

REVIEW

Systematic review and meta-analysis of islet autotransplantation after total pancreatectomy in chronic pancreatitis patients

Qian Wu¹⁾, Mei Zhang¹⁾, Yao Qin¹⁾, Ruimei Jiang¹⁾, Heng Chen¹⁾, Xinyu Xu¹⁾, Tao Yang¹⁾, Kuirong Jiang²⁾ and Yi Miao²⁾

¹⁾Department of Endocrinology, the First Affiliated Hospital with Nanjing Medical University, Nanjing Medical University, China

²⁾Pancreas Center, the First Affiliated Hospital with Nanjing Medical University, Nanjing Medical University, China

Abstract. Islet autotransplantation (IAT) is a viable treatment for patients with severe chronic pancreatitis, this modality may prevent brittle diabetes mellitus after pancreatectomy. This systematic review and meta-analysis was performed to evaluate the outcomes of IAT after TP and discuss the factors that may affect the efficacy of this procedure. MEDLINE, Embase, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1977 to 30 April 2014. Cohort Studies reported patients with IAT after TP were included. The studies and data were identified and extracted by two reviewers independently. Data were analyzed using STATA 12.0 and Comprehensive Meta Analysis V2 software. Random effects model, meta-regression analysis, sensitivity analysis and publication bias were conducted to improve the comprehensive analysis. Twelve studies reporting the outcomes of 677 patients were included in this review. The insulin independent rate for IAT after TP at last follow-up was 3.72 per 100 person-years (95% CI: 1.00-6.44). The 30-day mortality was 2.1% (95% CI: 1.2-3.8%). The mortality at last follow-up was 1.09 per 100 person-years (95% CI: 0.21-1.97). Factors associated with incidence density of insulin independence in univariate meta-regression analyses included islet equivalents per kg body weight (IEQ/kgBW) ($P=0.026$). Our systematic review suggests that IAT is a safe modality for patients with CP need to undergo TP. A significant number of patients will achieve insulin independence for a long time after receiving enough IEQ/kgBW.

Key words: Systematic review, Meta-analysis, Islet autotransplantation, Chronic pancreatitis

CHRONIC PANCREATITIS (CP) is a chronic inflammatory disease of pancreatic tissue caused by different kinds of causes, and can result to irreversible dysfunction of pancreas. Its pathological features are atrophy and damage of pancreatic acinar and interstitial fibrosis[1]. The main clinical symptoms are recurrent abdominal pain and (or) endocrine dysfunction of the pancreas, these can be accompanied with pancreatic parenchyma calcify, dilated pancreatic duct and pancreatic pseudocyst, etc. Total pancreatectomy (TP) was the final resort which could greatly reduce the intractable

pain for patients with severe CP, but can inevitably lead to irreversible dysfunction of endocrine and exocrine which can manifestation as “brittle diabetes”[2].

As we know, the world's first clinical islet autotransplantation (IAT) was performed at the University of Minnesota in 1977 [3] and shows an exciting result that the woman who underwent IAT after near-TP remained insulin independent for 6 years until died of a cause unrelated to IAT [4]. Since then, a growing number of centers started to do clinical trials of IAT. Now IAT has been thought to be an accepted modality of treatment for patients with CP in many western countries, this procedure may preserve the remaining beta cells function to prevent brittle diabetes mellitus so that can improve patients' quality of life.

To further evaluate outcomes of IAT after TP, we performed a systematic review of IAT after total pancreatectomy in chronic patients. Our aim was to analyze the rate of insulin independence, mortality and metabolic outcomes of IAT in the world's main IAT central.

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Correspondence to: Mei Zhang, Department of Endocrinology, the First Affiliated Hospital with Nanjing Medical University, Nanjing Medical University, 300 Guangzhou Road, Nanjing, Jiangsu, 210029, China. E-mail: zhangmei@njmu.edu.cn,

Abbreviations: CP, chronic pancreatitis; IAT, islet autotransplantation; IEQ/kgBW, islet equivalents per kg body weight; TP, total pancreatectomy; IQR, Inter Quartile Range

Materials and Methods

Literature and search strategy

Databases MEDLINE, EMBASE, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1977 to 30 April 2014. We used the National Library of Medicine's MeSH (Medical Subject Headings), and key words to construct our search strategy. The search strategy was #1: islet transplantation of langerhans; #2: islet autotransplantation; #3: transplantation, autologous; #4: pancreatitis; #5: pancreatectomy; #6: human; #7: ((#1 OR #2 OR #3) AND (#4 OR #5) AND #6). We imported the literature results into Endnote X7 and deleted duplicated studies. We also scanned the reference lists of included studies and relevant systematic reviews.

Inclusion and exclusion criteria

To determine whether an individual study was eligible for inclusion in the meta-analysis, all of the studies identified were carefully reviewed by two investigators working independently, any discrepancies were resolved by discussion and, when necessary, adjudicated by a third reviewer. The inclusion and exclusion criteria were as follows: Individuals of any age, gender and population that have been definitely diagnosed with chronic pancreatitis before underwent IAT into the liver post TP were included. Patients accompany with other diseases that can affect survival time, such as malignant tumor were excluded. Case reported studies were excluded. Clinical cohort studies report less than five patients or have a median length of follow-up less than 6 months were excluded. Studies not offer detail data we need were also excluded.

Data extraction

Data were independently extracted by two investigators who reached a consensus on all of the items. Information extracted from each study was considered as follows: first author, year of operation, descriptions of patients and the outcomes we interested in, such as insulin independence rate and mortality.

Quality assessment of included studies

Two reviewers assessed methodological quality independently according to the Newcastle-Ottawa Scale (NOS). Any discrepancies were resolved by discussion, if disagreements cannot be resolved, a third reviewer were consulted.

Statistical analysis

Data from studies' results were analyzed using STATA 12.0 and Comprehensive Meta AnalysisV2 software. For studies reported quantitative data, a meta-analysis were undertaken when studies are sufficiently homogeneous. Dealing with missing data: we contacted original authors to clarify missing data or data which were not clearly reported. Statistical heterogeneity was assessed by the forest plots. If more than three studies were to be identified, we performed random-effects analysis. If only two or three studies were to be identified, we performed a fixed-effects model meta-analysis. Insulin independence was defined as completely insulin-free state despite the C-peptide status. When describe the rates of mortality and insulin independence, we used number of positive patients per 100 person-years as incidence density to rule out the follow-up length heterogeneity in different studies. All summary effects are presented with 95% CI[5]. We determined the heterogeneity using the I^2 statistic which means the proportion of the unexplained heterogeneity by the estimates variability. I^2 values of <25%, 25–50% and >50% represent minimal, moderate and substantial heterogeneity, respectively[6]. Meta-regression analysis was used to test whether an association exists between the incidence density of insulin independence and the factors that may affect outcome of this procedure, such as the IEQ/kgBW, baseline diabetes mellitus proportion, alcoholic patients proportion, the female gender proportion, chronic pancreatitis duration and year of operation, Publication bias was assessed by the funnel plots and Egger's test.

Results

Characteristics of studies

We retrieved 529 references from the electronic database. The selection of the references was described in the Flow diagram in Fig. 1. 12 studies reporting the outcomes of 677 patients met the inclusion and exclusion criteria [7-18]. Main study characteristics were described in Table 1. The total patients number were 677, the mean age was 37.7 years and the duration of pancreatitis was 6.6 years. Among the patients included, the female percent was 70%. The follow-up length ranged from 1 to 210 months. The quality of the included studies was suboptimal (Table 2). The included studies were all single-centre case series. Loss of follow-up was reported in nine studies There

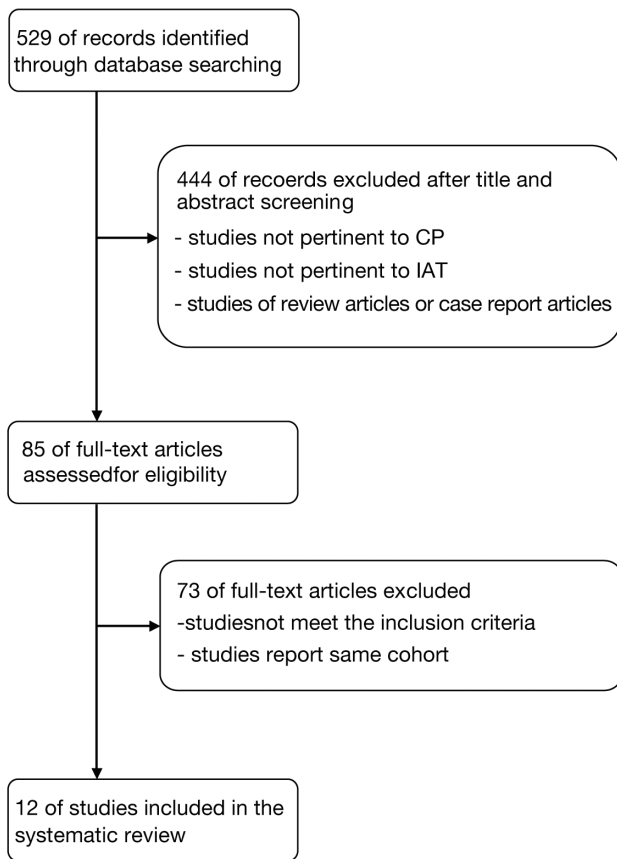


Fig. 1 Flow diagram of the references selection

was no evidence of publication bias (P values for Egger's test for all outcomes >0.05). However, tests for publication bias are unreliable when the included studies' number is <20 .

Outcomes of IAT post-TP

The raw data of outcomes reported by included studies were described in Table 3. Results of random effect meta-analysis were showed in Table 4. Fig. 2 depicted meta-analysis of incidence density of insulin independence and mortality. Fig. 3 showed the univariate meta-regression outcomes between incidence of density of insulin independence between IEQ/kgBW. Detail results of meta-regression analysis were showed in Table 5.

Insulin independent rate

When we analyzed the insulin independence rate at the last follow-up, 11 studies were included except one that not reported it (Table 3). The incidence density of insulin independence was 3.72 per 100 person-years (95% CI: 1.00–6.44, $I^2=73$) (Fig. 2). The insulin independence rate at 1 year follow-up was 28.4% (95% CI: 15.7–46.0) of 362 patients reported by five studies [7, 8, 10, 15, 17]. The insulin independence rate at 2 year follow-up was 19.7% (95% CI: 5.1–52.6%) of 297 patients reported by three studies [10, 15, 17]. The transient insulin independence rate was 7.01 per 100 person-

Table 1 Characteristics of patients undergone IAT after TP reported by included studies

Studies	Period of inclusion	Islet isolation Institution	No. of patients	Female %	Age (years)	Duration of CP(years)	Baseline DM%	Alcoholic %	Length of follow-up (months)	Transplanted IEQ/kg body weight
Cameron <i>et al.</i> [7]	1978-1980	Johns Hopkins	8	13	43.1 \pm 10.9	6.7(1-20)	0	75	NR	NR
Hinshaw <i>et al.</i> [8]	1979-1980	California	5	20	42.4 \pm 5.7	5.6 \pm 3.8	20	80	13 \pm 5.2	NR
Rastellini C <i>et al.</i> [9]	1990-1996	Pittsburgh Centre	5	NR	NR	NR	0	NR	3-64	NR
Oberholzer <i>et al.</i> [10]	1992-1999	Geneva	6	NR	NR	NR	NR	NR	45.7 \pm 17.5	2785 (386–3223)
Ahmad <i>et al.</i> [11]	2000-2004	Cincinnati	45	67	39(16-62)	NR	NR	4	18(1-46)	4933 \pm 520
Argo <i>et al.</i> [12]	2005-2007	UAB	21	40	43.5 \pm 2.4	NR	100	30	6.7 \pm 1.7	1551 \pm 368
Dixon <i>et al.</i> [13]	1998-2008	South Carolina	7	57	M:29,F:40	NR	0	NR	NR	NR
Takita <i>et al.</i> [14]	2006-2009	Baylor	17	76	40.1	7.0	6	12	7.3 \pm 2.6	5279 \pm 571
Sutherland <i>et al.</i> [15]	1977-2011	Minnesota	409	74	35.3(5-69)	6.6 \pm 0.3	8	7	NR	NR
Walsh <i>et al.</i> [16]	2007-2010	Cleveland Clinic	20	40	43 \pm 13.3	NR	0	25	12(6.75-24)	3846(3063-5430)
Dorlon <i>et al.</i> [17]	2009-2012	South Carolina	74	80	42(16-69)	8(1-28)	14	8	NR	4114
Garcea <i>et al.</i> [18]	1990-2013	Leicester	60	NR	43(21-65)	5(0.5-35)	NR	31.7	138(6-210)	NR

IAT, islet autotransplantation; TP, total pancreatectomy; IEQ, islet equivalents; DM, diabetes mellitus; NR, not reported. Results are reported as mean (range) or mean \pm SD.

Table 2 Quality of included studies

Studies	Selection	Comparability	Exposure	Total
Cameron <i>et al.</i> [7]	3	0	3	6
Hinshaw <i>et al.</i> [8]	2	0	3	5
Rastellini C <i>et al.</i> [9]	3	0	3	6
Oberholzer <i>et al.</i> [10]	2	0	3	5
Ahmad <i>et al.</i> [11]	2	0	2	4
Argo <i>et al.</i> [12]	2	0	2	4
Dixon <i>et al.</i> [13]	3	0	2	5
Takita <i>et al.</i> [14]	2	0	2	4
Sutherland <i>et al.</i> [15]	2	0	3	5
Walsh <i>et al.</i> [16]	3	0	2	5
Dorlon <i>et al.</i> [17]	2	0	3	5
Garcea <i>et al.</i> [18]	3	1	3	7

Table 3 Outcomes of interest

Studies	No. of patients	30-day mortality (%)	Cumulative mortality at last follow-up (%)	II rate at last follow-up (%)	II rate at 1-year follow-up (%)	II rate at 2-year follow-up (%)	Patients having some period of II (%)	Median length of II in patients having some period of II (months)	C-peptide at last follow-up (ng/mL)	HbA1c at last follow-up (%)	Insulin dosage in ID patients (U/day)
Cameron <i>et al.</i> [7]	8	13	13	38	25	NR	75	7.5 (3–22)	NR	NR	15–25 (at last follow up)
Hinshaw <i>et al.</i> [8]	5	0	0	40	67	NR	80	10.5 (2–20)	NR	NR	14–24 (at last follow up)
Rastellini C <i>et al.</i> [9]	5	NR	0	80	NR	NR	80	NR	NR	NR	NR
Oberholzer <i>et al.</i> [10]	6	0	67	0	50	40	67	16.5 (8–54)	NR	NR (5.88±0.84 at 6 months)	NR
Ahmad <i>et al.</i> [11]	45	2	7	40	NR	NR	NR	NR	NR	NR	18.9±2.9 (when discharge)
Argo <i>et al.</i> [12]	21	0	0	0	NR	NR	0	0	NR (1.7±0.57 at 6 months)	NR (7.5±0.47 at 6 months)	17.4±4.1 (3 month) 23±6 (6 month)
Dixon <i>et al.</i> [13]	7	0	14	20	NR	NR	20	12	NR	NR	NR
Takita <i>et al.</i> [14]	17	0	0	47	NR	NR	47	NR	NR (1.4±0.36 at 6 months)	NR (6.7 at 6 months)	NR
Sutherland <i>et al.</i> [15]	409	1.2	38	NR	28	32	NR	NR	NR (90%>0.6 at 3 year)	NR	NR
Walsh <i>et al.</i> [16]	20	0	0	20	NR	NR	20	NR	0.4	7.72	11.6 (3–33) (at last follow up)
Dorlon <i>et al.</i> [17]	74	0	0	5	12	5	16	NR	NR	NR (7.1 at 6 months 7.7 at 1 year 8.5 at 2 year)	19 (at 6 month) 21 (at 1 year) 26 (at 2 year)
Garcea <i>et al.</i> [18]	60	1.7	NR	18.6	NR	NR	21.6	NR	NR	NR	22(0–88)

II, insulin independence; ID, Insulin dependent; NR, not reported

Table 4 Results of random effects meta-analysis

	Studies	Events	Total	Rate	95%CI	I ²
II rate at the 1 year follow up (%)	5	94	362	28.4	15.7 - 46.0	69
II rate at the 2 year follow up (%)	3	74	297	19.7	5.1 - 52.6	87
II rate at the last follow up (100-PY)	11	55	268	3.72	1.00 - 6.44	73
II rate in patients with transient II (100-PY)	10	56	223	7.01	2.63 - 11.40	74
Length of transient II (months)	10	NA	NA	17.72	10.91 - 24.52	94
30-day mortality (%)	11	8	672	2.1	1.2 - 3.8	0
Cumulative mortality at last follow-up (100-PY)	11	164	617	1.09	0.21 - 1.97	64

II, insulin independence; NA, not applicable; PY, person-year

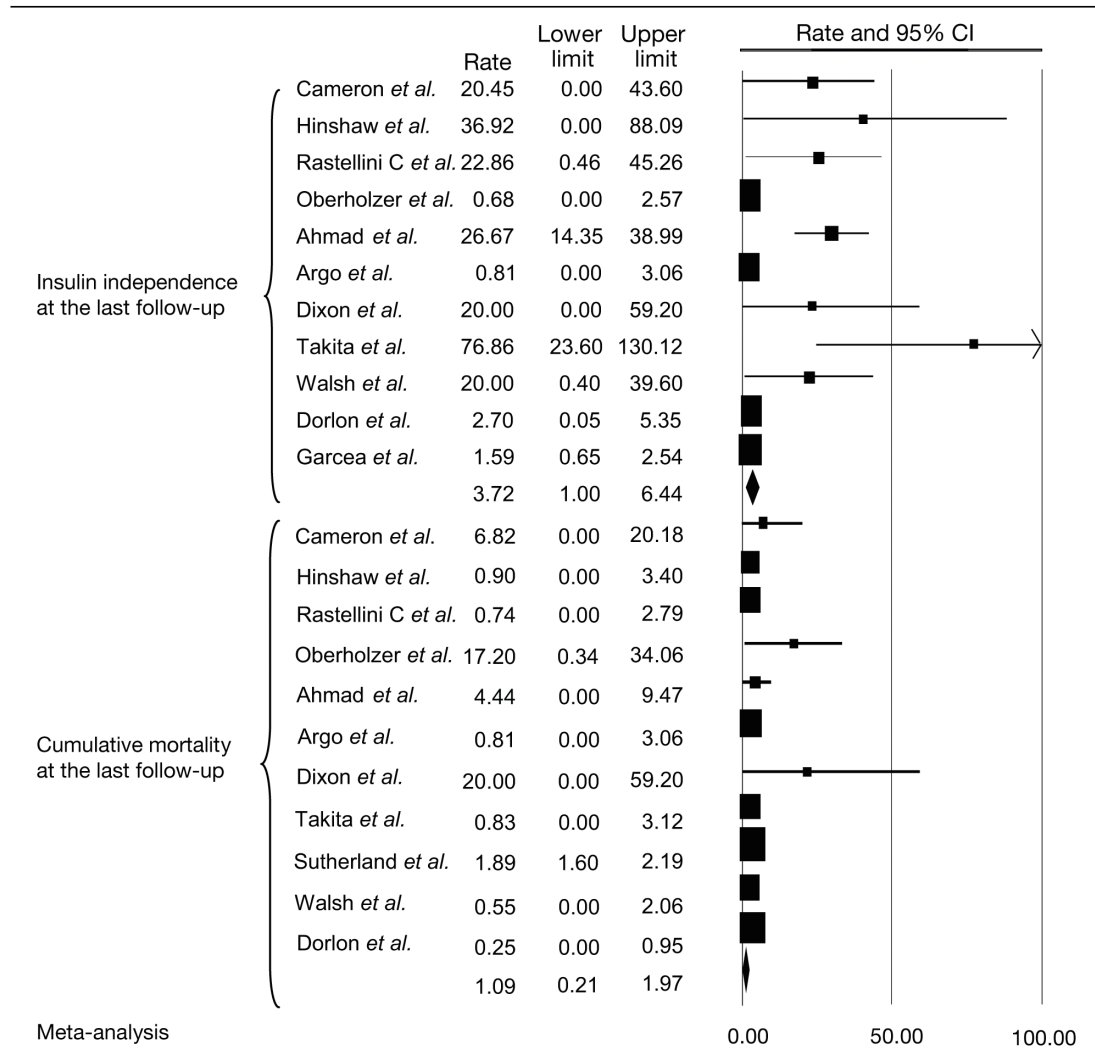


Fig. 2 Meta-analysis of insulin independence rate and cumulative mortality at last follow-up. (■ represent rate density of each study, ◆ represent the overall rate density)

Table 5 Results of meta-regression analysis

	No. of Studies	P
IEQ/kgBW	6	0.026
Baseline-DM	8	0.062
Al-P (%)	8	>0.05
Fe-P (%)	8	>0.05
CP-D	5	>0.05
Y	11	>0.05

DM, diabetes mellitus; Baseline-DM, baseline diabetes mellitus proportion; Al-P, alcoholic patients proportion; Fe-P, female gender proportion; CP-D, duration of chronic pancreatitis years; Y, year of operation

years (95% CI: 2.63-11.40, $I^2=74$). The length of transient insulin independence was 17.72 months (95%CI: 10.91-24.52) (Table 4). Islet equivalents per body weight (IEQ/kg) was reported in six studies [10-12, 14, 16, 17]. Factors associated with insulin independence in univariate meta-regression analyses included higher IEQ/kgBW ($P=0.026$) (Fig. 3). There was marginally significant association between insulin independence and baseline diabetes mellitus proportion ($P=0.062$). While, the alcoholic patients proportion, female gender proportion, chronic pancreatitis duration and the year of operation did not show statistical significance in univariate meta-regression analyze ($P>0.05$) (Table 5).

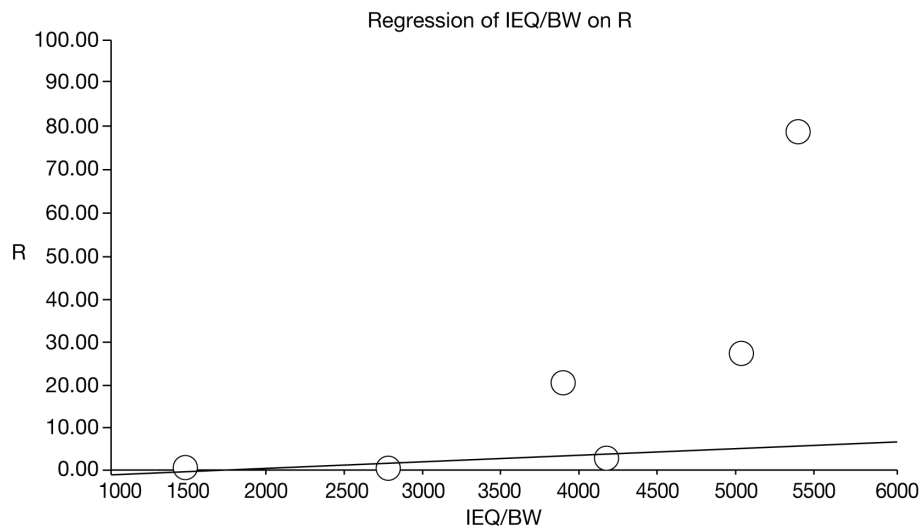


Fig. 3 Meta-regression between R and IEQ/kgBW ($P=0.026$) (R, insulin independence at the last follow up)

Mortality

11 studies reported mortality at last follow-up except one (Table 3). The incidence density of mortality was 1.09 per 100 person-years (95% CI: 0.21–1.97, $I^2=64$) (Fig. 2). The 30-day mortality was 2.1% (95% CI: 1.2–3.8%, $I^2=0$).

Metabolic outcomes

The HbA1c at 6 month was reported by three studies with mean being 7.5% [12], 7.1% [17], 6.7% [14], respectively. Dorlon *et al.* also reported HbA1c with mean being 7.7% and 8.5% at 1 year and 2 year, respectively. Wash *et al.* reported HbA1c with mean being 7.72% at last follow-up [16]. In addition, Garcea *et al.* reported lower HbA1c in the islet cell group [18]. Although there was no statistical significance between the islet and nonislet groups, patients receiving IAT had a significantly lower insulin requirement for a long time (60 months), the detail data was shown in their previous article [19]. C-peptide level at 6 month was reported by two studies with mean being 1.7 ng/mL (SD 0.57 ng/mL) [12], 1.4 ng/mL (SD 0.36 ng/mL) [14], respectively. Sutherland *et al.* reported 90% of the patients were C-peptide positive (>0.6 ng/dL) at 3 years postoperative [15]. Walsh *et al.* reported the median postoperative C-peptide level was 0.40 (IQR 0.27–1.00) at the last follow-up [16]. These data were not enough for meta-analysis.

Insulin requirement in insulin-dependent patients was showed in Table 3 reported by seven studies [7, 8, 11, 12, 16–18]. The average dose was obviously lower than patients who undergone TP alone.

Discussion

The last method for patients with severe CP is the surgical operation of the pancreas. The goals of operative therapy are to alleviate abdominal pain, preserve endocrine and exocrine function, and improve the patients' quality of life [20]. TP can totally remove the root cause of the pain, but almost 100% of the patients undergone TP alone will developed to DM [2]. We should also notice that the destructive pathology nature of CP will let a large number of CP patients to develop diabetes or impaired glucose tolerance, which means that the type of diabetes develops in these patients is similar to that following pancreatic resection [21], CP also predisposes to pancreatic cancer development [22]. Because of these bad outcomes of CP and the limits of TP, TP/IAT was an ideal treatment. This procedure can maximize the chance for patients to achieve goals of alleviate abdominal pain, preserve endocrine and exocrine function, and improve the patients' quality of life. Pediatric patients will be able to integrate back into their peer group, participate in extracurricular activities, and attend school consistently to promote mental and physical healthy. The adult patients can go back to work to realize their social value. However, published literature regarding variables relevant to the outcomes of islet autotransplantation was limited and heterogeneous. To obtain a more definitive conclusion, we conducted a meta-analysis of 12 published articles [7–18]. We believe such a meta-analysis has a much greater possibility of reaching reasonably strong conclusions.

Mortality analysis of IAT after CP indicated that IAT after TP is safe with a 30-day mortality of 2.1% and a long-term mortality of 1.09 per 100 person-years which is comparable with TP alone [23].

For the patients not achieved insulin independent, they also had partial functions of beta cells for a long time which was indicated by the high rates of C-peptide positive and no morbidity of brittle diabetes mellitus [15] and have an improved quality of life because of the intractable pain controlled, return to a normal diet, low insulin requirement than patients with TP alone and a decreasing frequency of hospital admissions. To further characterize the efficacy of IAT after CP, we performed univariate meta-regression analysis. Our analysis indicated that the IEQ/kgBW ($P=0.026$) can significantly influence the outcomes of IAT. In our data, the more IEQ/kgBW were transplanted, the higher insulin independence rate would like to be achieved (Fig. 3). Our results further verified the hypothesis conducted by Ming Dong *et al.* which reported a borderline significant association between insulin independence rate and the transplanted IEQ/kg ($P=0.055$) [24]. However, the transplanted IEQ/kg body weight related to many reasons, such as the duration, pathological of the CP and the islet isolation technique. Our analysis also showed marginally significant association between insulin independence rate and baseline diabetes mellitus proportion. The current results highlight the importance of IAT as soon as the uncontrolled CP being diagnosed or maybe an earlier timing to preserve more IEQ. The islet isolation technique is also a very important factor which directly influence the number of isolated islet cells. However, statistical significance between the incidence of density and the alcoholic patients proportion, female gender proportion, chronic pancreatitis duration or the year of operation was not observed. The meta-regression analyses should be verified in future work due to the small number of included studies.

The strength of our study is, in this meta-analysis, patients undergone partial pancreatectomy were excluded to rule out the impact on insulin independent due to the remaining pancreas. We only include studies with a mean or median length of follow-up more than 6 month and report at least 5 patients to prove confident results of IAT rather than the previous analysis conducted by Ming Dong *et al.*, which includes 354 patients undergone IAT after TP reported by fifteen studies of any number of patients and follow-up length [24]. In addition, the patients number in our analysis is

677, which is about twice than analyzed by the previous study conducted by Ming Dong, so it is more confident to some degree.

The results of the present meta-analysis should also be interpreted within the context of its limitations. The heterogeneity of insulin independent was high with $I^2>50\%$, this may be the different and evolved basic techniques of pancreatic resection and islet isolation of each centers over the years, which significantly affect the outcomes of IAT after TP. There were no RCT studies for analysis due to the ethical reasons of this procedure. But on the basis of our meta-analysis, we propose that IAT is a safe modality, it obviously improve patients' quality of life and can provide a significant number of patients to achieve insulin independence for quite a long time.

To our knowledge, since the university of Minnesota is the largest center to conducted this procedure in 1977, other centers like Leicester, Cincinnati, South Carolina and UAB attempt to the technology one by another and most of them have shown encouraging results. As a latest systematic review conducted by K. Bramis which included five studies showed that, TP/IAT had favourable outcomes of pain reduction and can enabled a large proportion of patients to remain insulin independent [25], we recommend more centers to do this procedure to promote the development of the technology.

In conclusion, our results indicate that IAT is a safe modality for patients with CP need to undergo TP. It can prevent brittle diabetes mellitus and improve patients' quality of life. Proper patients without malignant disease who will undergo pancreatectomy are candidates of IAT/TP.

Acknowledgements

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Disclosure

The authors declare no conflicts of interest.

References

1. Brock C, Nielsen LM, Lelic D, Drewes AM (2013) Pathophysiology of chronic pancreatitis. *World J Gastroenterol* 19: 7231-7240.
2. Blondet JJ, Carlson AM, Kobayashi T, Jie T, Bellin M, et al. (2007) The role of total pancreatectomy and islet autotransplantation for chronic pancreatitis. *Surg Clin North Am* 87: 1477-1501, x.
3. Sutherland DE, Matas AJ, Najarian JS (1978) Pancreatic islet cell transplantation. *Surg Clin North Am* 58: 365-382.
4. Farney AC, Najarian JS, Nakhleh RE, Lloveras G, Field MJ, et al. (1991) Autotransplantation of dispersed pancreatic islet tissue combined with total or near-total pancreatectomy for treatment of chronic pancreatitis. *Surgery* 110: 427-437; discussion 437-439.
5. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. *Control Clin Trials* 7: 177-188.
6. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. *BMJ* 327: 557-560.
7. Cameron JL, Mehigan DG, Broe PJ, Zuidema GD (1981) Distal pancreatectomy and islet autotransplantation for chronic pancreatitis. *Ann Surg* 193: 312-317.
8. Hinshaw DB, Jolley WB, Hinshaw DB, Kaiser JE, Hinshaw K (1981) Islet autotransplantation after pancreatectomy for chronic pancreatitis with a new method of islet preparation. *Am J Surg* 142: 118-122.
9. Rastellini C, Shapiro R, Corry R, Fung JJ, Starzl TE, et al. (1997) Treatment of isolated pancreatic islets to reverse pancreatectomy-induced and insulin-dependent type I diabetes in humans: A 6-year experience. *Transplant Proc* 29: 746-747.
10. Oberholzer J, Triponez F, Mage R, Anderegg E, Buhler L, et al. (2000) Human islet transplantation: Lessons from 13 autologous and 13 allogeneic transplantations. *Transplantation* 69: 1115-1123.
11. Ahmad SA, Lowy AM, Wray CJ, D'Alessio D, Choe KA, et al. (2005) Factors associated with insulin and narcotic independence after islet autotransplantation in patients with severe chronic pancreatitis. *J Am Coll Surg* 201: 680-687.
12. Argo JL, Contreras JL, Wesley MM, Christein JD (2008) Pancreatic resection with islet cell autotransplant for the treatment of severe chronic pancreatitis. *Am J Surg* 74: 530-536; discussion 536-537.
13. Dixon J, DeLegge M, Morgan KA, Adams DB (2008) Impact of total pancreatectomy with islet cell transplant on chronic pancreatitis management at a disease-based center. *Am J Surg* 74: 735-738.
14. Takita M, Naziruddin B, Matsumoto S, Noguchi H, Shimoda M, et al. (2010) Variables associated with islet yield in autologous islet cell transplantation for chronic pancreatitis. *Proc (Bayl Univ Med Cent)* 23: 115-120.
15. Sutherland DE, Radosevich DM, Bellin MD, Hering BJ, Beilman GJ, et al. (2012) Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *J Am Coll Surg* 214: 409-424; discussion 424-426.
16. Walsh RM, Saavedra JR, Lentz G, Guerron AD, Scheman J, et al. (2012) Improved quality of life following total pancreatectomy and auto-islet transplantation for chronic pancreatitis. *J Gastrointest Surg* 16: 1469-1477.
17. Dorlon M, Owczarski S, Wang H, Adams D, Morgan K (2013) Increase in postoperative insulin requirements does not lead to decreased quality of life after total pancreatectomy with islet cell autotransplantation for chronic pancreatitis. *Am Surg* 79: 676-680.
18. Garcea G, Pollard CA, Ilouz S, Webb MB, Metcalfe MS, et al. (2013) Patient satisfaction and cost-effectiveness following total pancreatectomy with islet cell transplantation for chronic pancreatitis. *Pancreas* 42: 322-328.
19. Garcea G, Weaver J, Phillips J, Pollard CA, Ilouz SC, et al. (2009) Total pancreatectomy with and without islet cell transplantation for chronic pancreatitis: A series of 85 consecutive patients. *Pancreas* 38: 1-7.
20. Drewes AM (2013) Understanding and treatment of chronic pancreatitis. *World J Gastroenterol* 19: 7219-7221.
21. Brunicaudi FC, Chaiken RL, Ryan AS, Seymour NE, Hoffmann JA, et al. (1996) Pancreatic polypeptide administration improves abnormal glucose metabolism in patients with chronic pancreatitis. *J Clin Endocrinol Metab* 81: 3566-3572.
22. Pinho AV, Chantrill L, Rooman I (2014) Chronic pancreatitis: A path to pancreatic cancer. *Cancer Lett* 345: 203-209.
23. Gourgiotis S, Germanos S, Ridolfini MP (2007) Surgical management of chronic pancreatitis. *Hepatobiliary Pancreat Dis Int* 6: 121-133.
24. Dong M, Parsaik AK, Erwin PJ, Farnell MB, Murad MH, et al. (2011) Systematic review and meta-analysis: Islet autotransplantation after pancreatectomy for minimizing diabetes. *Clin Endocrinol* 75: 771-779.
25. Bramis K, Gordon-Weeks AN, Friend PJ, Bastin E, Burls A, et al. (2012) Systematic review of total pancreatectomy and islet autotransplantation for chronic pancreatitis. *Br J Surg* 99: 761-766.