

**Mini-Review**

**Pancreatic Islet Autotransplantation with Total Pancreatectomy  
for Chronic Pancreatitis**

**Tamotsu Kuroki, Tomohiko Adachi, Shinichiro Ono, Takayuki Tanaka,  
Amane Kitasato, Susumu Eguchi**

**Running title:** Islet Autotransplantation for CP

**Department of Surgery, Nagasaki University, Graduate School of  
Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan**

**Correspondence to:** Tamotsu Kuroki, Department of Surgery,  
Nagasaki University, Graduate School of Biomedical Sciences,  
1-7-1 Sakamoto, Nagasaki 852-8501, Japan.

**e-mail:** tkuroki-gi@umin.ac.jp

**Telephone:** +81-95-8197316

**Fax:** +81-95-8197319

**Abstract**

Pain relief and improvement in quality of life are the main targets for treatment of chronic pancreatitis. The use of total pancreatectomy for chronic pancreatitis is a radical and in some ways ideal strategy. However, total pancreatectomy is associated with severe diabetic control problems. Total pancreatectomy with islet autotransplantation can relieve severe pain and prevent post-surgical diabetes. In islet autotransplantation, patients with chronic pancreatitis receive their own islet cells and therefore do not require immunosuppression. In the future, total pancreatectomy with islet autotransplantation may be considered a treatment option for chronic pancreatitis patients.

**Key words:** chronic pancreatitis, islet autotransplantation.

## **Introduction**

Chronic pancreatitis is a benign inflammatory disease characterized by fibrosis and destruction of the whole pancreas, which leads to irreversible and severe damage of both exocrine and endocrine functions.<sup>1-5</sup> This inflammation causes intractable abdominal pain. The purpose of surgical treatment for chronic pancreatitis is pain management.<sup>6</sup> Several surgical procedures have been proposed for the treatment of pain caused by chronic pancreatitis, including drainage procedures such as the Partington-Rochelle procedure and resection procedures such as pancreaticoduodenectomy, distal pancreatectomy, and total pancreatectomy.<sup>7-11</sup> Resection procedures, especially total pancreatectomy, cause severe and permanent pancreatic endocrine and exocrine insufficiency. On the other hand, total pancreatectomy with islet cell autotransplantation to treat chronic pancreatitis was first performed at the University of Minnesota in 1977.<sup>12</sup> Since then, more than 500 islet autotransplantations with near-total or total pancreatectomy have been performed for chronic pancreatitis.<sup>13</sup> This treatment strategy, which is a combination of a surgical procedure and

transplantation, has the potential to be the ideal therapy to resolve the patient's unbearable abdominal pain due to chronic pancreatitis without causing permanent pancreatic endocrine and exocrine insufficiency (Table 1).

## **Chronic Pancreatitis**

Severe recurrent abdominal pain is common and frequently debilitating in patients with chronic pancreatitis, and it is the symptom that most affects quality of life in patients with this condition.<sup>14-16</sup> The main cause of abdominal pain in chronic pancreatitis is the elevated pressure in the pancreatic ducts or in the pancreatic parenchyma due to the obstruction of the pancreatic ducts.<sup>6</sup> Therefore, surgical drainage or endoscopic therapy is associated with decompressing the pancreatic ducts to achieve pain relief in patients with chronic pancreatitis. However, recent studies found that severe pain is caused by nerve injury and a neuroimmune interaction between neuronal processes and chronic inflammation.<sup>17, 18</sup>

Cahen et al.<sup>19</sup> reported that, in a randomized trial, a surgical drainage procedure was more effective than endoscopic treatment in patients with obstruction of the pancreatic duct due to chronic pancreatitis. On the other hand, the choice of surgical methods used in various kinds of surgical procedures is important. Strate et al.<sup>20</sup> reported that there were no differences between radical resection (pylorus-preserving pancreatoduodenectomy)

and the organ-sparing extended drainage procedure (Frey procedure) with respect to quality of life and pain control after long-term follow-up, with no differences in the exocrine or endocrine functions. Total pancreatectomy is a radical and in some ways ideal treatment option, because this approach aims to completely remove the whole pancreas affected by chronic pancreatitis. Moreover, duodenum-preserving total pancreatectomy is the best procedure for the whole resection of the pancreatic parenchyma. However, it is well known that duodenum-preserving method is associated with duodenal ischemia by the interruption of the pancreaticoduodenal vascular arcade.<sup>7</sup> Although total pancreatectomy is a challenging procedure to perform and has been associated with high morbidity and mortality rates, recent reports comparing total pancreatectomy and pancreaticoduodenectomy demonstrate comparable outcomes.<sup>21, 22</sup> In addition, total pancreatectomy has an advantage as compared with the pancreatic resection procedures, in that there is no potential for pancreatic fistula, which is a lethal complication. However, patients undergoing total pancreatectomy often contact the brittle form of diabetes, in which the hyperglycemia and

hypoglycemia are particularly difficult to control.<sup>23, 24</sup>

Chronic pancreatitis patients undergoing total pancreatectomy are candidates for islet transplantation.<sup>25-30</sup> Other indications for islet transplantation are uncontrolled diabetes with pancreatic resection procedures or irreversible insufficiency of endocrine/exocrine function due to chronic pancreatitis. In addition, patients who have undergone near-total pancreatectomy for uncontrolled pancreatic pseudocyst or for pancreatic fistula associated with chronic pancreatitis are candidates for islet transplantation.

### **Islet Autotransplantation**

After excision of the whole pancreas, in general, the main pancreatic duct is cannulated and the pancreatic parenchyma is distended with collagenase and digested. Islet cells are liberated from the surrounding tissue, then isolated islet cells are infused and transplanted into the liver via the portal vein.

The purpose of islet autotransplantation following total pancreatectomy is to prevent postsurgical diabetes. Therefore, preoperative tests of glycemic control and islet function,

including the glucose tolerance test and serum Hemoglobin A1c level measurement, are important steps in determining the indications for islet autotransplantation following total pancreatectomy.<sup>25</sup> Patients who show normal results in preoperative testing of glycemic control and islet function can be considered for islet autotransplantation following total pancreatectomy. Ultimately, the decision to perform islet autotransplantation following total pancreatectomy, should be undertaken only after multidisciplinary discussions among the pancreatic surgeon, a diabetologist, a gastroenterologist, a pain specialist, and a medical psychologist.<sup>25</sup>

Determining the ideal timing for total pancreatectomy with islet autotransplantation for patients with chronic pancreatitis is important for better quality-of-life. Kobayashi et al.<sup>31</sup> reported that the degrees of pancreatic fibrosis and acinar atrophy were inversely correlated with islet yield in pediatric patients with chronic pancreatitis and suggested that total pancreatectomy with islet autotransplantation should be considered early in the course of chronic pancreatitis. In another report, the same Minnesota group<sup>32</sup> found that pancreatic biopsies

from three young patients who underwent total pancreatectomy with islet autotransplantation for the management of chronic pancreatitis provided unique evidence of islet neogenesis from pancreatic ductal progenitor cells. These findings suggest that pancreatic ductal precursors may play an important role as one source of islet neogenesis in patients with chronic pancreatitis. Thus, while chronic pancreatitis presents severe destructive inflammation with irreversible ductal and parenchymal destruction, islet neogenesis from ductal precursors can result from islet autotransplantation in chronic pancreatitis patients. Takita et al.<sup>33</sup> reported that excellent glycemic control was observed in both the early-stage and advanced-stage chronic pancreatitis groups who received total pancreatectomy with islet autotransplantation. Interestingly, the advanced-stage chronic pancreatitis group had larger islet size than the early-stage group, even though the total islet yield in this group was lower.

On the other hand, predictive factors associated with successful islet autotransplantation following total pancreatectomy are important. Several reports have suggested that the number of islets transplanted is a key factor in transplant

success. Sutherland et al.<sup>29</sup> reported that insulin independence was observed at 1 year following autotransplantation in 63% of patients receiving greater than 5,000 IE/kg. Bellin et al.<sup>34</sup> reported that an islet yield greater than 2,000 IE/kg was an important predictor of insulin independence. White et al.<sup>35</sup> reported that insulin independence appeared to be related to the number of islet cells transplanted (>3,000 IEQ/kg). On the other hand, Ahmad et al.<sup>36</sup> reported that transplantation of more than 6,635 IEQ/kg was associated with a chance of becoming insulin independent, and that patients with increased body mass indices were less likely to benefit from total pancreatectomy with islet autotransplantation and should be counseled to lose weight before islet autotransplantation. In this report, 40% of 45 chronic pancreatitis patients who underwent total pancreatectomy with autotransplantation were insulin free after a mean follow-up of 18 months. In another large series, the Minnesota group reported that 39% of 112 chronic pancreatitis patients with islet autotransplantation remained insulin independent.<sup>37</sup>

The aim of total pancreatectomy in the treatment of chronic pancreatitis is to relieve pain and restore quality of life.<sup>38</sup> It

is difficult to quantitatively evaluate the pain that the patient suffers after islet autotransplantation. A Cincinnati group<sup>36</sup> standardized narcotic usage by conversion to morphine equivalents, and found a marked reduction of postoperative morphine equivalents (mean 90 mg) after total pancreatectomy compared with preoperative morphine equivalents (mean 206 mg); in addition, 58% of chronic pancreatitis patients had a notable reduction in chronic abdominal pain as demonstrated by narcotic independence at the last follow-up. The Cincinnati series<sup>39</sup> also reported a significant improvement in quality of life using a validated standard assessment questionnaire (SF-36). The Minnesota group<sup>37</sup> reported that 72% of patients showed resolved or improved pain status after total pancreatectomy. Morgan et al.<sup>40</sup> reported that pain control and quality of life after total pancreatectomy with islet autotransplantation for chronic pancreatitis were measured by daily oral morphine equivalents and by the SF-12 questionnaire. On the other hand, Lieb et al.<sup>17</sup> reported the pain relief following the modified Puestow operation and lateral pancreaticojejunostomy, which are the most common surgical procedures for chronic pancreatitis, in a review article. They

showed that short-term pain relief is seen in about 80% of patients, but long-term pain relief (over five years) is observed in only about 50%.

## **Conclusion**

Although surgical drainage procedures and partial pancreatic resection have been recognized as the first surgical choices before total pancreatectomy in most institutions, indications for total pancreatectomy include small duct-type chronic pancreatitis, diffuse glandular involvement, and intractable pain after drainage and resection procedures have been performed. Total pancreatectomy alone will result in diabetes; therefore, it should be accompanied by islet autotransplantation whenever possible to prevent or minimize this development. In islet autotransplantation, patients with chronic pancreatitis receive their own islet cells and therefore do not require immunosuppression. In the future, total pancreatectomy with islet autotransplantation may be considered the gold-standard treatment for chronic pancreatitis patients.

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Table 1. Comparison of results of total pancreatectomy with islet cell autotransplantation for chronic pancreatitis.

First author	Reference	No. of patients	Operative mortality(%)	Perioperative morbidity(%)	Islet yield	Pain relief(%)	Insulin independent(%)
Gruessner	37	112	N/A	N/A	Puestow procedure subgroup Median IEQ/kg BW = 1,052 (23-5,362) Distal pancreatectomy subgroup Median IEQ/kg BW = 2,112 (861-6,102) Whipple procedure subgroup Median IEQ/kg BW = 4,719(3,761 and 5,676) None or other subgroup Median IEQ/kg BW = 3,249(92-12,601)	72	39
Sutherland	29	173	N/A	N/A	1977-1990 (n = 23) Median IEQ/kg BW = 1,375(49-12,470) 1991-1994 (n = 15) Median IEQ/kg BW = 4,558(111-17,035) 1995-2000 (n = 27) Median IEQ/kg BW = 3,121(225-10,000) 2001-2007 (n = 107) Median IEQ/kg BW = 3,054(23-8,558)	N/A	32
Ahmad	36	45	7	49	Insulin independent subgroup Mean IEQ/kg BW = 6,635 ± 229 Insulin dependent subgroup Mean IEQ/kg BW = 3,799 ± 629	72	40
Morgan	40	33	0	48	N/A	48	24
Takita	33	12	0	N/A	Advanced subgroup Mean IEQ/kg BW = 3,847 ± 739 Early subgroup Mean IEQ/kg BW = 8,556 ± 953	100	50
Argo	38	26	0	56	Mean IEQ/kg BW = 1,331 ± 304	80	N/A

N/A, data not available.

IEQ/kg BW, islet equivalents per kilogram body weight