Peer Review File

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Reviewer A

Comment 1:

The authors concluded that PD and DP had similar results. HOMA-IR is controlled at a lower value in DP in Table 1, and the residual pancreas is often normal in DP. On the other hand, stiffness of the pancreatic gland is associated with postoperative pancreatic function in PD, and the residual pancreas is sometimes hard in PD. Was there any difference between PD and DP in postoperative HOMA-IR?

Reply 1:

Thanks for the insightful comment and advice from the reviewer.

The HOMA-IR was lower in DP than PD but with no statistically significant difference. We consider the difference might be attributed to patients in PD have a higher average age than DP, as HOMA-IR is considered associating with aging (PMID: 21824674). However, as both age and HOMA-IR showed no significant difference between groups in our current study, it's had to assume that the patients had inequivalent baseline characteristics.

The texture of the remnant pancreas in PD and DP might do have a difference based on our clinical experience, especially under the circumstance of pancreatic malignancy. It might lead to a difference between PD and DP in postoperative HOMA-IR. However, it was a pity that the research we presented here failed to follow all participants for a long time due to some external policies. In fact, we only found that one participant had a record of postoperative HOMA-IR about three months after the surgery: the patient received DP for pancreatic cancer, with preoperatively C-peptide: 1.51 μg/L, HOMA-IR: 2.036, and postoperatively C-peptide: 0.90 μg/L, HOMA-IR: 0.733.

We acknowledge that lacking long-term follow-up data is a limitation for our study, so we added some related statements in the section discussing the limitation in the "discussion" part. Although our study is not able to give the answer, according to the research published by Tatsuya Fukuda et al. on *Diabetes Care*, patients who underwent DP had a significantly higher cumulative incidence rate of diabetes compared with those who underwent PD. We presume that DP might have a higher postoperatively HOMA-IR than PD.

We hope the reviewer would be satisfied with our data and our answer.

Changes in the text:

We added some statements about the limitation of lacking long-term follow-up data according to the reviewer's comment (see Page 21, line 15-18).

Comment 2:

Postoperative blood glucose levels were measured for 14 days. Were there any changes in the blood glucose levels between the early postoperative period (within 5-7 days) and the late postoperative period when postoperative inflammation improved (after 5-7 days)? Also, were there any effects of postoperative complications on postoperative blood glucose levels?

Reply 2:

We thank the reviewer for the constructive comments. Both postoperative complications and the difference between early and late postoperative periods were also in our concern when

we were analyzing and interpreting the data. Results on these two topics were presented below.

1) We analyzed the difference between early and late postoperative periods in PD, DP, and TP. The control group was not included because patients in this group were discharged earlier than others: for all 3 patients in the control group, 2 patients were discharged before day 6 after surgery. As CGM monitoring was stopped when 14 days had reached, or the patient was discharged, we do not have enough data to calculate the difference in the control group. Our results suggested that PD and DP had a higher mean glucose level in the first 5 days, while the TP group showed a higher mean glucose level after 5 days (all P values < 0.001, a table was presented below).

	First 5 days	After 5 days	P value
PD	6.67 ± 2.07	5.71 ± 2.24	<0.001
DP	6.28 ± 2.09	6.02 ± 1.94	<0.001
TP	8.02 ± 3.21	8.60 ± 4.13	<0.001

We assumed that the higher mean glucose level in the first 5 days in PD and DP was caused by postoperative stress and intravenous fluids in the first 3 to 5 days after surgery. When it comes to TP, although postoperative stress and fluids do play a role, the higher mean glucose after 5 days might reflect that oral diets could cause a more significant effect and exceed what was caused by fluids or stress.

As for MODD and CONGA, because a patient without major complications was usually discharged one week after the surgery, we did not have enough data to calculate these two parameters and could not compare the difference between them.

2) When analyzing the potential effect of postoperative complications, we focused on two crucial complications: POPF, which was specific for pancreatic surgery; major complications, which delayed the patient's discharge. Due to the overall incidence of complications was relatively low in these participants, to have enough data for statistical analysis and to avoid the potential bias between different surgery procedures, we decided to take data from PD and DP and treated them as a whole.

Our results found that patients without any grades of POPF seemed to have a higher mean glucose level than those with POPF, but they had no significant difference in glycemic variability. A similar result was also noticed between patients with and without major complications. Tables were presented below.

	With POPF (n=7)	Without POPF (n=6)	P value
Mean glucose value	5.77 ± 1.98	6.68 ± 2.24	<0.001
CV of mean glucose	0.3427	0.3354	0.138
CONGA, 2	1.69 ± 0.35	1.88 ± 0.40	0.705
MODD	0.38 ± 0.05	0.42 ± 0.08	0.353

	With complications (n=4)	Without complications (n=9)	P value
Mean glucose value	6.03 ± 2.50	6.17 ± 1.96	<0.001
CV of mean glucose	0.4151	0.3175	<0.001
CONGA, 2	1.78 ± 0.54	1.78 ± 0.31	0.179
MODD	0.42 ± 0.10	0.40 ± 0.06	0.212

The results above seemed just opposite to the hypothesis that hyperglycemia could lead to a poor surgical outcome. Our team considered that our postoperative management might cause the difference. For instance, when a patient had already or was about to develop comorbidities, we always started to give the patient more intensive glucose management than the previous period. Meanwhile, after a complication developed, discharging was delayed. These factors made patients with complications receive intensive glucose management for longer, finally leading to a lower average glucose level.

In the revised main text, we added several parts presenting and discussing the results above according to the comment and advice provided by the reviewer. However, as these results were extracted from limited data, we decided to put these related tables in the supplementary material rather than the main text.

Changes in the text:

To address these two topics as advised, we added the following parts in the main text:

1) We added the definition for complications in the "method" part (see Page 10, line 19-22).
2) We added the average CGM monitoring length (Page 12, line 17-18), incidence of complications (Page 13 line 10-14), and result of the analysis (Page 15, line 8-15) in the "results" part.
3) We added a brief discussion about the findings in the "discussion" part (see Page 18, line 14-21 & Page 19, line 1-10)
4) We added Supplementary Table S4-6 in the supplementary material.

Comment 3:

TP, PD, and DP groups used resectable diseases, whereas the control group used unresectable. Is it appropriate as a study design?

Reply 3:

We thank the reviewer for pointing out this issue.

We acknowledge that our control group in this study was not a "perfect" control group, just as we have already discussed about limitations in the "discussion" part. Nevertheless, one of the study's purposes was to compare the glycemic status between patients receiving pancreatectomy and no-pancreatectomy, so we had to choose patients with similar underlying pancreas diseases who underwent surgery but with no pancreatectomy as control. Due to the ethical policies, patients with unresectable diseases seemed to be our best choice under that circumstance.

Comparing patients with resectable disease and unresectable disease might bring some potential bias to the study. However, we believed that the bias would not be that significant. We considered it might be minor than the bias brought by different management strategies on postoperative diets (as we discussed about "external consistency" in the manuscript). We added some statements on this potential bias pointed out by the reviewer in the "discussion" part. In future studies, we will focus on only one or two specific types of pancreatic surgery, include a greater number of participants, and choose a more suitable control group for it.

Changes in the text:

We added some statements on potential bias might be caused by resectable and unresectable disease in the "discussion" part (see Page 21, line 11-13)

Comment 4:

Did the authors measure C-peptide as a pancreatic function?

Reply 4:

Thanks for the advice from the reviewer. We did measure C-peptide preoperatively as a pancreatic function. We have added the data about C-peptide in Table 1 as requested.

Changes in the text:

We added an additional line in Table 1 to present the result about C-peptide in Table 1 (see Table 1 and Page 12, line 22 in the main text).

Comment 5:

Did postoperative administration of insulin affect blood glucose levels? Did the authors consider differences between preoperative and postoperative insulin administration?

Reply 5:

Thanks for the perspective comments and advice from the reviewer.

Because only non-diabetic patients met the inclusion criteria, no preoperative insulin was prescribed before the surgery. Postoperative administration of insulin was also a concern of ours. When our team was talking about study protocols before making the final research plan, we found the effect brought by postoperative insulin was relatively hard to access. Therefore, we tried to minimize the effect by using standardized postoperative glucose management instead:

For patients who underwent PD, DP, and TP, 1 unit of insulin was applied with every 3 grams of carbohydrates if there were carbohydrates in the intravenous fluids. For patients in the control group, no intravenous insulin was applied with carbohydrates in fluids. Besides insulin prescribed with fluids, for patients in the control group, PD, and DP, subcutaneous insulin was prescribed on demand to keep the patient reach a target glucose level of 3.9-10mmol/L. In the TP group, an intravenous insulin pump was used to control glucose until the patient resumed oral intake. After a TP patient resumed oral intake, an insulin replacement therapy strategy combining subcutaneous rapid-acting and long-acting insulin was prescribed. The strategy was adjusted daily according to the glucose status on the previous day.

To help our potential readers access the potential effects brought by insulin administration, we added data about average daily extra insulin in Table 1. Detailed average insulin dose for each patient could be found in Supplementary Table S1.

Changes in the text:

1) We added a paragraph describing postoperative glucose management in the “methods” part (see Page 10, line 5-18).
2) We added a paragraph describing the result of postoperative insulin use in the “result” part (see Page 13, line 4-9).
3) We added an additional line in Table 1 to present the average daily extra insulin dose for every group (see Table1). We also added detailed data about the average daily extra insulin dose for each patient in Supplementary Table S1 (see Supplementary Table S1).

Comment 6:

Interestingly, Fig. 2 showed the diurnal variation of glucose levels after surgery. For

example, 4:00 AM seemed the lowest in TP, and 8:00 AM seemed the lowest in DP and PD. Did the diurnal variation affect postoperative administration of insulin?

Reply 6:

We thank the reviewer for giving us this wise and detailed comment.

In this study, the diurnal variation detected by CGM did not affect postoperative insulin administration for all participants included in this study. Just like we wrote in the "method" part: "During the whole process of the study, clinical decisions were made independent of the glucose value recorded by the CGM system."

Nevertheless, the phenomenon pointed out by the reviewer did make a difference in our postoperative glucose management after we finished this study. Currently, we begin to monitor the glucose level in the dawn for all TP patients routinely in the first 5 days after surgery. We found that some patients presented hypoglycemia events while others seemed to suffer the dawn phenomenon. The reason remained unknown, and now we are planning another research to study this problem.

Our experience above suggested that monitoring perioperative glucose with CGM for pancreatic surgeries was helpful for improving our perioperative management.

Changes in the text:

We added several sentences discussing the usefulness of the diurnal variation detected by CGM during postoperative management according to the reviewer's comments (see Page 19, line 15-18).

Reviewer B

Comment 1:

Since I think that the patients underwent perioperative insulin therapy, please show the data of daily amount of insulin use.

Reply 1:

Thanks for the insightful advice from the reviewer. Postoperative insulin therapy does play an important role in evaluating a patient's postoperative glycemic status.

According to the kind advice from the reviewer, and to help our potential readers access the potential effects brought by insulin administration, we added some demonstration about our strategy for postoperative glucose control, data about average daily extra insulin for each group and each patient. Please find these results in Table 1 and Supplementary Table S1.

Changes in the text:

1) We added a paragraph describing postoperative glucose management in the "methods" part (see Page 10, line 5-18).
2) We added a paragraph describing the result of postoperative insulin use for each group in the "result" part (see Page 13, line 4-9).
3) We added an additional line in Table 1 to present the average daily extra insulin dose for every group (see Table1). We also added detailed data about the average daily extra insulin dose for each patient in Supplementary Table S1 (see Supplementary Table S1).

Comment 2:

If the authors have the detail data of operation, please provide data on where the pancreas was transected during the DP, at least above the portal vein or more tail side of the pancreas.

Reply 2:

We thank the reviewer for providing us such constructive advice. The total volume and the radio of the remaining pancreas can also affect postoperative glycemic status due to the different volumes of beta-cell loss. For 5 patients in the DP group, 4 were pancreatic cancer, and the other was SCN. The pancreas was resected above the portal vein for 4 patients with pancreatic cancer, and the pancreas of the other patient with SCN was resected about 3cm left to the portal vein.

We added the data about where the pancreas was transected for patients in Supplementary Table S1. The supplementary table was listed below.

Patient	Diagnosis	Surgery	Resection line	Average daily extra insulin (IU)
1	PDAC	DP	Above PV	3.80
2	PDAC	PD	Above PV	2.00
3	IPMN	PD	Above PV	0
4	PDAC	TP	N/A	20.09
5	periampullary cancer	PD	Above PV	0
6	PDAC	DP	Above PV	2.44
7	PDAC	DP	Above PV	0.57
8	multiple myeloma	PD	Above PV	0.57
9	PDAC	DP	Above PV	0
10	PDAC	PD	Above PV	1.14
11	SCN	DP	3 cm left to PV	2.00
12	PDAC	TP	N/A	37.10
13	PDAC	Palliative gastrojejunostomy and cholangiojejunosotmy	N/A	0
14	PDAC	PD	Above PV	0.86
15	PDAC	Palliative gastrojejunostomy	N/A	0
16	PDAC	PD	Above PV	2.17
17	PDAC	“Open-close” laparotomy with biopsy for metastatic lesions on peritoneum	N/A	0.31
18	PDAC	PD	Above PV	0.86

Changes in the text:

We added data about this issue in Supplementary Table 1 in our supplementary materials.

Comment 3:

In addition, since the pancreatic cancer often causes atrophy of the remnant pancreas, please indicate the primary diseases in each surgical procedure, at least whether it was pancreatic cancer or not.

Reply 3:

Thanks to the reviewer for this kind comment. In our first submission, we have already provided the surgical procedure and the pathological diagnosis for each patient in our Supplementary Table S1. Nevertheless, the comments from the reviewer provoked us that we should provide more detailed information about these data. We have updated our Supplementary Table S1 with more detailed data, and we hope the reviewer would be satisfied with our data.

Changes in the text:

In our supplementary materials, we updated detailed information about patients' diagnoses and surgical procedures in Supplementary Table 1.