

# Evaluation of the Presumable Incidence of Pancreatic Islet Cell Transplantation in Nagasaki

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## Background

Pancreatic islet cell transplantation (ICT) is one of the standard treatments for type I diabetes mellitus (T1DM), based on the Edmonton protocol of 2000.<sup>1)</sup> A previous report presented the expected annual incidence of ICT recipients in Nagasaki Prefecture in 2006.<sup>2,3)</sup> This report presents variations in the background of T1DM patients followed in this department and evaluated the current annual incidence of possible ICT recipients.

## Methods

This study reviewed 128 T1DM patients followed at Nagasaki University Hospital in 2011, examined the annual incidence of ICT recipients based on the Japanese Islet Transplant Registry criteria and the population of Nagasaki, and compared those results in 2011 with those in 2006. In addition, the annual numbers of cardiac death donors who were considered ICT donor candidates in Nagasaki over this period were examined.

## Results

The proportion of candidates suitable to be recipients in Nagasaki changed from 4% (3/75) in 2006 to 7.8% (10/128) in 2011. The estimated incidence of suitable recipient candidates increased from 1.0 per year to 1.8 per year. On the other hand, though the estimated number of donor candidates was 2.6 per year, which was the mean for the 7 years between 2002 and 2009, only one candidate was reported in 2010 and no candidate was reported in 2011 in Nagasaki.

## Conclusion

Although securing donors has become difficult due to a new law on organ transplantation, the demand for ICT has increased and may continue increase in the future. Therefore, it is important to confirm the criteria in brain dead donors to determine whether the pancreas should be directed to the pancreatic transplantation or pancreatic islet transplantation.

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## Introduction

Pancreatic islet cell transplantation (ICT) is known all over the world as one of the treatments for type I diabetes mellitus (T1DM) and has advanced since the release of the Edmonton protocol in 2000.<sup>1)</sup> The ideal strategy for ICT re-

ipients was reviewed in 2006 by evaluating the actual and prospective numbers of ICT candidates in Nagasaki.<sup>2,3)</sup>

This report reviewed the background of the T1DM patients followed at Nagasaki University hospital and compared them with the incidence in 2006.

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## Subjects and Methods

The subjects of the previous study were 75 T1DM patients who had been followed at the First Department of Internal Medicine of Nagasaki University Hospital in March 2006.<sup>2),3)</sup> The current study evaluated 128 T1DM patients who were followed at the same hospital in July 2011. The study investigated the characteristics and the clinical data of these patients, identified the candidates for ICT according to the Japanese Islet Transplant Registry criteria<sup>4)</sup>, and evaluated the progress of the candidates. The annual incidence of ICT recipients in Nagasaki (A) was estimated based on (a) the annual incident rate of T1DM patients in Japan, (b) the population of Nagasaki Prefecture, and (c) the proportion of ICT recipients among T1DM patients followed in Nagasaki University Hospital in 2006 and 2011 ( $A=a \times b \times c$ ). Because islet cells are usually harvested from cardiac death donors,<sup>5)</sup> this investigation considered the annual numbers of donors following cardiac death as ICT donor candidates in Nagasaki over this period.

## Results

The 2006 study included 19 males and 56 females. The median age was 47.9 years (range: 14-84 years). The median (range) values for various parameters were as follow: DM duration, 13.8 (1-43) years; body mass index (BMI) 22.6 (16.4-38.5) kg/m<sup>2</sup>; insulin requirement, 41.4 (8-166) U/day; HbA1c, 7.7 (5.4-12.1) %; and serum C-peptide level, 0.20 (<0.01-0.94) ng/ml. (The council meeting of Japan Diabetes Society (JDS) decided to use HbA1c (National Glycohemoglobin Standardization Program: NGSP) values in clinical practice beginning April 1, 2012. Therefore, we used HbA1c (NGSP) in this report. HbA1c (NGSP) can be reasonably estimated using the equation HbA1c (JDS) % + 0.4%.)<sup>6-10)</sup> There were 36 males and 92 females in 2011. The median age was 44.0 (7-84) years. The DM duration was 9.5 (0.5-46) years; BMI: 21.9 (15.8-36.5) kg/m<sup>2</sup>; insulin requirement: 40 (8-108) U/day; HbA1c: 7.6 (5.4-13.6) %; and serum C-peptide level: 0.21 (<0.01- 3.01) ng/ml (Table 1). The Japanese Islet Transplant Registry criteria<sup>4)</sup> include the following: 1) DM duration over 5 years; 2) less than 75 years old; 3) BMI < 25 kg/m<sup>2</sup>; 4) HbA1c > 7.9%; 5) hypo-insulin secretion (serum C-peptide level<0.1 ng/ml); and 6) frequent severe hypoglycemia with coma. According to these criteria, 3 of 75 patients were judged to be candidates for ICT in 2006 (4%) and 10 of 128 patients in 2011 (7.8%). Seven of 10 patients in 2011 were new candidates.

**Table 1.** The characteristics of patients with T1DM in Nagasaki University Hospital

	2006 (n=75)	2011 (n=128)
gender( M:F )	19:56	360:92
age (range)	47.9(14-84)	44.0(7-84)
DM duration (year)	13.8(1-43)	9.5(0.5-46)
BMI (kg/m <sup>2</sup> )	22.6(16.4-38.5)	21.9(15.8-36.5)
HbA1c (%)	7.7(5.4-12.1)	7.6(5.4-13.6)
insulin requirement (U/day)	41.4(8-166)	40(8-108)
serum C-peptide (ng/ml)	0.20(<0.01-0.94)	0.21(<0.01-3.01)

The data characteristics in 2011 were similar to those in 2006.

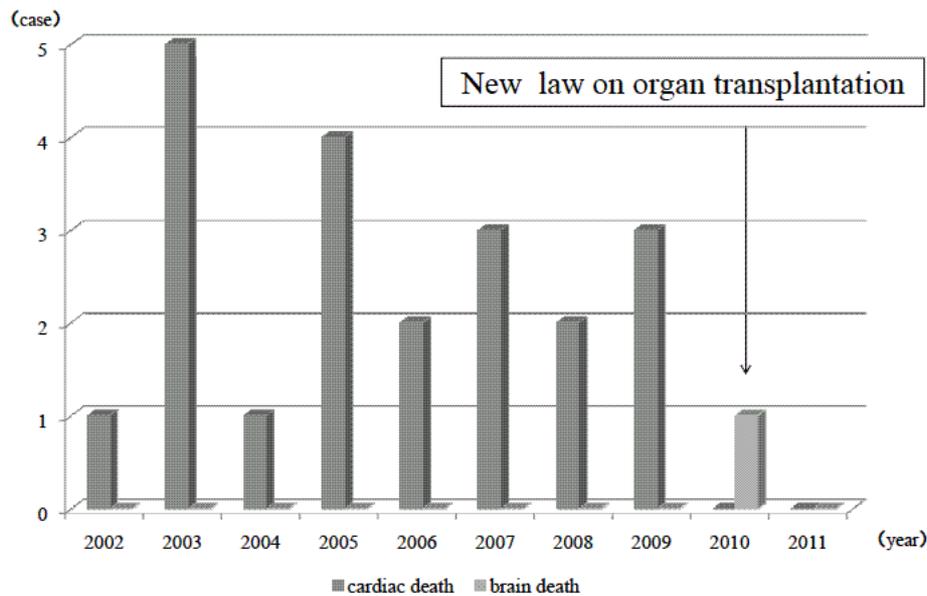
Furthermore, the number of new candidates for ICT in Nagasaki prefecture was estimated to be one per year in 2006 and 1.8 per year in 2011, based on the following epidemiologic factors: 1) the annual incidence of T1DM patients in Japan each year<sup>2)</sup>; 2) the population of Nagasaki prefecture each year; and 3) the proportion of ICT candidates followed at Nagasaki University Hospital each year (Table 2).

**Table 2.** The estimated incidence of the candidates for ICT in Nagasaki

	2006	2011
Annual incidence rate of T1DM patients in Japan	1.6/100,000/year	
Population in Nagasaki	1.5 million	1.42 million
Number of candidates for ICT in Nagasaki	3	10
Estimated incidence of candidates for ICT in Nagasaki	1.0/year	1.8/year

The estimated incidence of ICT candidates in 2011 with the previous study data in 2006

Islet cells are usually harvested from donors following cardiac death. Therefore, the annual number of donors for kidney transplantation provided an estimate of the annual number of islet cell donors. Although the estimated number of donor candidates was 2.6 per year from 2002 to 2009, there was only one brain dead donor in Nagasaki Prefecture in 2010 and the number was zero in 2011 (Figure 1).



**Figure 1.** The number of cardiac and brain death donors in Nagasaki. The estimated number of donor candidates was 2.6 per year between 2002 and 2009. The number of brain-dead donor in Nagasaki was one in 2010. The number was zero in 2011.

## Discussion

The medical treatment for T1DM is either internal treatment or surgical treatment. Surgical treatment is classified into pancreatic transplantation<sup>11)-13)</sup> and a pancreatic islet cell transplantation. The first pancreatic transplantation was performed in 1966 and pancreatic transplantation continues to be a widely accepted option for uremic, T1DM. On the other hand, pancreatic islet cell transplantation from donors after cardiac death has become a promising therapy for the treatment of T1DM since the Edmonton protocol was established in 2000.<sup>1)</sup>

There are estimated to be 246 million people with DM in the world.<sup>14)</sup> In Japan, Kawasaki et al. reported that the Japanese had the lowest incidence of childhood T1DM in the world, but the incidence of this disease is clearly increasing within the Japanese population and the overall incidence of new-onset patients with T1DM is estimated to be 1.6 per 100,000 / year.<sup>2)</sup> Therefore, the demand for T1DM therapy has increased in Japan. Although internal treatment has progressed, T1DM progresses gradually in some patients. The number of potential new recipient could have increased. However, ICT is classified as tissue transplantation in Japan. Therefore, it is illegal to use a brain-dead donor. Moreover, the frequency of brain-dead donors will increase and that of cardiac death donors will decrease because of a new law concerning organ transplantation. (Compared with the previous law, the new law incorporates the following

four changes. 1) For all patients with the possibility of brain death, the declaration of brain death is made irrespective of the intention of organ donation. 2) The judgment of brain death is considered to be "death" uniformly. 3) The donor card is abolished, and organ donation can be made from a patient in the state of brain death only with the family's consent. 4) When brain-dead patients are younger than 15 years old, organ donation will be possible if the family consents.<sup>15)</sup> Therefore, pancreas transplantation will increase and ICT will decrease. In addition, the recipient pool indicated for ICT will decrease because pancreases from donors will be used for pancreas transplantation preferentially. Therefore, although it is predicted that pancreatic transplantation will increase with the new law, there are no available criteria to classify the donor organs for pancreatic transplantation or pancreatic islet cell transplantation.

Several studies reported that BMI and body weight have been associated to isolate islet cells from pancreas successfully<sup>16)-18)</sup>. Therefore, when a donor matching with these criteria appears, it is more desirable for the donor's organ to be adapted for ICT than for pancreatic transplantation. However, there is still no clear strategy concerning the adaptation of a donor's organ.

In conclusion, although this analysis showed that the demand for transplantation as a treatment for T1DM has increased, the number of ICT will decrease. Therefore, it is important to establish the criteria in brain dead donors to determine whether the pancreas should be directed to the pancreatic transplantation or pancreatic islet transplantation.

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