

# Preoperative diabetes as a protective factor for pancreatic fistula after pancreaticoduodenectomy: a meta-analysis

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**BACKGROUND:** The role of diabetes mellitus (DM) in pancreatic fistula (PF) or clinical relevant PF (CR-PF) after pancreaticoduodenectomy (PD) or pylorus-preserving pancreaticoduodenectomy (PPPD) is unclear. We conducted a meta-analysis to investigate the relationship between DM and PF or CR-PF.

**DATA SOURCES:** Embase, MEDLINE and Cochrane databases were searched systematically for relevant articles from January 2005 to June 2013. The selected studies that examined clinical risk factors of PF or CR-PF were included. We created pooled estimates for our outcomes using the random-effects model.

**RESULTS:** Sixteen observational clinical studies were included. Pooling of PF rates from ten studies revealed that DM was associated with a decreased risk of PF ( $P=0.01$ ). CR-PF rates from 8 studies showed no significant difference between DM and control group ( $P=0.14$ ).

**CONCLUSIONS:** DM is not a risk factor for PF in patients undergoing PD or PPPD. On the contrary, patients without DM are at a higher risk of PF because the pancreases in these patients have more fatty tissue and the pancreas is soft.

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**KEY WORDS:** pancreatic fistula;  
diabetes;  
postoperative complication

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## Introduction

Pancreaticoduodenectomy (PD) is the well-known standard resection for various benign and malignant diseases of the periampullary region.<sup>[1, 2]</sup> The advances in operative techniques and postoperative management have greatly improved the safety of PD worldwide, the patients' perioperative mortality rates are significantly decreased and the quality of patients' life after PD was significantly improved.<sup>[3, 4]</sup> However, this complicated surgical procedure historically regarded as high operative mortality and morbidity,<sup>[5, 6]</sup> with 30%-40% of patients experiencing one or more postoperative complications.<sup>[7]</sup>

Pancreatic fistula (PF) is the most common complication after PD, with a frequency ranging from 2% to 20%. PF is associated with a longer hospital stay and more costs.<sup>[6, 8]</sup> In addition, PF could be related to some potentially life-threatening complications such as intra-abdominal hemorrhage and abscess, possibly leading to death. There are several risk factors for PF. The quality of the pancreatic parenchyma, such as soft pancreatic texture, non-dilated principal pancreatic duct or a thick pancreatic stump has been considered as the main risk factor.<sup>[9, 10]</sup> Obesity or high BMI is another risk factor causing a "fatty pancreas".<sup>[11, 12]</sup> A number of techniques have also been proposed to reduce PF following PD, such as the use of the somatostatin analogue octreotide,<sup>[13]</sup> reinforcing anastomosis with fibrin glue,<sup>[14]</sup> and placement of a pancreatic duct stent.<sup>[15, 16]</sup>

However, the role of diabetes mellitus (DM) in this setting is unclear. The correlation between DM and pancreatic ductal adenocarcinoma is well established.<sup>[17]</sup> Meanwhile, perioperative DM, especially if poorly controlled, has been shown to significantly impact postoperative complications after different operations.<sup>[18]</sup> In pancreatic resection, some studies showed that DM is a significant risk factor for PF after PD.<sup>[19-21]</sup> On the contrary, others revealed that patients with DM did not

show a greater rate of PF as compared with non-DM patients.<sup>[22-25]</sup> Because of the controversial results of these studies, we performed a meta-analysis focusing on the relationship between DM and PF in patients undergoing conventional PD or pylorus-preserving pancreaticoduodenectomy (PPPD).

### Methods

This meta-analysis was conducted according to the "meta-analysis of observational studies in epidemiology: a proposal for reporting".<sup>[26]</sup>

#### Search strategy

Embase, MEDLINE and Cochrane databases were searched to identify relevant articles published from January 2005 to June 2013. The search terms included "pancreaticoduodenectomy" or "pylorus-preserving pancreaticoduodenectomy" or "whipple" or "pancreatic surgery" or "pancreatic resection"; "pancreatic fistula" or "pancreatic leak" or "anastomotic leak"; "diabetes" or "diabetes mellitus". Then the reference lists of relevant articles were manually searched to find other potentially eligible studies. No language restrictions were applied and our search was limited to humans only. All searches were performed by two independent reviewers (XX and HC).

#### Study selection

The titles and abstracts of the search results were screened for eligible studies. All cohort studies (prospective and retrospective) and all case-control studies that investigated DM directly influencing the occurrence of PF after PD or PPPD were included. The following were excluded: abstracts only, comments, letters, expert opinions, reviews without original data, case reports, studies with distal pancreatectomy or pancreatic enucleation and studies without a control group. Both investigators (XX and HC) assessed all articles by these above criteria and scored on a standardized form. Disagreement was resolved by consensus; when this failed, a third investigator adjudicated. We contacted the authors to get missing data when important information in the published articles was not adequate.

#### Definition of PF and DM

The primary outcome evaluation was the incidence of PF, as described by the International Study Group on Pancreatic Fistula (ISGPF).<sup>[6]</sup> Output via an operative placed drain (or a subsequently placed, percutaneous drain) of any measurable volume of drain fluid on or after postoperative day 3, with an amylase content

greater than 3 times of the upper normal serum value. Then three different grades were defined according to the patients' clinical symptom: 1. Grade A has no clinical impact and requires little intervention in management; 2. Grade B needs some intervention such as partial or total parenteral or enteral nutrition, repositioning the drainage, antibiotics and somatostatin; 3. Grade C requires aggressive clinical intervention and sometimes reoperation. As the definition of the ISGPF has been commonly used for PF evaluation, any article that failed to meet this PF criterion would be eliminated.

The American Diabetes Association (ADA) has issued comprehensive diagnostic criteria for DM.<sup>[27]</sup> However, the definitions of DM in the published literature do not always follow the ADA criteria. In addition to ADA, various organizations (e.g., World Health Organization, International Diabetes Association) have their own diagnostic guidelines. Second, due to the retrospective data of most of our articles, the diagnosis of DM is mainly derived from medical history and self-reporting. Therefore, caution is required to compare results between studies that have different criteria for DM.

#### Data extraction

The following data were extracted by two independent reviewers (CG and QZJ): first author, year of publication, study design, sample size, operative techniques, DM rate, presence or absence of PF and grade if possible, and primary outcomes. Inconsistencies were resolved through discussion until consensus was made, or the third reviewer (HC) would participate in this discussion. Because patients with grade B and C PF were generally considered to show clinical symptoms differed from grade A, we defined grade B and C PF as clinical relevant PF (CR-PF) and thus categorized selected studies into two groups according to their study outcomes. In the event of multiple publications from the same cohort or overlapping series of patients, data included only once from the most recent article to avoid double counting of patients. Qualitative assessment of observational studies was based on the Newcastle-Ottawa Scale.<sup>[28]</sup> "Good" was defined as a total score of 7-9; "Fair", 4-6; and "Poor", less than 4.

#### Data analysis

Meta-analyses were performed for studies which provided comparative data on the outcomes of patients who underwent PD or PPPD with or without DM. The odds ratio (OR) was chosen as an effect measure for those dichotomous parameters, which were reported along with the corresponding 95% confidence intervals (CIs) and the  $P < 0.05$  level was utilized to specify statistical significance. Heterogeneity was evaluated by inspection of the

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