Parenteral nutrition and insulin per protocol improve diabetes management after total pancreatectomy

Sakshi Andersen[*, 1, 2], Andreas Andersen[*, 1, 2], Lene Ringholm[3], Carsten Palnæs Hansen[4], Jan Storkholm[4], Kerstin Lillpers[2], Charlotte Schiøtz[2] & Elisabeth Reinhardt Mathiesen[1, 2]

ABSTRACT

INTRODUCTION: Pancreatogenic diabetes develops in patients undergoing total pancreatectomy and complicates post-surgical management. The aim of this study was to compare parenteral nutrition (PN) with protocolled insulin treatment to intravenous glucose treatment after total pancreatectomy.

METHODS: This was a retrospective study of 97 patients undergoing total pancreatectomy between 2009 and 2014. Patients were divided into a PN cohort (n = 57) and a glucose cohort (n = 40). The PN cohort was given PN with one international unit (IU) rapid-acting insulin per 10 g of carbohydrate. The glucose cohort was given a continuous 5% glucose infusion with 2 IU rapid-acting insulin per 10 g of carbohydrate. Both cohorts were given insulin detemir 0.2 IU/kg/day.

RESULTS: Within the first 13 post-operative days, plasma glucose values were within the target range (4.0-10.0 mmol/l) in the PN cohort more frequently than in the glucose cohort (46% versus 42%, p = 0.01) without any increase in hypoglycaemia. Non-infectious complications occurred less frequently in the parenteral cohort than in the glucose cohort (23% versus 43%, p = 0.04). Infectious complications occurred in 19% versus 33% of patients, respectively (p = 0.14). The mean length of hospitalisation was 19.8 ± 12.7 versus 25.0 ± 21.5 days, p = 0.14.

CONCLUSIONS: After total pancreatectomy, PN with insulin treatment per protocol improves glycaemic control compared with glucose infusion and reduces the number of non-infectious post-operative complications without increasing hypoglycaemia.

FUNDING: none.

TRIAL REGISTRATION: not relevant.

Total pancreatectomy is mainly indicated for patients with pancreatic malignancy [1, 2]. The resulting pancreatogenic diabetes is characterised by hyperglycaemia, frequent episodes of hypoglycaemia during insulin treatment, but rarely by ketoacidosis [3, 4]. During insulin treatment after total pancreatectomy, patients sustain an increased risk of hypoglycaemia, especially during night time [3-5]. This susceptibility to hypoglycaemia may be aggravated by insufficient nutrition, leading to catabolism and glycogen depletion in the muscles and liver [3]. In addition to regulation of blood glucose, insulin is a major anabolic hormone, which increases protein synthesis and enhances macrophage infiltration in wounds, thus promoting tissue repair after surgery [6, 7]. Total pancreatectomy is a rare procedure performed by pioneers, while partial pancreatectomy is much more common. After partial pancreatectomy, hyperglycaemia within the first 24 hours is associated with an increased length of hospitalisation and an increased number of surgical complications [8, 9]. Post-operative parenteral nutrition (PN) is indicated where adequate enteral feeding is not expected within seven days after surgery [10]. Therefore, PN might be beneficial after major surgery, such as total pancreatectomy, although an increased prevalence of post-operative infections has also been described [11], and fear of hyperglycaemia may also be a barrier for PN. Appropriate nutrition and insulin treatment after total pancreatectomy is critical in these totally insulin-depleted patients. However, prospective randomised trials in this rare patient category are difficult to accomplish.

In our centre, the post-operative nutritional regimen after total pancreatectomy initially consisted of continuous intravenous glucose infusion based on the assumption that enteral feeding would be established within few days. However, for the majority of patients, this was not the case. In 2012, the post-operative nutritional regimen was therefore changed to include PN with insulin treatment according to a newly developed local protocol. The aim of this study was therefore to evaluate PN with protocolled insulin treatment versus intravenous glucose treatment for its effect on glycaemic control, post-operative complications and length of hospitalisation.

METHODS

Study design

This retrospective study included 97 (92%) out of 106 patients undergoing total pancreatectomy between December 2009 and November 2014 at the Department of Surgical Gastroenterology, Rigshospitalet, Copenhagen. Nine patients were excluded because their diabetes charts were unavailable. According to the post-operative nutritional regimen, patients were divided into two co-

ORIGINAL ARTICLE

1) Faculty of Health and Medical Sciences, University of Copenhagen
2) Department of Endocrinology, Rigshospitalet
3) Steno Diabetes Centre Copenhagen
4) Department of Surgical Gastroenterology, Rigshospitalet, Denmark

Dan Med J 2018;65(4):A5475

TABLE 1

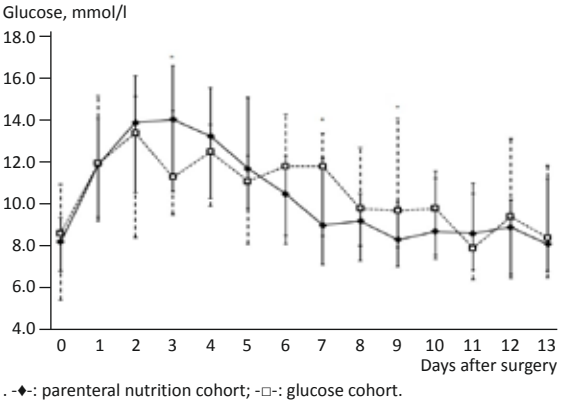
Baseline characteristics of two cohorts undergoing total pancreatectomy given routine postoperative parenteral nutrition treatment or glucose infusion, respectively.

	Parenteral nutrition cohort (n = 57)	Glucose cohort (n = 40)	p-value
Men/women, n	30/27	19/21	0.62
Age, yrs, mean ± SD	65.9 ± 9.7	65.1 ± 7.7	0.67
Weight, kg, mean ± SD	68.7 ± 2.0	72.8 ± 2.7	0.21
BMI, kg/m^2, mean ± SD	23.5 ± 4.7	24.2 ± 5.3	0.51
Preoperative diabetes mellitus, n (%)	12 (21)	16 (40)	0.04
Current smokers, n (%)	20 (35)	11 (28)	0.55
Alcohol exceeding recommendations[a], n (%)	9 (16)	6 (15)	0.79
Histology, n (%)			0.09
Adenocarcinoma	48 (84)	28 (70)	
Intraductal papillary mucinous neoplasm	6 (11)	2 (5)	
Chronic pancreatitis	1 (1.8)	2 (5)	
Cystadenoma (serous/mucinous)	0	3 (7.5)	
Neuroendocrine tumour	1 (1.8)	1 (2.5)	
Other	1 (1.8)	4 (10)	
Tumour limited to the pancreas[b], n (%)	6 (12)	5 (15)	0.72
Tumour extending beyond the pancreas[b], n (%)	44 (88)	29 (85)	
Lymph node metastasis[b], n (%)	37 (74)	27 (79)	0.57
Unilateral adrenalectomy, n (%)	5 (8.8)	0 (0)	0.05

SD = standard deviation.
a) Alcohol consumption exceeding the recommendation of The Danish Health Authority (women: 7 U/wk, men: 14 U/wk).
b) Tumour staging was performed in 50 and 34 patients, tumour staging included T1 and T2 or T3 and T4, staging according to the American Joint Committee on Cancer TNM staging system.

FIGURE 1

Median plasma glucose concentration during the first 13 post-operative days presented with interquartile range.



. -♦-: parenteral nutrition cohort; -□-: glucose cohort.
*) p < 0.05<

horts; the PN cohort (n = 57) including patients who had a total pancreatectomy from August 2012 to November 2014 and the glucose cohort (n = 40) including patients who had total pancreatectomy between December 2009 and July 2012.

The PN cohort started PN (SmofKabiven, Fresenius Kabi, Hamburg, Germany) on the first post-operative day. PN was given at a constant infusion rate over 20 hours per day. One international unit (IU) of rapid-acting insulin aspart (Novorapid, Novo Nordisk) per 10 g of carbohydrate was added to the PN. PN was administered according to preoperative body weight. Thus, patients received 125 g (40-50 kg), 187 g (51-70 kg), 250 g (71-90 kg), or 313 g (> 90 kg) of carbohydrate per day. PN was terminated when the patient had a sufficient oral daily intake of at least 150 g of carbohydrates.

The glucose cohort was treated with continuous intravenous infusion of isotonic glucose 5%, which was initiated on the first post-operative day. The infusion rate was 60 ml/hour, which is consistent with a 72-g carbohydrate intake per 24-hour period. According to local practice, 2 IU of insulin aspart was added per 10 g of carbohydrate. Only on various individual indications could patients initiate PN. Glucose infusion was terminated when a sufficient oral intake was restored.

Both cohorts had a routine 24-hour post-operative stay at the intensive care unit, where they were given individually titrated glucose-insulin infusion. When transferred to the surgical ward, the patients initiated treatment according to the post-operative nutritional regimen described above. Plasma glucose was measured at least five times daily. In order to ensure basic insulin requirements, patients were given long-acting insulin detemir (Levemir, Novo Nordisk) 0.2 IU/kg/day divided into two doses. Supplementary doses of insulin aspart were given when plasma glucose values exceeded 10 mmol/l. A meal bolus of insulin aspart (2 IU) was given when oral feeding was initiated along with protein energy drinks (2-4 IU). Supplementary digestive enzymes (Creon, Mylan) were given with every meal.

Data sampling and management

Clinical data were obtained from the hospital records including diabetes charts. Day 0 was defined as the day of surgery. The daily median plasma glucose level for each patient was calculated. Additionally, plasma glucose values were divided into five predefined intervals and the target range was defined as a plasma glucose between 4.0-10.0 mmol/l. Severe symptomatic hypoglycaemia was defined as events requiring assistance from another person to restore normal glucose values [12]. Data regarding complications including mortality within the first 13 post-operative days were obtained from the surgical records and subsequently divided into the following categories: infectious complications, non-infectious complications and major complications. Each category consisted of a number of pre-defined and well-established post-surgical complications. Reoperation was defined as intra-abdominal surgery requiring general anaesthesia excluding cases caused by wound infection or wound dehiscence.

Outcome measures

The primary outcome was glycaemic control, evaluated by distribution of plasma glucose levels < 4.0 mmol/l, 4.0-10.0 mmol/l or > 10.0 mmol/l, and length of hospitalisation. Secondary outcome measures were incidence of complications within the first 13 post-operative days.

Statistical analysis

Numerical variables are presented as mean ± standard deviation when regarded normally distributed, otherwise as median and range. Dichotomous variables are presented as numbers and percentages. Student's t test, the Mann-Whitney U-test and the chi-squared test were used as appropriate. p-values < 0.05 were considered significant. Statistical analyses were performed using SPSS Statistics 22 (IBM, Armonk, NY, USA).

Trial registration: not relevant.

RESULTS

Study population

The demographic and clinical characteristics of the two cohorts including tumour staging were comparable, with the exception that preoperative diabetes occurred less frequently in the PN cohort than in the glucose cohort (p = 0.04) (**Table 1**). In the glucose cohort, 11 (28%) patients received PN with a median duration of three days within the first 13 post-operative days in addition to glucose infusion, mostly in cases where post-operative complications caused a delay in achieving a sufficient oral intake.

Glycaemic control

In the PN cohort, 3,312 plasma glucose measurements were registered during 754 observation days. Similarly, in the glucose cohort, 2,143 plasma glucose measurements were registered during 553 observation days. The course of the plasma glucose followed a similar configuration throughout the post-operative period in the two cohorts, without any clinically significant differences (**Figure 1**). More plasma glucose measurements were within the target range 4.0-10.0 mmol/l in the PN cohort compared to the glucose cohort (p = 0.01) (**Table 2**) without any difference in prevalence of severe symptomatic hypoglycaemia (p = 0.10). No clinically significant weight loss was seen in either cohort (Table 2).

A sub-analysis was performed of the 32 patients who discontinued PN within the first 13 post-operative days. A pooled analysis of glucose data four days prior to and four days after discontinuation of PN revealed a median plasma glucose of 12.2 mmol/l and 8.4 mmol/l before and after discontinuation of PN, respectively (p < 0.001) (**Figure 2**). The prevalence of biochemical hypoglycaemia (< 4.0 mmol/l) was 0.7% out of 613 measurements before and 7.0% out of 591 measurements after discontinuation of PN (p < 0.001).

TABLE 2

Post-operative plasma glucose measurements, insulin treatment and postoperative complications for two cohorts following total pancreatectomy given routine parenteral nutrition treatment or glucose infusion.

	Parenteral nutrition cohort (n = 57)	Glucose cohort (n = 40)	p-value
Plasma glucose measurements, n	3,312	2,143	0.33
Plasma glucose measurements/patient/24 h, n, median (range)	5 (2.5-8.0)	5 (2.0-6.0)	0.78
Plasma glucose measurements, n (%)			
< 2.2 mmol/l	7 (0.2)	9 (0.4)	0.16
2.2-3.9 mmol/l	143 (4.3)	107 (5)	0.24
4.0-10.0 mmol/l	1,525 (46)	910 (42)	0.01
10.1-14.0 mmol/l	863 (26)	596 (28)	0.15
> 14.0 mmol/l	774 (23)	521 (24)	0.42
Insulin dose, IU/24 h at discharge, median (range)			
Rapid-acting insulin	6.0 (0-15)	6.0 (0-16)	0.84
Long-acting insulin	16.0 (5-33)	18.0 (7-36)	0.22
Subtotal	22.0 (8-48)	24.5 (8-48)	0.41
Days on glucose 5% infusion, n, median (range)	2 (1-10)	8 (2-14)	< 0.001
Days on parenteral nutrition, n, median (range)	8 (1-13)	0 (0-11)	< 0.001
Patients with severe symptomatic hypoglycaemia, n, median (range)	8 (14)	11 (28)	0.10
Change in body weight, kg, mean ± SD	0.4 ± 3.9	0.5 ± 3.6	0.90
Infectious complications, n (%)	11 (19)	13 (33)	0.14
Surgical site infections	4 (7)	2 (5)	
Abdominal abscess	3 (5)	2 (5)	
Pneumonia	5 (9)	8 (20)	
Sepsis	3 (5)	5 (13)	
Non-infectious complications, n (%)	13 (23)	17 (43)	0.04
Anastomotic leak	4 (7)	4 (10)	
Wound dehiscence	7 (12)	8 (20)	
Gastrointestinal bleeding	0	3 (8)	
Haemoperitoneum	1 (2)	0	
Respiratory failure	2 (4)	2 (5)	
Cardiac failure	0	1 (3)	
Major complications, n (%)	12 (21)	15 (38)	0.08
Reoperation	3 (5)	7 (18)	
Intensive care unit transfer	8 (14)	11 (28)	
Interventional radiology	4 (7)	2 (5)	
Length of hospitalisation, days, mean ± SD	19.8 ± 12.7	25.0 ± 21.5	0.14
Readmissions within 30 days after discharge, n (%)	12 (22)	3 (8)	0.07

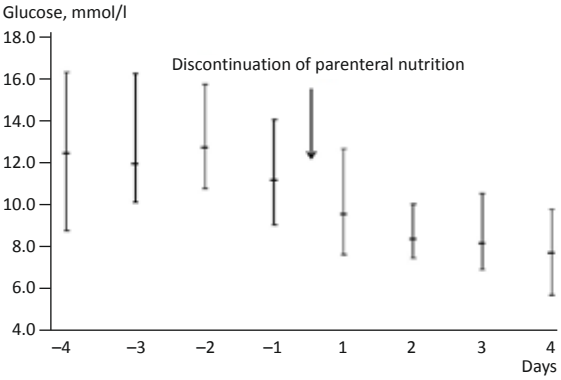
SD = standard deviation.

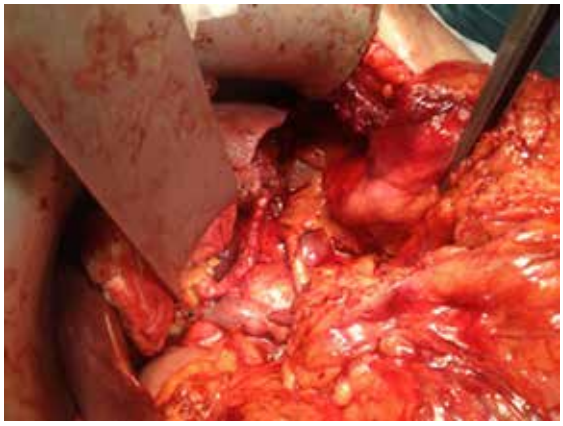
Post-operative complications

There were fewer non-infectious complications in the PN cohort than in the glucose cohort (23% versus 43%, p = 0.04), with wound dehiscence being the most prevalent complication in both groups. There was a smaller number of infectious complications and major complications in the PN cohort than in the glucose cohort, but the differences did not reach statistical significance. One patient in each cohort died within the first 14 days dur-

FIGURE 2

Median plasma glucose concentration before and after discontinuation of parenteral nutrition for patients in the parenteral nutrition cohort presented with interquartile range.





Intraoperative image during total pancreatectomy.

ing hospitalisation due to post-operative complications unrelated to hypoglycaemia. No significant differences in length of hospitalisation or readmission rates were detected (Table 1).

DISCUSSION

After total pancreatectomy, PN with insulin treatment per protocol improves glycaemic control compared with glucose infusion and reduces the number of non-infectious post-operative complications with no increase in hypoglycaemia. A non-significant reduction in length of hospitalisation was noted. Improved nutrition with PN was neither associated with incontrollable high blood glucose levels nor with a high prevalence of severe hypoglycaemia. PN and insulin per protocol offered slightly superior glycaemic control, but the median glucose levels were high during PN treatment. Based on this observation, it may be advisable to increase the amount of rapid-acting insulin added to the PN to 2 IU per 10 g of carbohydrate, which can probably be done without compromising treatment safety substantially.

We found a trend towards decreased prevalence of sepsis and other infectious complications during PN. This may be owed to the improved nutrition including additional carbohydrate, protein and lipids within the first eight post-operative days in the PN cohort. Supplementary protein intake in the post-operative period has previously been shown to decrease the incidence of minor complications following surgery including wound infection [13]. However, our results contradict a previous literature review concluding that PN increases the risk of infectious post-operative complications [11]. Additionally, in one study, patients who underwent partial pancreatectomy had a significant increase in infectious complications when receiving PN [14]. However, these results may not be representative for the patients in the present study because, unlike patients undergoing total pancreatectomy, patients with partial pancreatectomy maintain endogenous glucagon and insulin production. The reduced number of non-infectious complications in the PN cohort could be a result of the improved post-operative nutritional status and higher levels of circulating insulin in these vulnerable patients. We registered a shorter length of hospitalisation in the PN cohort than in the glucose cohort. However, this finding was not statistically significant, which might be due to the relatively small number of patients in the present study.

The glycaemic control during transition from PN to oral nutrition is also described in this paper. Initiation of oral nutrition post-operatively is often complicated by nausea, vomiting, and diarrhoea, which may result in a limited food intake and increase the risk of hypoglycaemia. To overcome this increased risk of hypoglycaemia, the long-acting insulin detemir with low day-to-day variability [15] was administered twice daily with a relatively low evening dose. Despite this strategy, the prevalence of hypoglycaemia rose tenfold when PN was discontinued, and reduction of the evening basal insulin dose was often necessary. At discharge, the total insulin dose was 22 IU/day corresponding to approximately 0.3 IU/kg/day, i.e. roughly half of the requirements of patients with Type 1 diabetes. This is in accordance with previous observations in patients after total pancreatectomy [1].

The use of continuous glucose infusion as the primary nutritional support before 2012 was based on the ASPEN guidelines and the expectation that most patients were able to initiate oral feeding within few days. However, our data demonstrate that sufficient oral feeding could not be expected within seven days, which supports the implementation of PN after total pancreatectomy.

The sample size in this study was large for this rare type of surgery [1, 2, 5, 16-20]. All patients were treated by the same two surgeons, who used the same surgical

technique, which minimised the risk that a difference in the number of post-operative complications was a result of variation in the surgeons' experience with the surgical procedure. Both cohorts were treated according to the same antibiotic regimen. All data were extracted and analysed according to a predefined protocol, and data regarding the primary outcomes were deemed accessible and reliable. In this retrospective study, data relied on information collected from medical and surgical records, so other causes for the decline in post-operative complications cannot be excluded. The number of readmissions was low in both cohorts, and larger studies are needed to evaluate any differences in readmission rate. Mortality during the first 13 post-operative days was comparable, and data on long-term survival were not included. The higher rate of preoperative diabetes in the glucose cohort might reflect a decreased peripheral insulin sensitivity leading to higher plasma glucose levels.

Previously, total pancreatectomy was discredited and nearly abandoned because of morbidity and mortality due to unstable plasma glucose values [18]. The present study and recent studies [17-19] indicate that total pancreatectomy can be performed safely when PN in combination with modern diabetes treatment is offered. Information from this study, which includes a detailed insulin protocol, may be of importance for future treatment of patients after total pancreatectomy.

CONCLUSIONS

After total pancreatectomy, PN with insulin per protocol improves glycaemic control compared to intravenous glucose infusion and reduces the number of non-infectious post-operative complications. Importantly, treatment with PN does not increase the number of infectious post-operative complications or hypoglycaemia.

CORRESPONDENCE: *Sakshi Andersen.* E-mail: saks88@gmail.com

ACCEPTED: 14 February 2018

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

ACKNOWLEDGEMENTS: *) *Sakshi Andersen* and *Andreas Andersen* contributed equally to this study.

LITERATURE

1. Janot MS, Belyaev O, Kersting S et al. Indications and early outcomes for total pancreatectomy at a high-volume pancreas center. HPB Surg World J Hepatic Pancreat Biliary Surg 2010;2010:686702.
2. Nikfarjam M, Low N, Weinberg L et al. Total pancreatectomy for the treatment of pancreatic neoplasms. ANZ J Surg 2014;84:823-6.
3. Maeda H, Hanazaki K. Pancreatogenic diabetes after pancreatic resection. Pancreatology 2011;11:268-76.
4. Slezak LA, Andersen DK. Pancreatic resection: effects on glucose metabolism. World J Surg 2001;25:452-60.
5. Dresler CM, Fortner JG, McDermott K et al. Metabolic consequences of (regional) total pancreatectomy. Ann Surg 1991;214:131-40.
6. Hrynyk M, Neufeld RJ. Insulin and wound healing. Burns J Int Soc Burn Inj 2014;40:1433-46.
7. Chen X, Liu Y, Zhang X. Topical insulin application improves healing by regulating the wound inflammatory response. Wound Repair Regen 2012;20:425-34.
8. Eshuis WJ, Hermanides J, van Dalen JW et al. Early postoperative hyperglycemia is associated with postoperative complications after pancreatoduodenectomy. Ann Surg 2011;253:739-44.
9. Okabayashi T, Shima Y, Sumiyoshi T et al. Intensive versus intermediate glucose control in surgical intensive care unit patients. Diabetes Care 2014;37:1516-24.
10. Braga M, Ljungqvist O, Soeters P et al. ESPEN Guidelines on Parenteral Nutrition: surgery. Clin Nutr 2009;28:378-86.
11. Ward N. Nutrition support to patients undergoing gastrointestinal surgery. Nutr J 2003;2:18.
12. Seaquist ER, Anderson J, Childs B et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95.
13. Smedley F, Bowling T, James M et al. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. Br J Surg 2004;91:983-90.
14. Brennan MF, Pisters PW, Posner M et al. A prospective randomized trial of total parenteral nutrition after major pancreatic resection for malignancy. Ann Surg 1994;220:436-441, discussion 441-4.
15. Heise T, Nosek L, Rønn BB et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes 2004;53:1614-20.
16. Billings BJ, Christein JD, Harmsen WS et al. Quality-of-life after total pancreatectomy: is it really that bad on long-term follow-up? J Gastrointest Surg 2005;9:1059-66, discussion 1066-7.
17. Hartwig W, Gluth A, Hinz U et al. Total pancreatectomy for primary pancreatic neoplasms: renaissance of an unpopular operation. Ann Surg 2015;261:537-46.
18. Müller MW, Friess H, Kleeff J et al. Is there still a role for total pancreatectomy? Ann Surg 2007;246:966-74, discussion 974-5.
19. Watanabe Y, Ohtsuka T, Matsunaga T et al. Long-term outcomes after total pancreatectomy: special reference to survivors' living conditions and quality of life. World J Surg 2015;39:1231-9.
20. Parsaik AK, Murad MH, Sathananthan A et al. Metabolic and target organ outcomes after total pancreatectomy: Mayo Clinic experience and meta-analysis of the literature. Clin Endocrinol (Oxf) 2010;73:723-31.