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Mini Review

Management of Total Pancreatectomy-Induced Diabetes Mellitus: A Mini-Review

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Abstract

Total pancreatectomy currently applies to only selective cases of pancreatic disorders, like pre-malignant lesions, familial pancreatic cancer, neuroendocrine tumors, fistulas, nesidioblastosis and finally chronic pancreatitis that are unresponsive to standard therapy. Metabolic effects associated with this surgical procedure are very difficult to treat. Infact, as results of total pancreatectomy, both exocrine function and endocrine secretions are lost. The aim of this mini-review is to summarize actual standards of care for this type of secondary diabetes (3c, T3cD) due to the lack of specific guidelines. Daily multiple exogenous insulin injections still represent the gold standard for treating T3cD. Continuous Glucose Monitoring and Subcutaneous Insulin Injection techniques help treatment of total pancreatectomy-related diabetes. While insulin represents gold standard therapy for T3cD, emerging evidence shows usefulness of autologous islet cell transplantation upon total pancreatectomy. Nevertheless, concerns about safety, efficacy and durability of this approach require further study.

Keywords: Hyperglycemia; Therapy; Brittle diabetes; Insulin supplementation; Islet auto graft

Abbreviations

T3cD: Type 3c Diabetes; TP: Total Pancreatectomy; MDI: Multi Daily Insulin Injections; CSII: Continuous Subcutaneous Insulin Infusion; IAT: Islet Autologous Transplantation

Mini Review

Nowadays, TP is a safe surgical procedure indicated for neoplastic and not neoplastic diffuse and otherwise untreatable pancreatic diseases. Main indications are premalignant lesions like pancreatic intraepithelial neoplasia, and intraductal papillary mucinous neoplasm; familial pancreatic cancers (essentially due to mutations of BRCA2, STK11, p16/CDKN2 and PALB2 genes); recurrent, multicentric and locally advanced neuroendocrine tumors; pancreatic fistula; and nesidioblastosis [1,2]. However, the most frequent cause of TP is severe chronic pancreatitis unresponsive to a variety of possible treatments, including dietary regimens, drugs (analgesic like opiates, anti-inflammatory, and neurotropic agents), as well as more or less invasive procedures like chemical neurolysis, Endoscopic Retrograde Cholangiopancreatography (ERCP), spinal cord stimulation or intrathecal drug delivery devices [3].

Both endocrine and exocrine functions of the pancreas are fatally lost after total pancreatectomy. As for the former, the intervention induces loss of both, the insulin secreting α-cells but also glucagon secreting α-cells. Loss of α-cells means abrogation of the counter-regulatory system that usually protects from deleterious effects of hypoglycemia, and greatly helps maintenance of normal Blood Glucose (BG) levels under any circumstances. On the non-endocrine pancreatic front, TP patients experience all the symptoms associated with exocrine pancreatic insufficiency: abdominal bloating, cramps after meals, flatulence, fatty or oily and frequent stools, indigestion and weight loss. In fact, the total absence of pancreatic exocrine enzymes leads to malabsorption of almost all nutrients, micronutrients and fat-soluble vitamins. Pancreatic Exocrine Enzyme Replacement Therapy (PERT) is therefore indispensable for control of the malabsorption syndrome. Moreover, impairment of digestive function in these patients makes it hard to manage insulin replacement therapy [4].

Following guidelines, because of similarities between T1D and T3cD, the gold standard for treating the latter is insulin. However, there are relevant differences between the two forms of diabetes, owing the total absence of the gland and its secretory products in T3cD. As above touched, the complete lack of glucagon and somatostatin production impairs extent of affordable glycemic control by insulin therapy, other than representing a tangible risk for patients undergoing hypoglycemia due to the absence of hypoglycemia-linked counter-regulatory system [5]. These points justify the term “brittle” used to define T3cD.

A pivotal role, in an attempt to improve glycemic control in these patients, is played by their education on adhering to correct dietary regimens, both, before and after TP. In particular, care should be taken to either avoid skipping meals, or having small and frequent meals, or measuring blood glucose levels on a frequent basis, or finally, minimizing high-sugar content/high-glycemic index food [6]. Moreover, carbohydrates counting may further help reaching stable blood glucose control during insulin therapy. An appropriate counseling for correct physical exercise could also help all patients with T3cD: all together, dietary prescriptions, exercise and appropriate insulin dosage synergistically act to prevent threatening severe hypoglycemic events.

Absence of the whole pancreas, upon TP, prevents other therapeutic approaches different from exogenous insulin

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supplementation. In particular, use of Metformin should not be recommended due to its adverse gastrointestinal side effects (floating, abdominal distension and discomfort, diarrhea) coupled with impaired absorption of micronutrients (ie Vitamin B12). The same applies to Acarbose. Incretin-system based agents (DPP4 inhibitors and GLP1 receptor agonists) cannot surrogate the total absence of insulin, and in addition to this, the action of GLP1 agonists on gastrointestinal motility could even worsen the patients' abdominal discomfort. No studies have investigated the role of SGLT2 inhibitors in this kind of patients [7]. However, all these statements about therapy are based on few studies because of both small number of TP patients and ethical concerns related to treatment of their brittle diabetes.

Hence, exogenous insulin actually represents the only viable treatment for T3cD. Multiple daily insulin injections are quite difficult to manage, because of a series of clinical problems that these patients developed after TP, especially those who never took medications for diabetes before. Apart from patients that receive TP because of chronic pancreatitis, all the others could should radically change their habits, as far as both nutritional and behavioral aspects are concerned. Scientific and technological improvements offer new helpful tools, such as new human insulin analogic molecules, that perform significantly better than older formulations, in conjunction with new insulin delivering systems and Continuous Glucose Monitoring devices. In the last years, FDA and other international Regulatory Agencies have approved for human clinical use new short- and long-term acting insulin analogues for basal and bolus administration purposes (or together within a basal-bolus intensive insulin therapy regimen). Insulins Degludec and Glargine U300 represent two new long acting analogues with a flat and stable pharmacokinetics and pharmacodynamics profile. These new insulin molecules have significantly improved basal glucose control and cut-off time periods uncovered by circulating insulin, as it happened with older long-acting previous preparations. Likewise, the new short-acting insulin molecules, lyspro, aspart and glulysine have afforded incomparably better control of meals-related BG over-excursions. Moreover, they cut-off the time of insulin administration before the meal. All these innovations greatly help patients to improve management of T3cD. Because of patients' possible poor compliance with these insulin therapy regimens, other options may apply. For instance, Continuous Subcutaneous Insulin Infusion (CSII) systems, avoiding multiple insulin injections, and Continuous Glucose Monitoring (CGM) devices could improve the quality of life of TP patients [8]. While high glycemic levels may be easy to control by multiple daily insulin injections, the risk of hypoglycemia continues to be a still threatening problem related to this approach, due to the mentioned lack of a glucagon based-counter-regulatory system. Waiting for clinical approval of intranasal glucagon as an immediate way of delivery of the hormone in case of severe hypoglycemia, CSII integrated with CGM may represent the best therapeutic option for TP patients, in terms of improvement of compliance with treatment and quality of life. Moreover, minimizing risk for severe hypoglycemia helps prevention of ominous consequences. In fact, sensor-augmented CSII therapy with predictive low glucose suspend manages to improve glycemic control in a few cases of Australian patient in a recent case report. The relative small number of patients suffering for T3cD could justify also in terms of pharmaco-economics, the extensive use of these newly affordable technologies to improve long-term BG control.

An a totally different, alternative therapeutic approach for TP could consist of Autologous Islet Auto-Transplantation (IAT) [9]. This kind of procedure was first performed in 1977 by the University of Minnesota Medical Center. Nowadays, beyond Minnesota, only a few Centers in the world have gained expertise for IAT. The main indication for TP-IAT is the otherwise untreatable chronic pancreatitis while intra-ductal pancreatic neoplasm and neuroendocrine tumors present only relative indications [3]. TP-IAT involves reinfusion of autologous isolated pancreatic islets most of times through the portal vein system. The presence of a laboratory with a solid expertise in islet isolation is mandatory while the appropriate islet isolation/purification process must be performed following FDA manufacturing practice regulation (GMP). In the literature, many pancreatic digestion methods are described, but the most used in the world is still today based on the perfusion of collagenase directly in the main pancreatic duct. The whole procedure maybe complicated by the actual organ conditions, because of a state of chronic inflammation affecting the gland (ie, chronic pancreatitis). The digestion enzyme infusion could be performed both, during the Major Surgery (TP) if the laboratory that operates pancreatic digestion and islet isolation is located in the same Medical Center or after the abdomen is closed, using a percutaneous approach if the laboratory is far from the operatory room. Instant Blood Mediated Inflammatory Reaction (IBMIR) and hyperglycemia immediately after TP are major problems associated with TP-IAT. Thrombin inhibition (obtained indirectly with heparin, or directly with new agents) and strict BG control (obtained by intravenous insulin delivery with BG levels clamped on 80-110 mg/dl) are mainstay to success. In fact they help both, to preserve islet function, as better as possible, by avoiding apoptosis, anoikis and other forms of cellular death (considering that almost 50% of cell dies during the first hour from transplantation).

Long-term attained insulin independence upon islet auto grafts has extensively been studied. The Minnesota group, in a recent review of their collection of patients undergoing TP-IAT, reported that 71% of patients demonstrated an improved insulin function (with 33% of insulin independence) in euglycaemia. However, the percentage of insulin function consistently decreased in the subsequent follow-up, by the years. Only a few data are available on pharmaco-economic implications of this procedure for the management of T3cD [10]. However, in selected cases of untreatable chronic pancreatitis, the procedure could certainly represent a way to substantially improve patients' quality of life, also in an attempt to avoid the onset of diabetes with its imminent difficulties for clinical management.

The islets employed for auto graft usually are not very pure; in fact it is possible to find within the preparations a certain number of acinar/ductal cells, cellular debris, damaged or dying cells and also cytokines and endotoxins [9]. If the lack of evidence of quantity or quality of the isolations is not a strict problem in order to try to avoid brittle diabetes in chronic pancreatitis TP patients, it could determine serious consequences if patients undergo TP to treat pancreatic neoplastic lesions. Some cases of metastatic pancreatic adenocarcinomas in the liver due to the inoculation of malignant cells mixed with isolated islets in TP-IAT are present in the literature [11]. These findings prevent the use of TP-IAT in patients with pancreatic

malignancies. Nevertheless, TP-IAT in patients with Pre-Malignant Pancreatic Lesions (IPMNs) or selected cases of neuroendocrine tumors (NET, up to grade 2) is approved in a few Centers worldwide. In particular, some very recent data demonstrate feasibility, efficacy, and safety of TP-IAT in patients with NET: the risk of tumor cells spreading in the liver was the same with or without isolated islets infusion [12].

In summary, T3cD remains a challenging and difficult problem in terms of clinical management. TP is a major but not unique cause for T3cD, with the typical abrogation of both endocrine and exocrine pancreatic functions. Up to now, there are no guidelines for the treatment of this form of diabetes that is usually treated like type 1 diabetes. Insulin represents the gold standard treatment option, especially using sensor augmented CSII in order to avoid severe hypoglycemia due to total absence of glucagon. However, in selected cases of patients who undergo TP for otherwise untreatable chronic pancreatitis a concurrent infusion of autologous isolated islets from the removed organ, in absence of the patient's immunosuppression, remains an option confined to few excellence Centers. Finally, there only is few data corroborating use of TP-IAT in patients with pre-malignant pancreatic lesions or neuroendocrine tumors.

References

1. Maker AV, Sheikh R, Bhagia V, Diabetes Control and Complications Trial (DCCT) Research Group. Perioperative management of endocrine insufficiency after total pancreatectomy for neoplasia. Langenbecks Arch Surg. 2017; 402: 873-883.
2. Del Chiaro M, Rangelova E, Segersvärd R, Arnelo U. Are there still indications for total pancreatectomy? Updates Surg. 2016; 68: 257-263.
3. Schrope B. Total pancreatectomy with autologous islet cell transplantation. Gastrointest Endoscopy Clin N Am. 2018; 28: 605-618.
4. Petzel MQB, Hoffman L. Nutrition implication for long-term survivors of pancreatic cancer surgery. Nutr Clin Prac. 2017; XX: 1-11.
5. Niwano F, Hiromine J, Noso S, Babaya N, Ito H, Yasutake S, et al. Insulin deficiency with and without glucagon: a comparative study between total pancreatectomy and type 1 diabetes. J Diabetes Investig. 2018; 9: 1084-1090.
6. Duggan SN, Ewald N, Kelleher L, Griffin O, Gibney J, Conlon KC. The nutritional management of type 3c (pancreatogenic) diabetes in chronic pancreatitis. Eur Clin Nutr. 2016; 1-6.
7. Makuc J. Management of pancreatogenic diabetes: challenges and solutions. 2016; 9: 311-315.
8. Scott ES, Fulcher GR, Clifton-Bligh RJ. Sensor-Augmented CSII therapy with predictive low-glucose suspend following total pancreatectomy. Endocrinology, Diabetes& Metabolism Case Report. 2017; 2017: 17.
9. Dunn TB, Wilhelm JJ, Bellin MD, Pruett TL. Autologous islet transplantation: challenges and lessons. CurrOpin Organ Transplant 2017; 22: 000-000.
10. Bellin MD, Abu-El-Haija M, Morgan K, Adams D, Beilman GJ, Chinnakotla S, et al. A multicenter study of total Pancreatectomy with Islet Autotransplantation (TPIAT): POST (Prospective Observational Study of TPIAT). Pancreatology. 2018; 1-5.
11. Muratore S, Zeng X, Korc M, McElyea S, Wilhelm J, Bellin M, et al. Metastatic pancreatic adenocarcinoma after total pancreatectomy islet autotransplantation for chronic pancreatitis. Am J Transplant. 2016; 16: 2747-2752.
12. Balzano G, Maffi P, Nano R, Mercalli A, Melzi R, Aleotti F, et al. Diabetes-free survival after extended pancreatectomy and Islet Autotransplantation for benign or borderline/malignant lesions of pancreas. Am J Transplant. 2018; 19: 920-928.

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