus.

Table 4: The characteristics of the patients are divided into two groups, the PG group and the PJ Group

Characteristics	PG (n = 15)	PJ (n = 15)	p-value
Age (years)			
Range	45–63	43–64	0.373
Mean ± SD	56 ± 5.03	53.7 ± 8.3	
Gender (n [%])			
Male	8 (53.3)	7 (46.7)	0.715
Female	7 (46.7)	8 (53.3)	
Smoking (n [%])	4 (26.7)	3 (20)	0.666
ASA (n [%])			
ASA Class 2	12 (80)	13 (86.7)	0.624
ASA Class 3	3 (20)	2 (13.3)	
BMI			
Range	19–28	18–28	0.098
Mean (± SD)	24.3 ± 2.91	22.5 ± 2.81	
DM (n [%])	1 (6.7)	1 (6.7)	1
COPD (n [%])	2 (13.3)	1 (6.7)	0.543
Preoperative solid GES percent of retention:			
at 30 min (Mean ± SEM)	93.67 ± 0.005	93.40 ± 0.01	0.2998
at 60 min (Mean ± SEM)	68.93 ± 0.01	69.40 ± 0.02	
at 90 min (Mean ± SEM)	37.33 ± 0.03	41.67 ± 0.02	
at 120 min (Mean ± SEM)	16.67 ± 0.02	17.53 ± 0.01	
Pre-operative solid GE T½ from the linear fit curve	105.95 ± 2.8 min	108.74 ± 2.8 min	0.490
Operative time (minute) (Mean ± SD)	386.7 ± 127.5	393.3 ± 106.8	0.878
Blood loss (cc) (Mean ± SD)	433.3 ± 301.5	403.3 ± 172	0.741
Blood transfusion			
1 unit	2 (13.3)	5 (33.3)	0.189
2 units	0 (0)	0 (0)	
3 units	2 (13.3)	0 (0)	
Lesion location (n [%])			
Ampulla of Vater	6 (40)	8 (53.3)	0.464
Head of the pancreas	9 (60)	7 (46.7)	
Pathology of the lesion (n [%])			
Invasive adenocarcinoma	13 (86.7)	15 (100)	0.343
Pseudopapillary cystic neoplasm	1 (6.7)	0 (0)	
Serous cystadenocarcinoma	1 (6.7)	0 (0)	
Tumor differentiation (n [%])			
Well-differentiated	2 (13.3)	1 (6.7)	0.561
Moderately differentiated	10 (66.6)	8 (53.3)	
Poorly differentiated	3 (20)	5 (33.3)	
Undifferentiated	0 (0)	1 (6.7)	
Lesion size (cc) (Median, range)	18 (0.75–720)	17.5 (1.6–672)	0.683
Perineural invasion (n [%])	4 (26.7)	5 (33.3)	0.960
TNM staging: (n [%])			
T			
T1	2 (13.3)	0 (0)	0.099
T2	2 (13.3)	0 (0)	
T3	11 (74.3)	15 (100)	
N			
N0	9 (60)	8 (53.3)	0.712
N1	6 (40)	7 (46.7)	
M (M0)	15 (100)	15 (100)	1
Number of resected lymph nodes (Range)	4–23	4–21	0.148
Number of positive lymph nodes (Range)	0–6	0–7	0.806
POPF (n [%])			
Biochemical Leak (BL)	0 (0)	2 (13.3)	0.504
POPF grade B	3 (20)	2 (13.3)	
Intra-abdominal collection (n [%])	3 (20)	4 (26.6)	0.666
Collection associated with POPF (n [%])	2 (13.3)	4 (26.6)	
Wound infection (n [%])			
Superficial infection	4 (26.6)	2 (13.3)	0.357
Deep infection	1 (6.7)	0 (0)	
Length of hospital stay (days)			
Range	14–28	10–34	0.056
Mean ± SD	17.13 ± 4.4	15.07 ± 7.6	
Started to tolerate a solid diet in:			
Range (days)	5–25	5–30	0.5331
Mean ± SD (days)	12 ± 6	10.4 ± 7.5	
DGE clinically: (ISGPS definition 2007)			
DGE A (n [%])	4 (26.6)	3 (20)	0.3035
DGE B (n [%])	3 (20)	2 (13.3)	
DGE C (n [%])	3 (20)	2 (13.3)	
Solid GES Post-operative (% of retention)			
At 30 min (Mean ± SEM)	95.93 ± 0.01	74.40 ± 0.05	<0.001
At 60 min (Mean ± SEM)	88.93 ± 0.02	50.60 ± 0.07	
At 120 min (Mean ± SEM)	80.00 ± 0.02	32.73 ± 0.09	
At 180 min (Mean ± SEM)	71.80 ± 0.31	23.73 ± 0.08	
Solid GES interpretation result			
Within normal values of GE (n [%])	0 (0)	7 (46.7)	0.001
DGE (n [%])	15 (100)	4 (26.6)	
RGE (dumping) (n [%])	0 (0)	4 (26.6)	
Percentage of delay of T½ "post versus pre solid GES"	260.35 ± 44.5	45.15 ± 34.45	< 0.001

POPF: Post-operative pancreatic fistula, RGE: Rapid gastric emptying, GE: Gastric emptying, DGE: Delayed gastric emptying, GES: Gastric emptying scintigraphy, SD: Standard deviation, DM: Diabetes mellitus.

this complication based solely on clinical criteria may be inaccurate due to many confounders [10], [16]. For instance, the intolerance to oral intake can be secondary to many other patient factors, for example, post-operative pain that leads to nausea and vomiting. Furthermore, there are cases of surgeon preference in terms of caution used in the removal and reinsertion of NGT in these patients. All these factors affect the clinical assessment of DGE grades based on the ISGPS definition. Hence, in this study, we used GES as an objective study to assess DGE and were used in other studies before [16]. Among our patients in the PJ group, three patients (20% of the group and 10% of all patients) were clinically diagnosed with DGE Grade A while the interpretation of GES showed no DGE.

Table 5: Multivariate analysis of significant factors causing DGE

Significant factor	Regression coefficient (β)	Estimate of Std. Error	p-value
Pancreatic anastomosis (PG)	−0.567	0.122	<0.001
POPF	−0.559	0.291	0.002
Number of LNs resected	−0.237	0.153	0.087
Wound infection	−0.148	0.130	0.231
Intra-abdominal collection	−0.016	0.315	0.992

POPF: Post-operative pancreatic fistula, PG: Pancreaticogastrostomy, DGE: Delayed gastric emptying.

Furthermore, GES diagnosed "RGE" (clinically as dumping syndrome) that was no way to classify using ISGPS definition. Fluid GES for fluids was performed after 10 days to detect early post-operative DGE, and solid GES was performed 30 days after to detect delayed post-operative DGE. None of the two tests were able to detect the three clinically classified cases as DGE grade A. This could be a falsely interpreted DGE by clinical presentation, and intolerance to solids can be due to other factors as mentioned earlier [16]. There is a wide variation in the incidence of DGE after PD because of the heterogeneity in the surgical technique as well as the definition of DGE. The reported incidence of DGE in studies including 500 or more PD patients ranges from 3.2% to 59.0% based on the ISGPS definition [5], [10]. DGE occurred in 56.6% of our patients based on the ISGPS definition (66.6% in the PG group while 46.7% in the PJ group) and was detected in 63.33% based on solid GES study interpretation. Meta-analysis studies were conducted to assess the variables such as age, gender, and smoking affecting DGE. Statistics showed that they were all none significantly affecting GE. Age was affecting DGE in groups of age older than 75 years old as mentioned in the meta-analysis with Ellis *et al*. [4], or maybe more, above the 80-year-old age group as stated by Cameron and He [6]. Our results run along with these outcomes regarding gender and smoking. Age also was not affecting GE in our study as we excluded the age group above 70 years old from our study to minimize the factors affecting GE while comparing the PG groups and the PJ group. There was controversy regarding the effect of gender on DGE, while some studies concluded that it was not affecting GE [6], [15], [16], [17], other studies described the significant effect of male gender on GE, as a risk factor increasing the incidence as in

Ellis *et al.* [4] that studied a cohort of 10502 patients post-PD and found out that male could be a risk factor (OR, 1.29; $p < 0.001$), Eisenberg *et al*. [17] also found that male could be a risk factor with $p < 0.001$ [4], [17], which was not found in our study. Regarding comorbidities, in our study, DM was found to be a non-significant affecting factor on DGE. Although the known pathophysiology of DM on gastroparesis [18], DM was not a determining factor for the development of DGE post PD. This result is consistent with the outcome of many previous randomized controlled trials and meta-analytic studies [4], [6], [7], [15]. The largest cohort study in the USA done by Ellis *et al*. [4] that was published in January 2019, showed that DM was not a factor contributing to post-operative DGE, with a $p = 0.376$ and the percentage of affected patients in diabetics and non-diabetics is nearly the same [4]. The incidence was also the same in the prospective study done by Mohammed *et al*. [19]. Nevertheless, in our study, the small number of cases encountered with DM (two patients only having DM with normal preoperative GE) may be one reason for our results. Smoking status, COPD, BMI, and ASA classification were statistically insignificantly affecting DGE in our study. The outcome of these factors on DGE was variable in different studies. Regarding smoking status and COPD, most of the studies found no effect on DGE [7], [17], [19], while other studies reported a correlation between it and GE [4], [17]. It was reported by Ellis *et al*. [4] that smokers were less likely to experience DGE (OR, 0.75; 95% CI, 0.63–0.89; $p = 0.001$). For BMI, the cutoff point for the BMI increasing the risk for DGE was different between studies, while Robinson *et al*. [7], reported that BMI >35 Kg/m^2 is a significant risk factor for DGE, and Ellis *et al*. [4], mentioned the cut-off point at 25 kg/m^2. Other studies did not find BMI as a risk factor [15], [17], [19]. ASA classification was also debatable, whether it could be a risk factor [7] or not [3], [4], [19]. The operative time and blood loss or transfusion was not determining factors for DGE either in our study. While blood loss or blood transfusion was agreed by previous studies not to be one of the factors leading to DGE [4], [7], [19], there was controversy regarding the effect of operative time on post-operative DGE. The operative time was not a risk factor as reported by Mohammed *et al*. [19], Robinson *et al*. [7], and Ellis *et al*. [4] stratified the duration of the operation into groups. Robinson *et al*. [7] studied the effect of operative time longer than 5.5 h and found it a significant risk factor (OR = 2.72; 95% CI 1.37–5.39, $p = 0.05$). Ellis *et al*. [4] added further stratification as they stratified the cohort according to operative time into <5 h, between 5 and 7 h, and more than 7 h. This stratification showed higher risk for DGE incidence with longer duration (OR, 1.22 for operative time between 5 and 7 h, compared with <5 h; 95%CI, 1.02–1.47; $p = 0.029$) and (OR, 1.38 for >7 h compared with <5 h; 95%CI, 1.10–1.72; $p = 0.005$). Increased complexity of the operation contributed to an increased OR time [7]. The lesion properties and tumor pathology were not one of the risk factors leading to DGE in our study, and this is consistent with the previously done studies [4], [16], [17], [19], As shown previously in Table 3, the extent of lymphadenectomy played a role in the development of DGE postoperatively. Our study showed that the risk of DGE increased with a larger number of resected lymph nodes ($p = 0.042$; OR = 0.791; 95% CI 0.631–0.991). The outcome was not affected by the extent of tumor deposits in lymph nodes ($p = 0.096$). In 1999, Yeo *et al*. [20] studied PD with or without extended retroperitoneal lymphadenectomy, and they found that DGE occurred more in the extended lymphadenectomy group (4% in standard lymphadenectomy vs. 16% in extended lymphadenectomy, $p = 0.03$). Moreover, there was a trend toward DGE in the extended lymphadenectomy group mentioned in the meta-analysis done by Michalski *et al*. [21] This might be explained by the effect of dissection on the vascular and nervous supply, affecting the motor function of the stomach [8]. The type of pancreatic anastomosis was affecting the GE in the group of patients in our study ($p = 0.018$), with pancreaticogastrostomy carrying a RR of 3.75 times (95% CI 1.62–8.679) in the development of post-operative DGE when compared with pancreaticojejunostomy. The operative technique has in many studies been suggested to play a role in the development of DGE [7]. The results of the studies comparing pancreaticogastrostomy versus pancreaticojejunostomy showed variations in the outcomes [4], [5], [22], [23]. POPF has been widely debated. The theory of deactivation of pancreatic enzymes in the case of pancreaticogastrostomy by the acidic medium of the stomach to decrease the incidence of the leak was not illustrated in most meta-analysis studies, as the incidence seems to be equal in both groups [22], as it was insignificantly different statistically in our study. But there are some other studies describing the edging of the PG over PJ regarding POPF [3], the study mentioned that there was no difference in clinically relevant POPF rate in pancreaticojejunostomy versus pancreaticogastrostomy (19.8% vs. 12.8%, $p = 0.09$) group. POPF rate in patients in that study with soft pancreas was significantly more in pancreaticojejunostomy group as compared to pancreaticogastrostomy group (25.4% vs. 17.3%, OR = 1.71, 95% CI = 1.15–2.53, $p = 0.008$). Although there is no difference in pancreaticogastrostomy as compared to pancreaticojejunostomy after PD to prevent clinically relevant POPF [3]. DGE is a multifactorial outcome that makes the interacting risk factors exceedingly difficult for study, analysis, and interpretation. Samaddar *et al*. [16] described the method of objective assessment of DGE in 2015 using GES. That study compared GES with the clinical DGE and found that the sensitivity, specificity, and positive and negative predictive values of post-operative 10^{th}-day gastric scintigraphy were 61.53, 100, 100, and 61.53%, respectively ($p = 0.004$). The sensitivity, specificity, and positive and negative predictive values of post-operative 21st-day gastric scintigraphy were 38.46, 100, 100, and 50%, respectively ($p = 0.04$). Although, our study expressed pancreaticogastrostomy as a risk factor (RR for PG anastomosis is 3.75 times more than PJ anastomosis, 95%CI, 1.62–8.679, $p = 0.018$). This result is based on the objective assessment by GES and not the clinical grading of DGE. The previous studies showed there was no significant difference based on the clinical correlation, and this finding is consistent with our study as there was no difference regarding the clinical outcome [4], [16], [22]. The dynamics of emptying in our study showed that the patient will not suffer difficulties with drinking fluid. While there are no significant changes in fluid emptying dynamics post-PJ, some patients with PG may complain during the 1st h after drinking, as there was statistically significant DGE about their baseline before surgery (at 30 min and 60 min $p < 0.001$), but the difference became statistically insignificant after 2 h ($p = 0.53$). The differences in the emptying dynamics were obvious with solid GE, PG group showed marked DGE as the patient evacuate nearly 29% only in 3 h ($p < 0.001$), which means that the patient will continue to feel fullness all through the day after meals. This finding was observed in our patients, and even the patients tolerating solid food, not complaining clinically from DGE, tend to eat lesser amounts of food rather than their average volume of meals. This may have many implications related to the nutritional status of the patient, and the patient's morbidity. Regarding solid emptying in PJ patients, solid GES showed a significant decrease in the receptive relaxation (accommodation phase) in the first 30–60 min (at 30 min, $p = 0.002$ and 60 min, $p = 0.05$), otherwise by the end of emptying there was no significant difference ($p = 0.57$) comparing the whole group. All four patients who developed DGE were associated with POPF, indicating that POPF is one of the risk factors for DGE. Four patients developed dumping (RGE) only in the PJ group (26.6% in the PJ group). Dumping and decreased ability of receptive relaxation as consequences of denervation during dissection and antrectomy as a part of the operation with an incidence of 13–43% [24]. It could be masked in the PG group by the severe DGE. The mobilization of the residual pancreas to create the PG may entail more nerve damage to branches of the celiac and superior mesenteric ganglia. The mechanical traction by anastomosis could be another explanation for the severe DGE [25]. In the univariate logistic regression analysis, there were other factors affecting the post- PD DGE in our study, and they included POPF, intra-abdominal collection, and wound infection. The association between POPF and intra-abdominal collection on one side and the DGE on the other side was studied by many protocols of research, showing a strong correlation between their presence and DGE [4], [5], [7], [15], [16], [19], [22]. The independent risk factors leading to post-operative DGE, as computed by the multivariate regression analysis, were the method of pancreatic anastomosis (correlating the GES objective measurements) and POPF. This finding is consistent with most of the earlier studies [4], [5], [7], [15], [16], [19], [22]. Regarding morbidity, pancreaticogastrostomy patients showed higher morbidity in terms of later tolerance to a solid diet and longer hospital stay. Furthermore, DGE has been obvious morbidity in our patients, in terms of lifestyle, tolerance to food ($p < 0.001$), and length of hospital stay ($p = 0.006$). The morbidity and financial implications of DGE were obvious in the previous studies, and strategies should be studied to decrease this burden of DGE [17]. The limitation of this study is the small number of patients included and the small number of diabetic patients included. Further studies should be conducted to study the dynamics of gastric motility post PD, aiming for a definitive diagnosis for the risk factors and how to avoid or treat them in the future.

Conclusion

DGE is significantly more in PG rather than PJ. The mechanical effect of PG anastomosis could be one reason. This difference might not be projected clinically, but it is revealed by an objective test such as GES. POPF is an independent factor contributing to DGE. Clinical assessment of DGE is subjective, while the objective assessment by GES has revealed more cases that were originally asymptomatic. Vague clinical symptoms such as fullness and bloating can be hidden symptoms of DGE. Patients who are already eating small volume meals might be asymptomatic for DGE. Pancreaticojejunostomy is recommended over pancreaticogastrostomy to avoid the potential DGE.

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