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FACTORS THAT AFFECTING HUMAN ISLET ISOLATION

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Abstract

More than 10,000 IEQ/kg recipient weight islets are often necessary to achieve insulin independence in patients with type 1 diabetes. Several studies have identified high BMI donor and pancreas size are important factors for the success of human islet isolation. However, donor shortage underscores the need to improve isolation outcomes from lower BMI pancreas donors and/or small pancreata. Aim of this study was to identify the critical factors affecting isolation outcome. The data from 207 isolations performed from 2002 to 2006 were analyzed with respect to donor characteristics, pancreas condition and processing variables. More than 3,000 IEQ/g pancreas weight were considered as an acceptable isolation outcome (AIO). AIO were obtained from donors with a BMI>30kg/m^2 (p=0.002). The pancreatic surface integrity was also a significant factor towards AIO (p=0.02). Moreover, a longer digestion time (p=0.04) and the proportion of trapped islet negatively affected AIO rates (p=0.004). As previously reported, pancreata from high BMI donors were suitable for islet isolation and transplantation, as they yielded higher total islet particle numbers and higher IEQ/g. Although BMI and pancreas size are not controllable due to organ donor shortage, factors such as pancreatic surface integrity, shorter digestion and lower proportions of trapped islet were found to be significant factors to obtain higher rates of AIO. The development of better protocol and systematic training of processing and procurement teams will be of assistance in increasing the number of successful human islet isolations.

Islet transplantation has become a viable therapy for patients with Type 1 diabetes (1-3). However, more than one islet preparation per recipient is generally required to achieve insulin independence after transplantation and there is an urgent need to perform efficient processing to maximize both islet cell recovery and quality. Previous studies have identified donor and isolation factors affecting the outcome of islet isolation: high BMI donor and/or larger size

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pancreata have been recognized as positively correlating with higher islet yields (4-8). Aim of the present study was to evaluate donor and isolation variables that associate with the success of human islet isolations in a single processing center toward the definition of more stringent parameters for human donor pancreas and optimization of organ utilization for islet transplantation. We have analyzed the effects of donor characteristics, condition of donor pancreata, isolation and assessment for human islet isolations performed at the Human Islet Cell Processing Facility of the Diabetes Research Institute at the University of Miami Leonard M. Miller School of Medicine (DRI-UM).

MATERIAL AND METHODS

Pancreas Procurement

Pancreata were obtained from heart-beating, multiorgan cadaveric donors after cerebral death for which consent for islet transplantation was given from relatives. Data collected from 207 charts and isolation records relative to pancreas processing done from January 1, 2002 through end of 2005 was retrospectively reviewed.

Statistical Analysis

All results are expressed as mean ± SE. Comparisons between groups were performed by Student *t* tests and differences between proportions were compared using Fisher exact tests. The Chi-square test was performed when both the variable and outcome were nominal values. All comparisons are two-tailed. A p-value <0.05 was considered to be statistically significant.

RESULTS

From January 1, 2002 through end of 2005, a single team at our institute processed 350 human deceased donor pancreata. Of these 207 pancreata accepted for islet transplantation were retrospectively reviewed. Islet isolations were deemed successful if yielded adequate numbers of more than 3,000 IEQ/pancreas weight (adequate islets obtained. AIO). Collectively, the number of AIO and non-AIO were 97 (46.8%) and 110 (53.2%), respectively.

Table 1 summarizes donor variables comparing islet preparations that yielded adequate and inadequate islets respectively. Body mass index (BMI) was significantly higher in the group that yielded adequate islet numbers, when compared to the unsuccessful group (31.7±6.6 vs. 28.5±6.2; $p=0.0023$). In other donor characteristics no differences were observed between two groups.

All pancreata were preserved flushed, and with comparable patterns and similar texture appearance (Table 2). Fatty pancreata were mostly observed in the AIO group and possibly associated with the higher BMI, but did not reach statistical significance. The weight of the pancreas after removal of surrounding tissue was comparable in both groups (Table 2). The presence of intact pancreatic capsule was the only organ factor showing statistical significant difference between AIO and unsuccessful islet preparations ($p<0.02$)(Table 2).

Even if the distension score showed no statistical differences, the duration of digestion phase was significantly shorter in preparations yielding adequate islet numbers, when compared to the inadequate group (15.0±4.6 min *vs*. 16.7±5.6, $p=0.04$)(Table 3). Pre- and post-purification islet yields were significantly higher in the AIO groups respectively ($p<0.0001$) and percentage of trapped islet in AIO group was statistically lower than non-AIO groups (12.4±18.0% *vs*. 23.2±23.5%)(Table 3).

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DISCUSSION

Islet transplantation offers a viable option to improve metabolic in patients with type 1 diabetes. A limiting factor to the widespread application of islet transplantation is the need for large numbers of islets, generally obtained from more than one donor pancreas per recipient. Multiple variables may affect the success rate of human islet isolations. Previous studies have demonstrated that high BMI donors and large pancreas size are important for successful human islet isolation yielding higher islet isolation success rates (4-8), which was confirmed in our series. We found that other factors, such as pancreatic surface integrity was associated with better islet yields, pointing at the critical importance of careful pancreas recovery on the success of the islet isolation (8,9). Additionally, shorter digestion and lower proportions of trapped islet were found to be significant factors to obtain higher rates of islet yield in our study. To overcome these issues, the development of better protocol and systematic training of processing and pancreas recovery teams will be necessary to maximize the number of successful human islet isolations.

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Table 1

Affecting factors of donor characteristics for human islet isolation

	>3000IEQ/g	<3000IEQ/g	*P*-value
Age (yr)	41.2±11.7	42.7±11.6	N.S.
Gender (male/female)	61/36	67/43	N.S.
BMI(kg/m2)	31.7±6.6	28.5±6.2	0.0023
Cardiac arrest laboratory dates	8/95	10/108	N.S.
Maximum amylase(U/l)	208.7±444.4	1063.9±696.9	N.S.
Maximum glucose (mg/dl)	222.1±88.5	246.2±91.5	N.S.
Insulin use	34/92	38/96	N.S.
Steroid use	52/88	63/105	N.S.
Vasopressor use	86/96	94/111	N.S.

NS= not significant

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Table 2

Affecting factors of donor pancreata for human islet isolation

	>3000IEQ/g	<3000IEQ/g	*P*-value
Storage solution			
two-layer method	65/97	67/109	N.S.
Organ condition			
Edematous	3/95	7/110	N.S.
Fatty infiltrate	74/95	77/110	N.S.
Fibrotic change	12/97	11/110	N.S.
Capsule intact	89/95	88/108	<0.02
Duodenum attached	88/95	94/107	N.S.
Cold ischemia time(min)	588.5±212.0	582.8±271.1	N.S.
Procurement team			
local/distant	24/73	32/78	N.S.
Pancreas weight(g)	104.6±24.7	107.0±35.1	N.S.

NS= not significant

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Table 3

Affecting factors of isolation and assessment result for human islet isolation

	>3000IEQ/g	<3000IEQ/g	*P*-value
Distension score[a]	3.3±0.7	3.1±0.7	N.S.
Digestion time(min)	15.0±4.6	16.7±5.6	0.04
%trapped	12.4±18.0	23.2±23.5	<0.004
Pre-purification(IEQ)	582,618±197,009	329,618±168,761	<0.0001
Post-purification(IEQ)	487,586±151,483	159,276±116,586	<0.0001
Maximum viability	83.8±28.7	90.3±21.0	N.S.

[a]Distension assess score: Excellent 4 point, very good 3 point, average 2 point, poor 1 point.

NS= not significant