World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i19.5794

World J Gastroenterol 2015 May 21; 21(19): 5794-5804
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Pathophysiology after pancreaticoduodenectomy

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Author contributions: Kang CM designed research and wrote the paper; and Lee JH contributed to the data acquisition and performed research.
Conflict-of-interest: Chang Moo Kang and Jin Ho Lee have nothing to disclose about this review.

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Received: November 22, 2014
Peer-review started: November 23, 2014
First decision: January 22, 2015
Revised: February 25, 2015
Accepted: April 17, 2015
Article in press: April 17, 2015
Published online: May 21, 2015

Abstract

Pancreaticoduodenectomy (PD) will result in removal of important multiorgans in upper intestinal tract and subsequently secondary physiologic change. In the past, surgeons just focused on the safety of surgical procedure; however, PD is regarded as safe and widely applied to treatment of periampullary lesions. Practical issues after PD, such as, effect of duodenectomy, metabolic surgery-like effect, alignment effect of gastrointestinal continuity, and non-alcoholic fatty liver disease were summarized and discussed.

Key words: Pancreaticoduodenectomy; Delayed gastric emptying; Metabolic surgery; Exocrine insufficiency; Fatty liver; Postoperative pancreatic fistula

Core tip: In the past, pancreaticoduodenectomy (PD) should be avoided because of its extremely high morbidity and mortality. With the advance of surgical techniques and perioperative management, PD has been regarded as good choice for the treatment of periampullary pathologic conditions. In this moment, turning our interest to potential physiological change following PD may be necessary, because PD always results in removal of important internal organs in upper gastrointestinal tract and altering normal path of gastrointestinal flow. Well awareness of these "internal" changes will be helpful for proper management of the patients with PD.

Kang CM, Lee JH. Pathophysiology after pancreaticoduodenectomy. *World J Gastroenterol* 2015; 21(19): 5794-5804 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i19/5794.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i19.5794

INTRODUCTION

In the past, it was thought that pancreaticoduodenectomy (PD) should be avoided because of its extremely high rates of morbidity (greater than 70%) and mortality (greater than 30%)[1]. More recently, many surgeons have focused on technical innovation to reduce postoperative severe morbidity after PD. Based on advancements in surgical experiences, perioperative management and interventional radiology, it is thought that most

Table 1 Experimental study showing the relationship between motilin and duodenectomy

Ref.	Year	Study design and model	Primary end point	Observations
Tanaka *et al*[74]	1987	Normal dog *vs* Duodenectomized dog	Phase Ⅲ contraction, plasma level of motilin	All control dogs showed characteristic MMC Duodenectomized dog showed non-typical, irregular and non-cyclic pattern of contraction Duodenectomized dog showed low plasma concentration of motilin without cyclical variation
Tanaka *et al*[75]	1988	Normal dog *vs* Duodenectomized dog	Inter-digestive gastric and small intestinal MMC plasma level of motilin and Polypeptide Y	MMC was abolished in duodenectomized dogs (3 out of 4 dogs) The other dogs showed intermittent cyclic, but markedly abnormal characteristics of gastric contraction Jejunal MMC appeared with short interval Duodenectomy abolished cyclic variation of plasma motilin and polypeptide Y
Suzuki *et al*[76]	2001	Conscious dog *vs* Duodenectomized dog	Phase Ⅲ contraction, plasma level of insulin, and motilin	Duodenectomy resulted in no phase Ⅲ contraction in upper GI tract Duodenectomy resulted in no fluctuation of plasma motilin (low level of motilin) Exogenous administration of motilin resulted in comparable response of phased Ⅲ as shown in control
Malfertheiner *et al*[77]	1989	Normal dog *vs* Duodenectomized dog	Pancreatic trypsin GI motility plasma motilin, PPY	In duodenectomized dog Trypsin secretion was not coordinated with inter-digestive motility, motilin, and PPY Inter-digestive motility was altered Plasma level of motilin and PPY were reduced, and showed no cyclic pattern
Itoh *et al*[78]	1976	Normal dog	GI motility plasma motilin	Gastrointestinal contractile activity in the conscious dog, Digestive states: motilin had no influence upon the motor activity Inter-digestive states: had influence upon the motor activity
Vantrappen *et al*[79]	1979	Human	GI motility plasma motilin level	The effect of exogenous motilin on interdigestive migrating motor complex Plasma motilin levels is one of the factor involved in the production of the activity front of the MMC in man
Sarna *et al*[80]	1983	Normal dog	Plasma motilin levels Migrating myoelectric complexes (MMCs)	Cause and effect relationship between plasma motilin levels and migrating myoelectric complexes Endogenous motilin does not initiate spontaneous mmcs MMC contractions release motilin

GI: Gastrointestinal.

complications related to PD can be managed in a conservative way. Based on the literature, mortality after PD is now considered to be 2%-5% and morbidity is reported to be 33%-64%[2-4]. PD recently has gained wide acceptance as a safe surgical method of choice for the treatment of periampullary pathological conditions.

PD consists of two surgical components: (1) resection phase: removal of pancreatic head, common bile duct, gallbladder, and duodenum along with some part of the proximal jejunum. Partial gastrectomy can be included; and (2) reconstruction phase: gastrointestinal continuity is created by pancreatico-enterostomy [pancreaticogastrostomy (PG) or pancreaticojejunostomy (PJ)], hepaticojejunostomy, and duodeno-or, gastro-jejunostomy.

When surgical technique is largely standardized, potential physiological changes following PD need to be concerned because PD results in the removal of important internal organs in the upper gastrointestinal tract and alters the normal path of the gastrointestinal flow. Therefore, surgeons who perform PD should be well aware of these "internal" challenges for proper management of patients with PD. Herein, the following issues will be discussed to understand the practical pathophysiological changes that occur after PD.

EFFECTS OF DUODENECTOMY

The duodenum is a source of various peptide hormones. Among them, motilin is a 22 amino acids peptide that is primarily localized in enterochromaffin cells of the duodenum and proximal jejunum[5], which is known to be responsible for phase Ⅲ activity of the gastroduodenal migrating motor complex (MMC)[5]. It was found that exogenous motilin could induce premature phase Ⅲ contraction in the upper gastrointestinal tract. Moreover, reduced plasma concentrations of motilin were associated with gastroparesis (Table 1). Therefore, PD can lead to the inevitable removal of the duodenum, which can reduce plasma levels of motilin, resulting in delayed gastric emptying (gastroparesis) by reducing coordinated stomach, duodenum and proximal jejunum movements.

Motilin is not yet available for clinical use. However, there is some clinical evidence to support these experiments and hypotheses. Naritomi *et al*[6] evaluated the first occurrence of MMC and motilin in patients with pylorus-preserving pancreaticoduodenectomy (PPPD) and duodenum-preserving pancreatic head resection (DPPHR). They found that the PPPD group required a longer amount of time for initial gastric phase Ⅲ

recovery, and the plasma levels of motilin were lower. Yeo *et al*[7] performed a prospective randomized placebo-controlled trial and found that erythromycin could significantly accelerate gastric emptying after PD and reduce the incidence of delayed gastric emptying (DGE) by 37%. Indeed, erythromycin can act as a motilin agonist by binding motilin receptors, and its clinical benefit to improve gastric emptying has been demonstrated in diabetic gastroparesis[8] and postvagotomy gastroparesis[9]. Matsunaga *et al*[10] also showed manometric evidence of improved early gastric stasis by erythromycin after PPPD. Administration of saline caused no changes in gastric or jejunal motility; however, erythromycin could induce phase Ⅲ-like gastric contraction and reduce the amount of gastric juice output in all patients.

Duodenectomy also influences on the secretion of other gastrointestinal hormones. Malfertheiner *et al*[11] showed that plasma levels of pancreatic polypeptide (PP) were altered with no cyclic pattern in duodenectomized dogs. Müller *et al*[12] evaluated changes in CCK, PP, and gastrin in PPPD and DPPHR patients. They found that PP was significantly reduced in both PPPD and DPPHR, and cholecystokinin (CCK) was reduced in an early postoperative period after PPPD. Tangoku *et al*[13], and Kingsnorth *et al*[14] evaluated plasma gastrin and CCK responses between standard PD and PPPD. Basal plasma levels of gastrin and CCK were significantly higher in controls compared with patients with standard PD ($P < 0.05$), suggesting that preservation of the stomach and part of the duodenum (pylorus-preserving) appeared to be a more physiological procedure for performing PD.

Regarding reduced gastrin levels following PD, it has been proposed that postoperative atrophic changes in the remnant pancreas after PD can be derived from removal of the duodenum and distal stomach because these organs are a source of gastric stimulation[15]. Jang *et al*[16] investigated the effects of induced hypergastrinemia on the prevention of pancreatic atrophy after PPPD. They performed a randomized control study and successfully demonstrated that induced hypergastrinemia by Lansoprazole could prevent postoperative volume change of the remnant pancreas and preserve long-term exocrine and endocrine function in patients with PPPD. This study is a good example to show how potential physiological changes can be translated into clinical practice for proper management of patients who undergo PD.

Furthermore, Chung *et al*[17] investigated the role of vagal and efferent adrenergic innervation to coordinate the gastric and small intestinal MMCs after removing the pylorus, duodenum, and upper jejunum in three dogs. They concluded that duodenectomy could reestablish gastric MMC-like activity without motilin, showing a peak after 1-4 mo, and it appeared to require extrinsic innervation. PD sometimes (depending on the surgeons' preference and disease extent) requires extensive soft tissue dissection around a major arterial system, including the celiac axis, common hepatic artery, and superior mesenteric artery for margin-negative resection. Too much dissection of soft tissue (for example, extended PD) can result in surgical denervation of visceral autonomic nerves and can be one of the reasons for transient delayed gastric emptying in a clinical setting[18,19].

Based on this brief review of the literature, it can be noted that duodenectomy not only disrupts the coordination of gastric and intestinal MMC but also disrupts the coordination between inter-digestive motility and pancreatic secretion and abolishes the inter-digestive cyclic variations in plasma gastrointestinal hormones, such as motilin, CCK, gastrin, and pancreatic polypeptide (PP). Additionally, extensive soft tissue dissection-induced disconnection of neural stimulation and secondary postoperative inflammatory insults can cause pathophysiological changes after PD, which can be attributed to a clinical delay in postoperative recovery.

METABOLIC SURGERY-LIKE EFFECTS

The bariatric surgical procedures were attempted to promote weight loss by restricting food intake and promoting malabsorption. The most commonly performed procedures were Roux-en-Y gastric bypass (46.6%), vertical sleeve gastrectomy (27.8%), adjustable gastric banding (17.8%), and biliopancreatic diversion with duodenal switch (2.2%)[20]. Interestingly, when looking at schematic figures showing PD, it could be noted that PD is somewhat similar in appearance to Roux-en-Y gastric bypass (Figure 1). The food passage after PD could be similar to that after Roux-en-Y gastric bypass, bypassing duodenum and passing directly into distal jejunum. Natural bile and pancreatic flow can be thought of as a Roux-en-Y loop in PD. Therefore, PD might cause the physiological changes that appear after bariatric surgery.

Notably, glucagon-like peptide-1 (GLP-1) is an interesting gastrointestinal hormone. After Roux-en-Y gastric bypass, GLP-1 is secreted by L cells of the small bowel, with higher concentrations in the distal ileum and colon. This peptide is produced in response to a meal and decreases food intake through its effects on the hypothalamus and brainstem. Additionally, GLP-1 is known to slow gastric emptying, inhibit glucagon release and stimulate the pancreas to secrete insulin (incretin effect)[21,22]. Recently, You *et al*[23] showed that about 30% of patients with PD were found to have hypertrophic changes in the remnant pancreas, and Wu *et al*[24] also reported resolution of diabetes after PD. They observed resolution of long-standing diabetes after PD in patients with (3, 9.1% of 33 patients, $P = 0.005$) and without (6, 9.8% of 61 patients) pancreatic cancer, suggesting that PD-associated anatomical changes might play an important role in the resolution of DM after PD.

Despite conflicting observations about GLP-1 levels

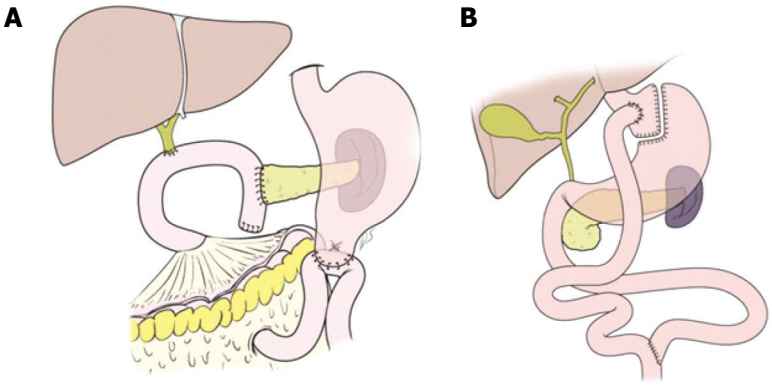

Figure 1 Schematic diagrams of pancreaticoduodenectomy and Roux-en-Y gastric bypass.

after PD[25], several studies have investigated changes in plasma GLP-1 levels after PD. Ohtsuka *et al*[26] previously showed that improved glucose metabolism after PD was mainly influenced by improved insulin resistance. They observed significantly increased plasma GLP-1 levels after PD; however, even after removal of the pancreatic head (reduced pancreatic volume), β-cell function did not change. Muscogiuri *et al*[27] evaluated the effect of duodenectomy on GLP-1 secretion after PD. They found that PPPD was associated with a remarkable increase in GLP-1 levels, which reached levels comparable with those observed after gastric bypass[28]. Harmuth *et al*[29] reported that conventional PD was associated with accelerated gastric emptying, enhanced postprandial GLP-1 release, and improved insulin sensitivity. The rapid transport of unabsorbed nutrients to the distal bowel triggers enhanced release of GLP-1, resulting in improved glycemic control.

Notably, GLP-1 agents used to control diabetes have been associated with an increased risk of pancreatic cancer in patients with type 2 diabetes[30]. However, a recent study demonstrated that GLP-1 could harbor anticancer properties against pancreatic cancer. GLP-1 receptor activation has anti-tumor effects on human pancreatic cancers *via* inhibition of the PI3K/Akt pathway[31]. Additionally, activation of the GLP-1 receptor was found to inhibit growth and promote apoptosis of human pancreatic cancer cells[32]. PD-induced GLP-1 release can be used for future treatment of resected pancreatic head cancer, although further investigations are warranted.

ALIGNMENT EFFECT OF GI CONTINUITY

In addition to the direct effects of removing organ by resection, pathophysiological changes after PD will also be influenced by how the gastrointestinal alignment is rearranged in the reconstructive phase. Various methods for reconstruction, similar to gastrointestinal alignment, have been reported in PD, such as Billroth Ⅰ (the Imanaga method)[33], Billroth Ⅱ (the Whipple and/or Child method)[34], Roux-en-Y loop fashion[35], an additional Braun anastomosis[36], and retrocolic/antecolic reconstruction[37]. In clinical practice, DGE appears to represent the pathophysiological changes that occur after PD. Conflicting observations have been reported about the incidence of DGE, and the exact mechanisms to explain the occurrence of DGE according to different reconstruction method remain to be determined. However, robust evidence is accumulating about the incidence of DGE according to different gastrointestinal reconstructive methods following PD (Table 2).

Short-term perioperative outcomes, such as postoperative complications, length of hospital stay, and resuming of acceptable diet, are the main concerns after PD. Miyakawa *et al*[38] demonstrated that fat absorption after Billroth Ⅰ PG (PG-Ⅰ) is superior to that after Billroth Ⅱ PJ (PJ-Ⅱ) in patients with disordered exocrine function of the pancreatic remnant, suggesting that PG-I allows for more effective utilization of the exocrine enzymes of the pancreatic remnant because of elimination of the blind loop characteristic of the PJ-Ⅱ. Ohtsuka *et al*[39] evaluated nutritional status and quality of life after PD, and compared these data between 18 patients with end-to-end (Imanaga) and 13 patients with end-to-side (Traverso) gastrointestinal reconstruction. They found that the scores of psychosocial conditions remained low, even over a long-term, in both groups. However, the values of nutritional parameters showed no significant difference between the two groups at each time point, suggesting that the postoperative quality of life and nutritional status were not different between Imanaga and Traverso reconstructions after PPPD. However, a paucity of high-level evidence exists about long-term outcomes, including nutritional outcomes and quality of patients' life, which could be influenced by potential pathophysiological changes after PD according to reconstruction methods.

Some recent trials showed that removal of the pylorus could result in a lower incidence of DGE. Matsumoto *et al*[40] performed a prospective randomized comparison between PPPD and modified classical PD, and assessed the effects stomach-preserving PD on

Table 2 Incidence of delayed gastric emptying according to different gastrointestinal reconstructive methods following pancreaticoduodenectomy

Ref.	Year	Study design	Primary end point	Observations
Eshuis *et al*[81]	2014	In PPPD Antecolic (n = 125) *vs* Retrocolic (n = 121)	DGE	No differences in DGE (45 patients (36%) *vs* 41 (34%), absolute risk difference: 2.1% (95%CI: -9.8-14.0) No differences in need for postoperative nutritional support, other complications, hospital mortality, and median length of hospital stay
Tamandl *et al*[82]	2014	In PPPD, antecolic (n = 36) *vs* retrocolic (n = 28)	DGE	No differences in DGE (17.6% *vs* 23.1%, P = 0.628) No differences in length of hospital stay [13.0 (10.0-17.5) *vs* 12.5 (11.0-17.0) days; P = 0.446], time to regular diet [5 (5-7) d *vs* 5 (4-6) d, P = 0.353], and NG tube requirement [4 (3-7) d *vs* 3 (3-5) d, P = 0.600]
Imamura *et al*[83]	2014	In PPPD, antecolic (n = 58) *vs* vertical retrocolic (n = 58)	DGE	No difference in DGE (12.1% *vs* 20.7%, P = 0.316) At postoperative 6 mo, DGE was accelerated in antecolic group At postoperative 12 mo, better postoperative weight recovery in vertical retrocolic group (93.8% ± 1.2% *vs* 98.5 % ± 1.3%, P = 0.015)
Tani *et al*[84]	2014	In PD, Conventional (n = 76) *vs* Isolated Roux-en-Y (n = 77)	POPF/DGE	No differences in DGE and POPF POPF: conventional (34%) *vs* isolated Roux-en-Y (33%), P = 0.909 DGE: conventional (12%) *vs* isolated Roux-en-Y (15%), P = 0.609
Shimoda *et al*[85]	2013	In SSPPD, Billroth Ⅱ (n = 52) *vs* Roux-en-Y (n = 49)	DGE	Lower DGE in Billroth Ⅱ: (5.7% *vs* 30.4%, P = 0.028) Shorter hospital stay in Billroth Ⅱ (31.6 ± 15.0 d *vs* 41.4 ± 20.5 d, P = 0.037) Significant association between POPF and DGE (P = 0.037)
Ke *et al*[86]	2013	In PD Continuous loop (n = 109) *vs* Roux-en-Y (n = 107)	DGE/POPF	No differences in DGE and POPF POPF: continuous loop (17.6%) *vs* Roux-en-Y (15.7%), P > 0.05 DGE: continuous loop (25%) *vs* Roux-en-Y (23%), P > 0.05
Gangavatiker *et al*[87]	2011	In conventional PD and PPPD Antecolic (n = 32) *vs* Retrocolic (n = 36)	DGE	No difference in DGE (34.4% *vs* 27.8%, P = 0.6)
Kurahara *et al*[88]	2011	In SSPPD, Antecolic (n = 24) *vs* retrocolic (n = 22)	DGE	Lower incidence of DGE in the antecolic group [20.8% *vs* 50%, P = 0.0364, especially in the incidence of DGE grade B/C (4.2% *vs* 27.3%, P = 0.0234)] Significantly shorter time to full resumption of diet in antecolic group No significant difference in other postoperative complications
Chijiiwa *et al*[89]	2009	In PPPD, Antecolic (n = 17) *vs* retrocolic (n = 18)	DGE	No difference in DGE DGE: 6% *vs* 22%, P = 0.34

PPPD: Pylorus-preserving pancreaticoduodenectomy; DGE: Delayed gastric emptying; PD: Pancreaticoduodenectomy; POPF: Postoperative pancreatic fistula.

Table 3 Definition of postoperative pancreatic fistula

	Postoperative pancreatic fistula		
Grade	A	B	C
General appearance (clinical condition)	Well	Often Well	Ill appearing, Bad
Medical or interventional approach	No	Yes or No	Yes
Postoperative radiologic finding (US/CT)	Negative	Negative or Positive	Positive
Long-time drainage (≥ 21 d)	No	Usually Yes	Yes
Reoperation	No	No	Yes
Mortality related to POPF	No	No	Possibly yes
Sign of infection	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes or No	Yes or No

US: Ultrasonography; CT: Computed tomographic scan; POPF: Postoperative pancreatic fistula.

postoperative DGE occurrence and long-term nutritional status. They observed that the incidence of DGE, as assessed by the International Study Group of Pancreatic Surgery, was similar (20% *vs* 12%, P = 0.414), and long-term nutritional status indicated by serum albumin levels, serum total cholesterol levels, and body mass index during the 3-year follow-up) were also comparable between the two groups. Similarly, Kawai *et al*[41] reported their prospective, randomized, controlled study comparing PPPD and Pylorus-resecting PD (PrPD), showing that PrPD was associated with a low incidence of DGE; however, during a 6-mo follow-up period, comparable outcomes for quality of life, weight loss, and nutritional status between the two groups were observed.

REMNANT PANCREATIC FUNCTION

Previously, most concerns after PD were postoperative pancreatic fistula, because it was one of the main causes of significant morbidity and mortality related to PD. However, with advances in surgical techniques,

Table 4 Recent clinical studies about fatty liver after pancreaticoduodenectomy

Ref.	Year	Patient number	Follow-up period (mo)	Definitions of NAFLD	Incidence of fatty liver, *n* (%)	Risk factors/observation
Song *et al*[90]	2011	228	16	When CTS-L was equal to or less than 10 HU When CTL/S was equal to or less than 0.9 HU	15 (7.8)	In multivariate analysis, Pancreatic fistula (HR = 3.332, P = 0.037) External pancreatic duct stent (HR = 4.530, P = 0.017)
Sato *et al*[91]	2014	110	6	Hepatic CT value of less than 40 HU	44 (40)	In multivariate analysis, Younger age (OR = 1.079, P = 0.002), Female (OR = 6.102, P < 0.001) Small remnant pancreatic volume (< 10 mL), OR = 4.109, P = 0.009 Suspicion infection on POD7-28 (OR = 3.109, P = 0.027)
Kato *et al*[92]	2010	54	7.7 ± 2.1	Hepatic CT value of less than 40 HU a	20 (37.0)	In multivariate analysis, Pancreatic adenocarcinoma (P < 0.05) Pancreatic resection line (left side of SMA, SMA/PV) (P < 0.01) Diarrhea (P < 0.05)
Nagai *et al*[71]	2014	361	6	When CTL/S was equal to or less than 0.9 HU	30 (8.3)	In patients with NAFLD, CTL/S ratio was significantly improved by pancrelipase treatment Nutritional status by total protein, albumin, and cholesterol was significantly improved by pancrelipase treatment Severe diarrhea was improved Malnutrition after PD might be cause for postoperative NAFLD
Ito *et al*[93]	2014	100	NA	When CTL/S was equal to or less than 0.9 HU	12 (12)	In multivariate analysis, Blood loss (HR = 1.001, P = 0.016)
Nakagawa *et al*[94]	2014	104	Median 7.7 (2.5-23.6)	When CTS-L was equal to or less than 10 HU	26 (25)	In multivariate analysis, Postoperative pancreatic exocrine insufficiency (HR = 4.16, P = 0.02)
Tanaka *et al*[72]	2011	60	12	When CTL/S was equal to or less than 0.9 HU When CTL/S was equal to or less than 0.9 HU	14 (23)	In multivariate analysis, Pancreatic head cancer (OR = 12.0, P = 0.006) *De novo* NAFLD after PD was associated with body weight loss and decreases in serum levels of albumin, cholinesterase, and total cholesterol After administration of pancreatic enzyme, body weight and serum concentrations of albumin, cholinesterase, and total cholesterol were markedly increased In addition, hepatic steatosis and serum AST and ALT levels were also significantly improved by treatment *De novo* NAFLD after PD was primarily caused by pancreatic exocrine insufficiency

NAFLD: Non-alcoholic fatty liver disease; NA: Not available; AST: Aspartate transaminase; PD: Pancreaticoduodenectomy.

perioperative management, and interventional radiology, most PD-related complications can now be managed by conservative methods, and surgeons have begun to focus on long-term functional outcomes after PD.

Several reports have shown a potential relationship between morphologic changes (pancreatic atrophy, stricture, and main pancreatic duct dilatation) and remnant pancreatic function after PD[42-46]. Notably, Lemaire *et al*[47] evaluated pancreatic function, pancreatic atrophy, and main pancreatic duct dilation in the remnant pancreas after PD. They found a significant reduction in pancreatic parenchymal thickness and increased dilation of the main pancreatic duct in remnant pancreas. Finally, pancreatic atrophy tended to develop over time, and all patients were reported to have reduced levels of fecal-1 elastase. Nakamura *et al*[48] also demonstrated reduced pancreatic parenchymal thickness (atrophy), which indicated pancreatic exocrine insufficiency after PD. Therefore, this morphological change can indirectly show the some aspects of exocrine function in the remnant pancreas remain after PD. Tomimaru *et al*[49] reported a significant atrophy of the pancreatic parenchyma that occurred postoperatively in the PG and PJ groups (P < 0.0001), but these changes were more severe in the PG group than in the PJ group (P = 0.0018), suggesting that PJ was preferable to PG after PD. Fang *et al*[50] evaluated the long-term morphological and functional outcomes of the remnant pancreas after PD. The pancreatic duct diameter in the remnant pancreas usually increased, but there was no

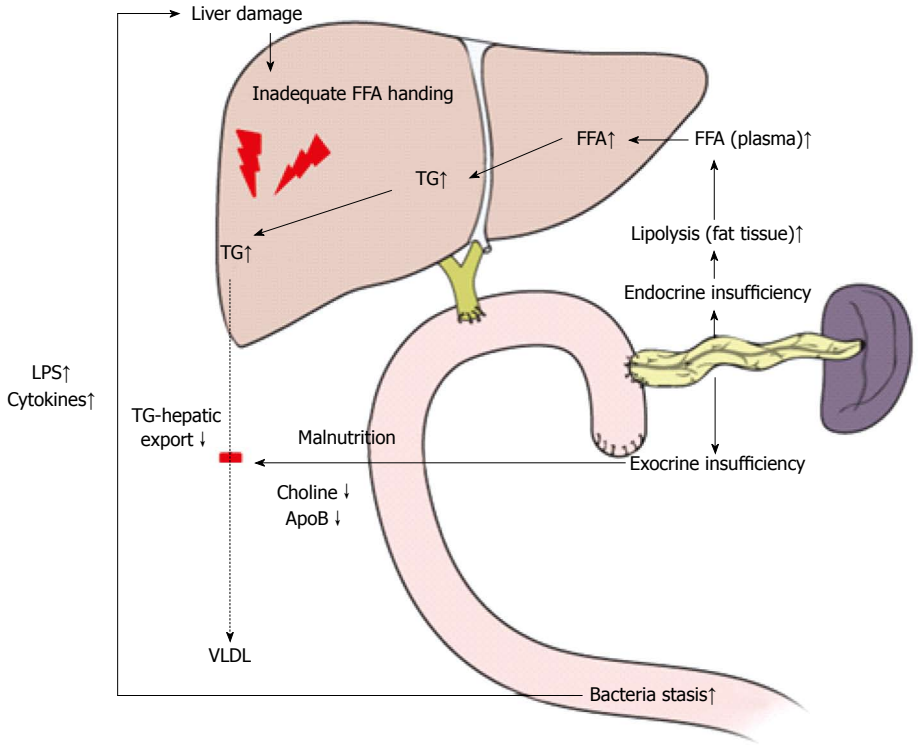

Figure 2 Mechanisms underlying non-alcoholic fatty liver disease after pancreaticoduodenectomy. FFA: Free fatty acid; TG: Triglyceride.

significant difference in the pancreatic duct diameter in both the PJ and PG groups, indicating that there was no significant difference in pancreatic exocrine or endocrine insufficiency, or pancreatic morphological changes. This evidence strongly suggests that the remnant pancreas following PD will have a chance to undergo atrophic changes and deteriorating exocrine pancreatic function after a long period of time.

Generally, there are two methods for remnant pancreatic reconstruction; PJ and PG. Several theoretical concerns exist regarding the functional outcome of the remnant pancreas following PD, which are as follows: (1) because of the absence of ampullary function, the remnant pancreas is thought to be vulnerable to regurgitation of gastrointestinal fluid into the main pancreatic duct. Most notably in PG, reflux of ingested food and low pH-gastric juice to the pancreatic duct can result in chronic inflammation, stenosis, and inactivation of pancreatic enzymes, leading to insufficiency of the remnant pancreas[51,52]; (2) in PJ, the easy activation of pancreatic enzymes can occur by intestinal enterokinase and an alkaline pH, resulting in irritating the remnant pancreas and clinically relevant pancreatic fistula[53]; and (3) reduced plasma levels of gastrin resulting from removal of the duodenum and distal part of stomach can affect atrophic changes of the remnant pancreas[15,16].

Interestingly, no significant difference in postoperative morbidity has been observed, even for postoperative pancreatic fistula[54] (POPF, Table 3), between PG and PJ[55-58]. However, a recent meta-analysis[59] demonstrated that PG was associated with lower postoperative pancreatic and biliary fistula rates in PD. One RCT dataset[60] showed that PG was related not only to a lower POPF rate but also to lower weight loss and better exocrine pancreatic function compared with PJ, suggesting that the "battle" between PG and PJ is ongoing. Most available reports on the functional outcome of the remnant pancreas following PD were based on retrospective study designs and limited numbers of patients. Most RCTs that tested PG and PJ focused on short-term perioperative outcomes, such as morbidity and mortality. Therefore, further evidence-based clinical investigations about remnant pancreatic function following PD should be performed.

NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD) is thought to be associated with excessive nutrition and is one of the most common forms of chronic liver disease[61]. This disease started to be reported in late 1980[62], and a few clinical investigations correlating fatty liver and PD reported that PD can influence hepatic fat content, which was associated with frequent hepatic steatosis[63,64]. In severe cases, even steatohepatitis leading to hepatic decompression can develop because of malnutrition after PD[65]. Therefore, surgeons need to be concerned about this condition, especially in patients expecting long-term survival following PD. Recent clinical studies of fatty liver after PD are summarized in Table 4.

The mechanisms underlying NAFLD after PD (Figure 2) might differ from usual NAFLD associated

with metabolic syndrome because NAFLD after PD was related to non-obese status, malnutrition, and a lack of hyperlipidemia or insulin resistance[66]. Most studies listed in Table 4 directly and indirectly suggest that malnutrition resulting from exocrine pancreatic insufficiency might cause NAFLD after PD. Pancreatic exocrine insufficiency induced malabsorption of essential amino acids, such as choline, which might result in the development of NAFLD after PD[67]. It has been shown that choline deficiency reduces plasma levels of apoprotein B[68], a major component very-low-density lipoprotein (VLDL), suggesting impaired hepatic export of TG in the form of VLDL. Insufficient secretion of insulin could play another role in the development of NAFLD after PD, which can enhance peripheral lipolysis and increase hepatic FFA uptake, and liver could have some difficulty in handling hepatic fat secretion by coupling triglyceride to apoprotein B[69], which plays an important role in secreting triglycerides from hepatocytes as VLDL particles. Overgrowth of small intestinal bacteria and hepatic stimulation of LPS[70] because of intestinal motor dysfunction and stasis can reduce the secretion of gastric juices and blind loops can also play an important role in NAFLD after PD. Therefore, NAFLD after PD represent the nutritional status of patients and is clinical reflection of the pathophysiological changes that occur after PD. Interestingly, NAFLD after PD is known to be associated with pancreatic cancer[71,72] and chemotherapy[73], so it will be interesting to investigate the potential correlation between the degree of post-hepatic steatosis and oncologic outcomes in resected pancreatic head cancer.

CONCLUSION

Previously, surgical techniques and safety were the only concerns regarding PD. This technique was regarded as one of the most complex and risky surgical procedures. However, as a consequence of advances in surgical experiences, techniques, and perioperative management, PD has become safer and the gold standard for treating periampullary pathologies. PD accompanies the removal of important organs and rearrangement of flow in the upper gastrointestinal tract, which can result in altered normal physiology and distinct clinical manifestations. In addition to proper surgical techniques, pancreatic surgeons need to understand these potential pathophysiological changes that can occur after PD for proper patients care in clinical practice. Further studies to link these potential pathophysiological changes with clinical outcomes will yield new insights to better understand how PD affects the lives of patients.

ACKNOWLEDGMENTS

The authors would like to express special thanks to Dong-Su Jang (Medical Illustrator, Medical Research Support Section, Yonsei University College of Medicine, Seoul, Korea) for his excellent illustrations in the papers.

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P- Reviewer: Bove A, Cho A, Goetze TO, Marrelli D
S- Editor: Ma YJ **L- Editor**: A **E- Editor**: Liu XM

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ISSN 1007-9327