**Pathophysiology after Pancreaticoduodenectomy**

Chang Moo Kang, M.D., Ph.D. and Jin Ho Lee, M.D.

Department of Hepatobiliary and Pancreatic Surgery, Yonsei University College of Medicine

Pancreaticobiliary Cancer Clinic, Yonsei Cancer Center, Severance Hospital, Seoul, Korea

**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](#_ENREF_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 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% [[2-5](#_ENREF_2)]. 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. **(2)** *Reconstruction phase*: gastrointestinal continuity is created by pancreatico-enterostomy (pancreaticogastrostomy or pancreaticojejunostomy), 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
* Metabolic surgery-like effects
* Alignment effects of GI continuity
* Remnant pancreatic function
* Non-alcoholic fatty liver disease

**Effects of Duodenectomy**

The duodenum is a source of various peptide hormones. Among them, motilin is a 22 amino acid peptide that is primarily localized in enterochromaffin cells of the duodenum and proximal jejunum[[6](#_ENREF_6)], which is known to be responsible for phase III activity of the gastroduodenal migrating motor complex (MMC)[[6](#_ENREF_6)]. 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[[7](#_ENREF_7)] 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[[8](#_ENREF_8)] 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[[9](#_ENREF_9)] and postvagotomy gastroparesis[[10](#_ENREF_10)]. Masunaga et al[[11](#_ENREF_11)] 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[[12](#_ENREF_12)] showed that plasma levels of pancreatic polypeptide (PP) were altered with no cyclic pattern in duodenectomized dogs. Muller et al[[13](#_ENREF_13)] 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[[14](#_ENREF_14)], and Kingsnorth et al[[15](#_ENREF_15)] 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[[16](#_ENREF_16)]. Jang et al[[17](#_ENREF_17)] 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[[18](#_ENREF_18)] 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 months, 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[[19](#_ENREF_19),[20](#_ENREF_20)].

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%)[[21](#_ENREF_21)]. 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).[[22](#_ENREF_22),[23](#_ENREF_23)] Recently, You et al[[24](#_ENREF_24)] showed that ~30% of patients with PD were found to have hypertrophic changes in the remnant pancreas, and Wu et al[[25](#_ENREF_25)] 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 after PD[[26](#_ENREF_26)], several studies have investigated changes in plasma GLP-1 levels after PD. Ohtsuka et al[[27](#_ENREF_27)] 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[[28](#_ENREF_28)] 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[[29](#_ENREF_29)]. Harmuth et al[[30](#_ENREF_30)] 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[[31](#_ENREF_31)]. 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[[32](#_ENREF_32)]. Additionally, activation of the GLP-1 receptor was found to inhibit growth and promote apoptosis of human pancreatic cancer cells[[33](#_ENREF_33)]. 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)[[34](#_ENREF_34)], Billroth II (the Whipple and/or Child method)[[35](#_ENREF_35)], Roux-en-Y loop fashion[[36](#_ENREF_36)], an additional Braun anastomosis[[37](#_ENREF_37)], and retrocolic/antecolic reconstruction[[38](#_ENREF_38)]. 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[[39](#_ENREF_39)] demonstrated that fat absorption after Billroth I pancreaticogastrostomy (PG-I) is superior to that after Billroth II pancreaticojejunostomy (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[[40](#_ENREF_40)] 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[[41](#_ENREF_41)] performed a prospective randomized comparison between PPPD and modified classical PD, and assessed the effects stomach-preserving PD on 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[[42](#_ENREF_42)] 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-month 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, 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[[43-47](#_ENREF_43)]. Notably, Lemaire et al[[48](#_ENREF_48)] 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[[49](#_ENREF_49)] 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[[50](#_ENREF_50)] 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. Fnag et al[[51](#_ENREF_51)] 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 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; pancreaticojejunostomy (PJ) and pancreaticogastrostomy (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[[52](#_ENREF_52),[53](#_ENREF_53)]. (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[[54](#_ENREF_54)]. (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[[16](#_ENREF_16),[17](#_ENREF_17)].

Interestingly, no significant difference in postoperative morbidity has been observed, even for postoperative pancreatic fistula[[55](#_ENREF_55)] (POPF, **Table 3**), between PG and PJ[[56-59](#_ENREF_56)]. However, a recent meta-analysis[[60](#_ENREF_60)] demonstrated that PG was associated with lower postoperative pancreatic and biliary fistula rates in PD. One RCT dataset[[61](#_ENREF_61)] 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[[62](#_ENREF_62)]. This disease started to be reported in late 1980[[63](#_ENREF_63)], 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[[64](#_ENREF_64),[65](#_ENREF_65)]. In severe cases, even steatohepatitis leading to hepatic decompression can develop because of malnutrition after PD[[66](#_ENREF_66)]. 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[[67](#_ENREF_67)]. 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[[68](#_ENREF_68)]. It has been shown that choline deficiency reduces plasma levels of apoprotein B[[69](#_ENREF_69)], a major component 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[[70](#_ENREF_70)], which plays an important role in secreting triglycerides from hepatocytes as very-low-density lipoprotein (VLDL) particles. Overgrowth of small intestinal bacteria and hepatic stimulation of LPS[[71](#_ENREF_71)] 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[[72](#_ENREF_72),[73](#_ENREF_73)] and chemotherapy[[74](#_ENREF_74)], 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.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Authors | Year | Study Design & Model | Primary End point | Observations  |
| Tanaka, et al[[75](#_ENREF_75)] | 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[[76](#_ENREF_76)] | 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[[77](#_ENREF_77)] | 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[[78](#_ENREF_78)] | 1989 |  Normal dog vs. Duodenectomized dog | pancreatic trypsinGI motilityplasma 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[[79](#_ENREF_79)] | 1976 | Normal dog | GI motilityplasma 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[[80](#_ENREF_80)] | 1979 | Human | GI motilityplasma motilin level | The effect of exogenous motilin on interdigestive migrating motor complex (MMC)-plasma motilin levels is one of the factor involved in the production of the activity front of the MMC in man |
| Sarna, et al[[81](#_ENREF_81)] | 1983 | Normal dog | plasma motilin levelsmigrating myoelectric complexes (MMCs) | Cause and effect relationship between plasma motilin levels and migrating myoelectric complexes (MMCs)-endogenous motilin does not initiate spontaneous MMCs-MMC contractions release motilin |

**Table 1.** An experimental study showing the relationship between motilin and duodenectomy

**Table 2.** The incidence of DGE according to different gastrointestinal reconstructive methods following PD

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Authors | Year | Study Design | Primary End point | Observations  |
| Eshuis, et al[[82](#_ENREF_82)] | 2014 | In PPPDAntecolic (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[[83](#_ENREF_83)] | 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) vs. 5 (4–6) days; p = 0.353), and NG tube requirement (4 (3–7) vs. 3 (3–5) days; p = 0.600)  |
| Imamura, et al[[84](#_ENREF_84)] | 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 month, DGE was accelerated in antecolic group\*At postoperative 12 months, better postoperative weight recovery in vertical retrocolic group (93.8 ± 1.2%; vs. 98.5 ± 1.3%, p = 0.015) |
| Tani et al[[85](#_ENREF_85)] | 2014 | In PD,Conventional (n=76) vs. Isolated Roux-en-Y (n=77) | POPF/DGE | No differences in DGE and POPFPOPF: conventional (34%) vs. Isolated Roux-en-Y (33%), p=0.909DGE: conventional (12%) vs. Isolated Roux-en-Y (15%), p=0.609 |
| Shimoda, et al[[86](#_ENREF_86)] | 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 days vs. 41.4 ± 20.5 days, P = 0.037)Significant association between POPF and DGE (p=0.037)  |
| Ke, et al[[87](#_ENREF_87)] | 2013 | In PDContinuous loop (n=109) vs. Roux-en-Y (n=107) | DGE/POPF | No differences in DGE and POPFPOPF: continuous loop (17.6%)vs. Roux-en-Y (15.7%), p>0.05DGE: continuous loop (25%) vs. Roux-en-Y (23%), p>0.05 |
| Gangavatiker, et al[[88](#_ENREF_88)] | 2011 | In conventional PD & PPPDAntecolic (n=32) vs. Retrocolic (n=36) | DGE | No difference in DGE(34.4% vs. 27.8%; p = 0.6) |
| Kurahara, et al[[89](#_ENREF_89)] | 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 antecholic group. No significant difference in other postoperative complications. |
| Chijiiwa K, et al[[90](#_ENREF_90)] | 2009 | In PPPD,Antecolic (n=17) vs. retrocolic (n=18) | DGE | No difference in DGEDGE: 6% vs. 22%, p=0.34 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Authors |  Year | Patient Number | Follow-up period (months) | Definitions of NAFLD | Incidence of fatty liver, N (%) | Risk factors/ Observation |
| Song, et al[[91](#_ENREF_91)] | 2011 | 228 | 16 | when CTS-L was equal to or less than 10 HUwhen 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[[92](#_ENREF_92)] | 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[[93](#_ENREF_93)] | 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) |
| Nagi, et al[[72](#_ENREF_72)] | 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 pancrealipase treatment.Nutritional status by total protein, albumin, and cholesterol was significantly improved by pancrealipase treatment severe diarrhea was improved. Malnutrition after PD might be cause for postoperative NAFLD |
| Ito, et al.[[94](#_ENREF_94)] | 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) |
| Nagakawa, et al | 2014 | 104 | median 7.7 (2.5-23.6) | when CTS-L was equal to or less than 10 HUwhen CTL/S was equal to or less than 0.9 HU | 26 (25) | In multivariate analysis,postoperative pancreatic exocrine insufficiency (HR=4.16, P=0.02) |
| Tanaka, et al[[73](#_ENREF_73)] | 2011 | 60 | 12 | 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 primarilycaused by pancreatic exocrine insufficiency. |

**Table 4.** Recent clinical studies of fatty liver after PD

**Table 3**. Definition of POPF

|  |  |
| --- | --- |
|  | Postoperative Pancreatic Fistula (POPF) |
| 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 days) | 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

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



**Figure 2.** The mechanisms underlying NAFLD after PD.



**References**

1 Fortner JG. Regional pancreatectomy for cancer of the pancreas, ampulla and other related sites. *Jpn J Surg* 1983; **13**: 385-394 [PMID:6366309]

2 Wellner UF, Sick O, Olschewski M, Adam U, Hopt UT, Keck T. Randomized controlled single-center trial comparing pancreatogastrostomy versus pancreaticojejunostomy after partial pancreatoduodenectomy. *J Gastrointest Surg* 2012; **16**: 1686-1695 [PMID:22744638 DOI:10.1007/s11605-012-1940-4]

3 Topal B, Fieuws S, Aerts R, Weerts J, Feryn T, Roeyen G, Bertrand C, Hubert C, Janssens M, Closset J, Belgian Section of H, Pancreatic S. Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy for pancreatic or periampullary tumours: a multicentre randomised trial. *Lancet Oncol* 2013; **14**: 655-662 [PMID:23643139 DOI:10.1016/S1470-2045(13)70126-8]

4 Figueras J, Sabater L, Planellas P, Munoz-Forner E, Lopez-Ben S, Falgueras L, Sala-Palau C, Albiol M, Ortega-Serrano J, Castro-Gutierrez E. Randomized clinical trial of pancreaticogastrostomy versus pancreaticojejunostomy on the rate and severity of pancreatic fistula after pancreaticoduodenectomy. *Br J Surg* 2013; **100**: 1597-1605 [PMID:24264781 DOI:10.1002/bjs.9252]

5 Fernandez-Cruz L, Cosa R, Blanco L, Lopez-Boado MA, Astudillo E. Pancreatogastrostomy with gastric partition after pylorus-preserving pancreatoduodenectomy versus conventional pancreatojejunostomy: a prospective randomized study. *Ann Surg* 2008; **248**: 930-938 [PMID:19092337 DOI:10.1097/SLA.0b013e31818fefc7]

6 Brown JC, Cook MA, Dryburgh JR. Motilin, a gastric motor activity-stimulating polypeptide: final purification, amino acid composition, and C-terminal residues. *Gastroenterology* 1972; **62**: 401-404 [PMID:5011531]

7 Naritomi G, Tanaka M, Matsunaga H, Yokohata K, Ogawa Y, Chijiiwa K, Yamaguchi K. Pancreatic head resection with and without preservation of the duodenum: different postoperative gastric motility. *Surgery* 1996; **120**: 831-837 [PMID:8909518]

8 Yeo CJ, Barry MK, Sauter PK, Sostre S, Lillemoe KD, Pitt HA, Cameron JL. Erythromycin accelerates gastric emptying after pancreaticoduodenectomy. A prospective, randomized, placebo-controlled trial. *Ann Surg* 1993; **218**: 229-237; discussion 237-228 [PMID:8103982]

9 Janssens J, Peeters TL, Vantrappen G, Tack J, Urbain JL, De Roo M, Muls E, Bouillon R. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. *N Engl J Med* 1990; **322**: 1028-1031 [PMID:2320062 DOI:10.1056/NEJM199004123221502]

10 Mozwecz H, Pavel D, Pitrak D, Orellana P, Schlesinger PK, Layden TJ. Erythromycin stearate as prokinetic agent in postvagotomy gastroparesis. *Dig Dis Sci* 1990; **35**: 902-905 [PMID:2364846]

11 Matsunaga H, Tanaka M, Takahata S, Ogawa Y, Naritomi G, Yokohata K, Yamaguchi K, Chijiiwa K. Manometric evidence of improved early gastric stasis by erythromycin after pylorus-preserving pancreatoduodenectomy. *World J Surg* 2000; **24**: 1236-1241; discussion 1242 [PMID:11071469]

12 Malfertheiner P, Sarr MG, Nelson DK, DiMagno EP. Role of the duodenum in postprandial release of pancreatic and gastrointestinal hormones. *Pancreas* 1994; **9**: 13-19 [PMID:8108366]

13 Muller MW, Friess H, Beger HG, Kleeff J, Lauterburg B, Glasbrenner B, Riepl RL, Buchler MW. Gastric emptying following pylorus-preserving Whipple and duodenum-preserving pancreatic head resection in patients with chronic pancreatitis. *Am J Surg* 1997; **173**: 257-263 [PMID:9136776 DOI:10.1016/S0002-9610(96)00402-3]

14 Tangoku A, Nishikawa M, Adachi A, Suzuki T. Plasma gastrin and cholecystokinin response after pylorus-preserving pancreatoduodenectomy with Billroth-I type of reconstruction. *Ann Surg* 1991; **214**: 56-60 [PMID:2064472]

15 Kingsnorth AN, Formela LJ, Chen D, Rehfeld JF. Plasma gastrin and cholecystokinin responses after pylorus-preserving pancreatoduodenectomy and defunctioned Roux loop pancreaticojejunostomy. *Br J Surg* 1994; **81**: 1356-1359 [PMID:7953412]

16 Hashimoto N, Yasuda T, Haji S, Nomura H, Ohyanagi H. Comparison of the functional and morphological changes in the pancreatic remnant between pylorus-preserving pancreatoduodenectomy and pancreatoduodenectomy. *Hepatogastroenterology* 2003; **50**: 2229-2232 [PMID:14696504]

17 Jang JY, Kim SW, Han JK, Park SJ, Park YC, Joon Ahn Y, Park YH. Randomized prospective trial of the effect of induced hypergastrinemia on the prevention of pancreatic atrophy after pancreatoduodenectomy in humans. *Ann Surg* 2003; **237**: 522-529 [PMID:12677149 DOI:10.1097/01.SLA.0000059985.56982.11]

18 Chung SA, Rotstein O, Greenberg GR, Diamant NE. Mechanisms coordinating gastric and small intestinal MMC: role of extrinsic innervation rather than motilin. *Am J Physiol* 1994; **267**: G800-809 [PMID:7977742]

19 Iqbal N, Lovegrove RE, Tilney HS, Abraham AT, Bhattacharya S, Tekkis PP, Kocher HM. A comparison of pancreaticoduodenectomy with extended pancreaticoduodenectomy: a meta-analysis of 1909 patients. *Eur J Surg Oncol* 2009; **35**: 79-86 [PMID:18356005 DOI:10.1016/j.ejso.2008.01.002]

20 Michalski CW, Kleeff J, Wente MN, Diener MK, Buchler MW, Friess H. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. *Br J Surg* 2007; **94**: 265-273 [PMID:17318801 DOI:10.1002/bjs.5716]

21 Buchwald H, Oien DM. Metabolic/bariatric surgery worldwide 2011. *Obes Surg* 2013; **23**: 427-436 [PMID:23338049 DOI:10.1007/s11695-012-0864-0]

22 Larsen PJ, Tang-Christensen M, Holst JJ, Orskov C. Distribution of glucagon-like peptide-1 and other preproglucagon-derived peptides in the rat hypothalamus and brainstem. *Neuroscience* 1997; **77**: 257-270 [PMID:9044391]

23 Miras AD, le Roux CW. Mechanisms underlying weight loss after bariatric surgery. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 575-584 [PMID:23835488 DOI:10.1038/nrgastro.2013.119]

24 You DD, Choi SH, Choi DW, Heo JS, Ho CY, Kim WS. Long-term effects of pancreaticoduodenectomy on glucose metabolism. *ANZ J Surg* 2012; **82**: 447-451 [PMID:22571457 DOI:10.1111/j.1445-2197.2012.06080.x]

25 Wu JM, Kuo TC, Yang CY, Chiang PY, Jeng YM, Huang PH, Tien YW. Resolution of diabetes after pancreaticoduodenectomy in patients with and without pancreatic ductal cell adenocarcinoma. *Ann Surg Oncol* 2013; **20**: 242-249 [PMID:22864799 DOI:10.1245/s10434-012-2577-y]

26 Mori Y, Ohtsuka T, Tsutsumi K, Yasui T, Ueda J, Takahata S, Nakamura M, Tanaka M. Different incretin responses after pancreatoduodenectomy and distal pancreatectomy. *Pancreas* 2012; **41**: 455-460 [PMID:22422137 DOI:10.1097/MPA.0b013e3182319d7c]

27 Ohtsuka T, Kitahara K, Kohya N, Miyoshi A, Miyazaki K. Improvement of glucose metabolism after a pancreatoduodenectomy. *Pancreas* 2009; **38**: 700-705 [PMID:19506534 DOI:10.1097/MPA.0b013e3181a7c916]

28 Muscogiuri G, Mezza T, Prioletta A, Sorice GP, Clemente G, Sarno G, Nuzzo G, Pontecorvi A, Holst JJ, Giaccari A. Removal of duodenum elicits GLP-1 secretion. *Diabetes Care* 2013; **36**: 1641-1646 [PMID:23393218 DOI:10.2337/dc12-0811]

29 Korner J, Bessler M, Inabnet W, Taveras C, Holst JJ. Exaggerated glucagon-like peptide-1 and blunted glucose-dependent insulinotropic peptide secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. *Surg Obes Relat Dis* 2007; **3**: 597-601 [PMID:17936091 DOI:10.1016/j.soard.2007.08.004]

30 Harmuth S, Wewalka M, Holst JJ, Nemecek R, Thalhammer S, Schmid R, Sahora K, Gnant M, Miholic J. Distal gastrectomy in pancreaticoduodenectomy is associated with accelerated gastric emptying, enhanced postprandial release of GLP-1, and improved insulin sensitivity. *J Gastrointest Surg* 2014; **18**: 52-59 [PMID:24002756 DOI:10.1007/s11605-013-2283-5]

31 Nauck MA, Friedrich N. Do GLP-1-based therapies increase cancer risk? *Diabetes Care* 2013; **36 Suppl 2**: S245-252 [PMID:23882053 DOI:10.2337/dcS13-2004]

32 Zhao H, Wang L, Wei R, Xiu D, Tao M, Ke J, Liu Y, Yang J, Hong T. Activation of glucagon-like peptide-1 receptor inhibits tumourigenicity and metastasis of human pancreatic cancer cells via PI3K/Akt pathway. *Diabetes Obes Metab* 2014; **16**: 850-860 [PMID:24641303 DOI:10.1111/dom.12291]

33 Zhao H, Wei R, Wang L, Tian Q, Tao M, Ke J, Liu Y, Hou W, Zhang L, Yang J, Hong T. Activation of glucagon-like peptide-1 receptor inhibits growth and promotes apoptosis of human pancreatic cancer cells in a cAMP-dependent manner. *Am J Physiol Endocrinol Metab* 2014; **306**: E1431-1441 [PMID:24801389 DOI:10.1152/ajpendo.00017.2014]

34 Imanaga H. A new method of pancreaticoduodenectomy designed to preserve liver and pancreatic function. *Surgery* 1960; **47**: 577-586 [PMID:13852739]

35 Whipple AO, Parsons WB, Mullins CR. Treatment of Carcinoma of the Ampulla of Vater. *Ann Surg* 1935; **102**: 763-779 [PMID:17856666]

36 Kingsnorth AN, Berg JD, Gray MR. A novel reconstructive technique for pylorus-preserving pancreaticoduodenectomy: avoidance of early postoperative gastric stasis. *Ann R Coll Surg Engl* 1993; **75**: 38-42 [PMID:8093656]

37 Hochwald SN, Grobmyer SR, Hemming AW, Curran E, Bloom DA, Delano M, Behrns KE, Copeland EM, Vogel SB. Braun enteroenterostomy is associated with reduced delayed gastric emptying and early resumption of oral feeding following pancreaticoduodenectomy. *J Surg Oncol* 2010; **101**: 351-355 [PMID:20112274 DOI:10.1002/jso.21490]

38 Tani M, Terasawa H, Kawai M, Ina S, Hirono S, Uchiyama K, Yamaue H. Improvement of delayed gastric emptying in pylorus-preserving pancreaticoduodenectomy: results of a prospective, randomized, controlled trial. *Ann Surg* 2006; **243**: 316-320 [PMID:16495694 DOI:10.1097/01.sla.0000201479.84934.ca]

39 Miyakawa S, Niwamoto N, Horiguchi A, Hanai T, Mizuno K, Ishihara S, Miura K. Fat absorption after pylorus-preserving pancreatoduodenectomy reconstructed with Billroth II pancreaticojejunostomy or Billroth I pancreaticogastrostomy. *Hepatogastroenterology* 2000; **47**: 264-268 [PMID:10690619]

40 Ohtsuka T, Yamaguchi K, Chijiiwa K, Tanaka M. Effect of gastrointestinal reconstruction on quality of life and nutritional status after pylorus-preserving pancreatoduodenectomy. *Dig Dis Sci* 2002; **47**: 1241-1247 [PMID:12064798]

41 Matsumoto I, Shinzeki M, Asari S, Goto T, Shirakawa S, Ajiki T, Fukumoto T, Suzuki Y, Ku Y. A prospective randomized comparison between pylorus- and subtotal stomach-preserving pancreatoduodenectomy on postoperative delayed gastric emptying occurrence and long-term nutritional status. *Journal of Surgical Oncology* 2014; **109**: 690-696 [DOI:10.1002/jso.23566]

42 Kawai M, Tani M, Hirono S, Okada K-i, Miyazawa M, Yamaue H. Pylorus-Resecting Pancreaticoduodenectomy Offers Long-Term Outcomes Similar to Those of Pylorus-Preserving Pancreaticoduodenectomy: Results of a Prospective Study. *World Journal of Surgery* 2014; **38**: 1476-1483 [DOI:10.1007/s00268-013-2420-z]

43 Yoo D, Hwang S, Kim KH, Ahn CS, Moon DB, Ha TY, Jung DH, Park GC, Jung BH, Kang SH, Lee SG. Pancreatic atrophy relative to external versus internal drainage of the pancreatic duct after pylorus-preserving pancreaticoduodenectomy. *J Gastrointest Surg* 2014; **18**: 1604-1609 [PMID:25002021 DOI:10.1007/s11605-014-2583-4]

44 Kitamura T, Anaguchi-Hirao R, Kouhara H. Combination of type 2 diabetes and malnutrition worsened by anastomotic stenosis and pancreas atrophy following resection of pancreas head. *Intern Med* 2008; **47**: 1225-1230 [PMID:18591845]

45 Kim JH, Yoo BM, Kim JH, Kim WH. Which method should we select for pancreatic anastomosis after pancreaticoduodenectomy? *World J Surg* 2009; **33**: 326-332 [PMID:19057947 DOI:10.1007/s00268-008-9827-y]

46 Sato N, Yamaguchi K, Yokohata K, Shimizu S, Chijiiwa K, Tanaka M. Long-term morphological changes of remnant pancreas and biliary tree after pancreatoduodenectomy on CT. *Int Surg* 1998; **83**: 136-140 [PMID:9851331]

47 Nakamura H, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Ohge H, Sueda T. Predictive factors for exocrine pancreatic insufficiency after pancreatoduodenectomy with pancreaticogastrostomy. *J Gastrointest Surg* 2009; **13**: 1321-1327 [PMID:19415402 DOI:10.1007/s11605-009-0896-5]

48 Lemaire E, O'Toole D, Sauvanet A, Hammel P, Belghiti J, Ruszniewski P. Functional and morphological changes in the pancreatic remnant following pancreaticoduodenectomy with pancreaticogastric anastomosis. *Br J Surg* 2000; **87**: 434-438 [PMID:10759738 DOI:10.1046/j.1365-2168.2000.01388.x]

49 Nakamura H, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Ohge H, Sueda T. Reduced pancreatic parenchymal thickness indicates exocrine pancreatic insufficiency after pancreatoduodenectomy. *J Surg Res* 2011; **171**: 473-478 [PMID:20605585 DOI:10.1016/j.jss.2010.03.052]

50 Tomimaru Y, Takeda Y, Kobayashi S, Marubashi S, Lee CM, Tanemura M, Nagano H, Kitagawa T, Dono K, Umeshita K, Wakasa K, Monden M. Comparison of postoperative morphological changes in remnant pancreas between pancreaticojejunostomy and pancreaticogastrostomy after pancreaticoduodenectomy. *Pancreas* 2009; **38**: 203-207 [PMID:19034058 DOI:10.1097/MPA.0b013e31818e1772]

51 Fang WL, Su CH, Shyr YM, Chen TH, Lee RC, Tai LC, Wu CW, Lui WY. Functional and morphological changes in pancreatic remnant after pancreaticoduodenectomy. *Pancreas* 2007; **35**: 361-365 [PMID:18090244 DOI:10.1097/MPA.0b013e3180d0a8d5]

52 Idezuki Y, Goetz FC, Lillehei RC. Late effect of pancreatic duct ligation on beta cell function. *Am J Surg* 1969; **117**: 33-39 [PMID:4882420]

53 Ohshio G, Saluja A, Steer ML. Effects of short-term pancreatic duct obstruction in rats. *Gastroenterology* 1991; **100**: 196-202 [PMID:1700960]

54 Mackie JA, Rhoads JE, Park CD. Pancreaticogastrostomy: a further evaluation. *Ann Surg* 1975; **181**: 541-545 [PMID:1130872]

55 Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M, International Study Group on Pancreatic Fistula D. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005; **138**: 8-13 [PMID:16003309 DOI:10.1016/j.surg.2005.05.001]

56 Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak ML, Talamini MA, Lillemoe KD, Pitt HA. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. *Ann Surg* 1995; **222**: 580-588; discussion 588-592 [PMID:7574936]

57 Bassi C, Falconi M, Molinari E, Salvia R, Butturini G, Sartori N, Mantovani W, Pederzoli P. Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study. *Ann Surg* 2005; **242**: 767-771, discussion 771-763 [PMID:16327486]

58 Duffas JP, Suc B, Msika S, Fourtanier G, Muscari F, Hay JM, Fingerhut A, Millat B, Radovanowic A, Fagniez PL, French Associations for Research in S. A controlled randomized multicenter trial of pancreatogastrostomy or pancreatojejunostomy after pancreatoduodenectomy. *Am J Surg* 2005; **189**: 720-729 [PMID:15910726 DOI:10.1016/j.amjsurg.2005.03.015]

59 Wente MN, Shrikhande SV, Muller MW, Diener MK, Seiler CM, Friess H, Buchler MW. Pancreaticojejunostomy versus pancreaticogastrostomy: systematic review and meta-analysis. *Am J Surg* 2007; **193**: 171-183 [PMID:17236843 DOI:10.1016/j.amjsurg.2006.10.010]

60 Menahem B, Guittet L, Mulliri A, Alves A, Lubrano J. Pancreaticogastrostomy Is Superior to Pancreaticojejunostomy for Prevention of Pancreatic Fistula After Pancreaticoduodenectomy: An Updated Meta-analysis of Randomized Controlled Trials. *Ann Surg* 2014 [PMID:24979604 DOI:10.1097/sla.0000000000000806]

61 Figueras J, Sabater L, Planellas P, Muñoz-Forner E, Lopez-Ben S, Falgueras L, Sala-Palau C, Albiol M, Ortega-Serrano J, Castro-Gutierrez E. Randomized clinical trial of pancreaticogastrostomy versus pancreaticojejunostomy on the rate and severity of pancreatic fistula after pancreaticoduodenectomy. *British Journal of Surgery* 2013; **100**: 1597-1605 [DOI:10.1002/bjs.9252]

62 Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221-1231 [PMID:11961152 DOI:10.1056/NEJMra011775]

63 Kita T, Nakamura K, Kida H, Kawarada Y, Mizumoto R. [Pathophysiology during follow-up after extensive pancreatectomy]. *Nihon Geka Gakkai Zasshi* 1988; **89**: 1426-1429 [PMID:3226397]

64 Nirei K, Ogihara N, Kawamura W, Kang W, Moriyama M. Rapid recovery from acute liver failure secondary to pancreatoduodenectomy-related non-alcoholic steatohepatitis. *Case Rep Gastroenterol* 2013; **7**: 49-55 [PMID:23467319 DOI:10.1159/000347154]

65 Nomura R, Ishizaki Y, Suzuki K, Kawasaki S. Development of hepatic steatosis after pancreatoduodenectomy. *AJR Am J Roentgenol* 2007; **189**: 1484-1488 [PMID:18029889 DOI:10.2214/AJR.07.2809]

66 Sim EH, Kwon JH, Kim SY, Jung SM, Maeng LS, Jang JW, Chung KW. Severe steatohepatitis with hepatic decompensation resulting from malnutrition after pancreaticoduodenectomy. *Clin Mol Hepatol* 2012; **18**: 404-410 [PMID:23323257 DOI:10.3350/cmh.2012.18.4.404]

67 Satoh D, Yagi T, Nagasaka T, Shinoura S, Umeda Y, Yoshida R, Utsumi M, Tanaka T, Sadamori H, Fujiwara T. CD14 upregulation as a distinct feature of non-alcoholic fatty liver disease after pancreatoduodenectomy. *World J Hepatol* 2013; **5**: 189-195 [PMID:23671723 DOI:10.4254/wjh.v5.i4.189]

68 Tanaka N, Takahashi S, Fang Z-Z, Matsubara T, Krausz KW, Qu A, Gonzalez FJ. Role of white adipose lipolysis in the development of NASH induced by methionine- and choline-deficient diet. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 2014; **1841**: 1596-1607 [DOI:<http://dx.doi.org/10.1016/j.bbalip.2014.08.015>]

69 Yao ZM, Vance DE. Reduction in VLDL, but not HDL, in plasma of rats deficient in choline. *Biochem Cell Biol* 1990; **68**: 552-558 [PMID:2344402]

70 Soliman AT, Alsalmi I, Asfour M. Hypoinsulinaemia has an important role in the development of oedema and hepatomegaly during malnutrition. *J Trop Pediatr* 1996; **42**: 297-299 [PMID:8936962]

71 Lewis JR, Mohanty SR. Nonalcoholic fatty liver disease: a review and update. *Dig Dis Sci* 2010; **55**: 560-578 [PMID:20101463 DOI:10.1007/s10620-009-1081-0]

72 Nagai M, Sho M, Satoi S, Toyokawa H, Akahori T, Yanagimoto H, Yamamoto T, Hirooka S, Yamaki S, Kinoshita S, Nishiwada S, Ikeda N, Kwon AH, Nakajima Y. Effects of pancrelipase on nonalcoholic fatty liver disease after pancreaticoduodenectomy. *J Hepatobiliary Pancreat Sci* 2014; **21**: 186-192 [PMID:23798362 DOI:10.1002/jhbp.14]

73 Tanaka N, Horiuchi A, Yokoyama T, Kaneko G, Horigome N, Yamaura T, Nagaya T, Komatsu M, Sano K, Miyagawa S, Aoyama T, Tanaka E. Clinical characteristics of de novo nonalcoholic fatty liver disease following pancreaticoduodenectomy. *J Gastroenterol* 2011; **46**: 758-768 [PMID:21267748 DOI:10.1007/s00535-011-0370-5]

74 Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *Br J Surg* 2007; **94**: 274-286 [PMID:17315288 DOI:10.1002/bjs.5719]

75 Tanaka M, Sarr MG. Total duodenectomy: effect on canine gastrointestinal motility. *J Surg Res* 1987; **42**: 483-493 [PMID:3586622]

76 Tanaka M, Sarr MG. Role of the duodenum in the control of canine gastrointestinal motility. *Gastroenterology* 1988; **94**: 622-629 [PMID:3338632]

77 Suzuki H, Mochiki E, Haga N, Shimura T, Itoh Z, Kuwano H. Effect of duodenectomy on gastric motility and gastric hormones in dogs. *Ann Surg* 2001; **233**: 353-359 [PMID:11224622]

78 Malfertheiner P, Sarr MG, Spencer MP, DiMagno EP. Effect of duodenectomy on interdigestive pancreatic secretion, gastrointestinal motility, and hormones in dogs. *Am J Physiol* 1989; **257**: G415-422 [PMID:2782411]

79 Itoh Z, Honda R, Hiwatashi K, Takeuchi S, Aizawa I, Takayanagi R, Couch EF. Motilin-induced mechanical activity in the canine alimentary tract. *Scand J Gastroenterol Suppl* 1976; **39**: 93-110 [PMID:1069368]

80 Vantrappen G, Janssens J, Peeters TL, Bloom SR, Christofides ND, Hellemans J. Motilin and the interdigestive migrating motor complex in man. *Dig Dis Sci* 1979; **24**: 497-500 [PMID:456236]

81 Sarna S, Chey WY, Condon RE, Dodds WJ, Myers T, Chang TM. Cause-and-effect relationship between motilin and migrating myoelectric complexes. *Am J Physiol* 1983; **245**: G277-284 [PMID:6192727]

82 Eshuis WJ, van Eijck CH, Gerhards MF, Coene PP, de Hingh IH, Karsten TM, Bonsing BA, Gerritsen JJ, Bosscha K, Spillenaar Bilgen EJ, Haverkamp JA, Busch OR, van Gulik TM, Reitsma JB, Gouma DJ. Antecolic versus retrocolic route of the gastroenteric anastomosis after pancreatoduodenectomy: a randomized controlled trial. *Ann Surg* 2014; **259**: 45-51 [PMID:24096769 DOI:10.1097/SLA.0b013e3182a6f529]

83 Tamandl D, Sahora K, Prucker J, Schmid R, Holst JJ, Miholic J, Goetzinger P, Gnant M. Impact of the reconstruction method on delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy: a prospective randomized study. *World J Surg* 2014; **38**: 465-475 [PMID:24121364 DOI:10.1007/s00268-013-2274-4]

84 Imamura N, Chijiiwa K, Ohuchida J, Hiyoshi M, Nagano M, Otani K, Kondo K. Prospective randomized clinical trial of a change in gastric emptying and nutritional status after a pylorus-preserving pancreaticoduodenectomy: comparison between an antecolic and a vertical retrocolic duodenojejunostomy. *HPB (Oxford)* 2014; **16**: 384-394 [PMID:23991719 DOI:10.1111/hpb.12153]

85 Tani M, Kawai M, Hirono S, Okada KI, Miyazawa M, Shimizu A, Kitahata Y, Yamaue H. Randomized clinical trial of isolated Roux-en-Y versus conventional reconstruction after pancreaticoduodenectomy. *Br J Surg* 2014; **101**: 1084-1091 [PMID:24975853 DOI:10.1002/bjs.9544]

86 Shimoda M, Kubota K, Katoh M, Kita J. Effect of billroth II or Roux-en-Y reconstruction for the gastrojejunostomy on delayed gastric emptying after pancreaticoduodenectomy: a randomized controlled study. *Ann Surg* 2013; **257**: 938-942 [PMID:23579543 DOI:10.1097/SLA.0b013e31826c3f90]

87 Ke S, Ding XM, Gao J, Zhao AM, Deng GY, Ma RL, Xin ZH, Ning CM, Sun WB. A prospective, randomized trial of Roux-en-Y reconstruction with isolated pancreatic drainage versus conventional loop reconstruction after pancreaticoduodenectomy. *Surgery* 2013; **153**: 743-752 [PMID:23601899 DOI:10.1016/j.surg.2013.02.008]

88 Gangavatiker R, Pal S, Javed A, Dash NR, Sahni P, Chattopadhyay TK. Effect of antecolic or retrocolic reconstruction of the gastro/duodenojejunostomy on delayed gastric emptying after pancreaticoduodenectomy: a randomized controlled trial. *J Gastrointest Surg* 2011; **15**: 843-852 [PMID:21409601 DOI:10.1007/s11605-011-1480-3]

89 Kurahara H, Shinchi H, Maemura K, Mataki Y, Iino S, Sakoda M, Ueno S, Takao S, Natsugoe S. Delayed gastric emptying after pancreatoduodenectomy. *J Surg Res* 2011; **171**: e187-192 [PMID:22001182 DOI:10.1016/j.jss.2011.08.002]

90 Chijiiwa K, Imamura N, Ohuchida J, Hiyoshi M, Nagano M, Otani K, Kai M, Kondo K. Prospective randomized controlled study of gastric emptying assessed by (13)C-acetate breath test after pylorus-preserving pancreaticoduodenectomy: comparison between antecolic and vertical retrocolic duodenojejunostomy. *J Hepatobiliary Pancreat Surg* 2009; **16**: 49-55 [PMID:19083149 DOI:10.1007/s00534-008-0004-3]

91 Song SC, Choi SH, Choi DW, Heo JS, Kim WS, Kim MJ. Potential risk factors for nonalcoholic steatohepatitis related to pancreatic secretions following pancreaticoduodenectomy. *World J Gastroenterol* 2011; **17**: 3716-3723 [PMID:21990953 DOI:10.3748/wjg.v17.i32.3716]

92 Sato R, Kishiwada M, Kuriyama N, Azumi Y, Mizuno S, Usui M, Sakurai H, Tabata M, Yamada T, Isaji S. Paradoxical impact of the remnant pancreatic volume and infectious complications on the development of nonalcoholic fatty liver disease after pancreaticoduodenectomy. *J Hepatobiliary Pancreat Sci* 2014; **21**: 562-572 [PMID:24824077 DOI:10.1002/jhbp.115]

93 Kato H, Isaji S, Azumi Y, Kishiwada M, Hamada T, Mizuno S, Usui M, Sakurai H, Tabata M. Development of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) after pancreaticoduodenectomy: proposal of a postoperative NAFLD scoring system. *J Hepatobiliary Pancreat Sci* 2010; **17**: 296-304 [PMID:19809782 DOI:10.1007/s00534-009-0187-2]

94 Ito Y, Kenmochi T, Shibutani S, Egawa T, Hayashi S, Nagashima A, Kitagawa Y. Evaluation of predictive factors in patients with nonalcoholic fatty liver disease after pancreaticoduodenectomy. *Am Surg* 2014; **80**: 500-504 [PMID:24887731]