

Diabetes Mellitus: A Risk or Protective Factor for Pancreatic Fistula after Pancreatic Resection?

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Pancreatic resection is the standard therapy for a variety of malignant and benign lesions involving the pancreas and periampullary region. Although a significant reduction in postoperative morbidity and mortality rates has been achieved in high volume hospitals as low as 28.1-41% and 1.2-5.9% [1-4], pancreatic fistula remains by far the most lethal complication of the procedure. Many risk factors including general factors [age, gender, Body Mass Index (BMI), jaundice level, comorbid illness], pancreas factors (pancreatic pathology, pancreatic texture, pancreatic duct size, pancreatic juice output), and procedure-related factors (operation time, intraoperative blood loss, anastomotic technique) have been identified to be related to postoperative pancreatic fistula after pancreatic resection [5-8]. Diabetes mellitus (DM) has been demonstrated by a large number of epidemiological studies as a potential risk factor for many types of cancers, such as pancreatic adenocarcinoma, colorectal cancer and liver cancer [9-12]. It is positively associated with increased risk of these cancers. Furthermore, associations between adverse postoperative complications and diabetes have also been well established [13,14]. However, the effect of diabetes on pancreatic fistula after pancreatectomy is controversial.

A recent report by Chu et al. [6] showed that patients with diabetes had a higher likelihood of developing pancreatic fistula (with diabetes 10.3% vs. without diabetes 3.7%, $p=0.04$), and diabetes was an independent risk factor for pancreatic fistula [Odds Ratio (OR) 4.3, 95% CI 1.18-15.8, $p=0.027$] when adjusted for age, co-morbidities, BMI, preoperative albumin level, type of operation, surgery time, and pancreatic quality. While in the subgroup analysis, the authors found that the frequency of clinically significant pancreatic fistula (grades B or C) did not differ in patients with and without diabetes (5.2% vs. 4.4%, $p=0.8$). When stratified by type of operation, diabetic patients had a higher pancreatic fistula rate only after left pancreatectomy (33% vs. 0%, $p=0.02$). Comparison of preoperative variables in diabetic and non-diabetic patients showed that patients with diabetes were older, more likely to have additional co-morbidities, and had lower serum albumin and higher BMI, although of no statistical significance. All these factors more or less influence the formation of pancreatic fistula. This study includes a large number of patients, while there are still some limitations. First, the number of patients developing postoperative pancreatic fistula is so small that the statistical significance is limited and does not indicate replicability of the data. Second, the study included patients undergoing pancreatic resection before 2005, when there were wide variations in the definition of pancreatic fistula prior to the new grading system presented by the International Study Group for Pancreatic Fistula (ISGPF) [15]. This means that the study has a nature of retrospective. Third, the lower incidence rate of postoperative pancreatic fistula in this study may not be representative as compared with many other studies [16,17]. Fourth, although no difference of operation type was found between patients with and without diabetes ($P=0.4$), the two patients receiving total pancreatectomies didn't have diabetes. As it is well-known that there is no possibility of pancreatic fistula after total pancreatectomy, these two patients may bring selection bias to the study. Last but not the least, the authors only analyzed patients with pancreatic ductal

adenocarcinoma, a group in which pancreatic duct commonly dilated and risk of pancreatic fistula was reduced compared with that in other pathological diseases.

By contrast, Mathur et al. [5] found that diabetes might offer a protective benefit against pancreatic fistula, which was consistent with other reports [18]. The authors analyzed forty patients who developed postoperative pancreatic fistula defined by criteria set by the ISGPF [15], and showed that patients with pancreatic fistula had increased pancreatic fat and decreased pancreatic fibrosis. Another forty control patients without fistula were matched for multiple parameters including age, sex, pancreatic pathology, surgeon, and type of surgery. Interestingly, the authors found that patients developed pancreatic fistula were less likely to have diabetes ($P<0.05$), with incidence rate of 13%, which was significantly lower ($P<0.05$) than that of patients in the control group (33%). The reason why the controls had a higher incidence of diabetes may be that these patients had less pancreatic fat and more pancreatic fibrosis.

In conclusion, the impact of diabetes on postoperative pancreatic fistula after pancreatectomy should be further explored. Multicenter prospective studies in large cohorts including a sufficient number of patients needed before conclusions could be drawn about the effect on diabetes on pancreatic fistula after pancreatic resection [19]. In order to do this trial, pancreatic fistula should be strictly defined according to ISGPF classification [15], and definition of diabetes should use the American Diabetes Association (ADA) criteria [20].

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