

Figure 1. Relationships between relative insulin dose versus islet yield/body weight (left) and average SUITO index (right). The average SUITO index correlated with relative insulin dose.

SUITO index (4,10). In that study, an average SUITO index (from POD 3 to 30) of more than 26 was associated with insulin independence (10).

In this study, the average SUITO index but not islet yield/body weight correlated with relative insulin dose. An islet yield/body weight ratio of more than 10,000 IE/kg is associated with insulin independence according to the Edmonton protocol (15). In this study, we found that the average SUITO index was a better indicator of clinical outcome than islet yield/body weight. This is reasonable because islet yield did not reflect viability or en-

graftment of transplanted islets. On the contrary, the SUITO index was calculated based on secreted C-peptide stimulated by glucose, which should reflect islet mass and function. The average SUITO index of approximately 30 was associated with insulin independence after islet transplantation from brain-dead donors when we extrapolated the data. This result is similar to the results of islet transplantation from non-heart-beating and living donors.

HbA_{1c} were all improved, irrespective of islet mass or SUITO index. This is most likely because islets can

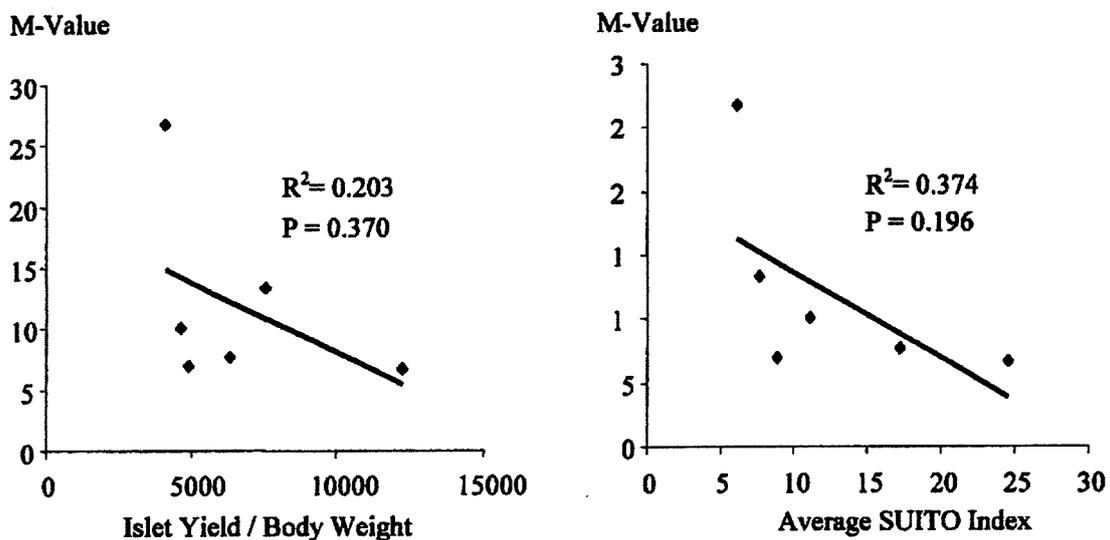


Figure 2. Relationships between M-values versus islet yield/body weight (left) and average SUITO index (right). Neither islet yield/body weight nor the average SUITO index correlated with the M-values.

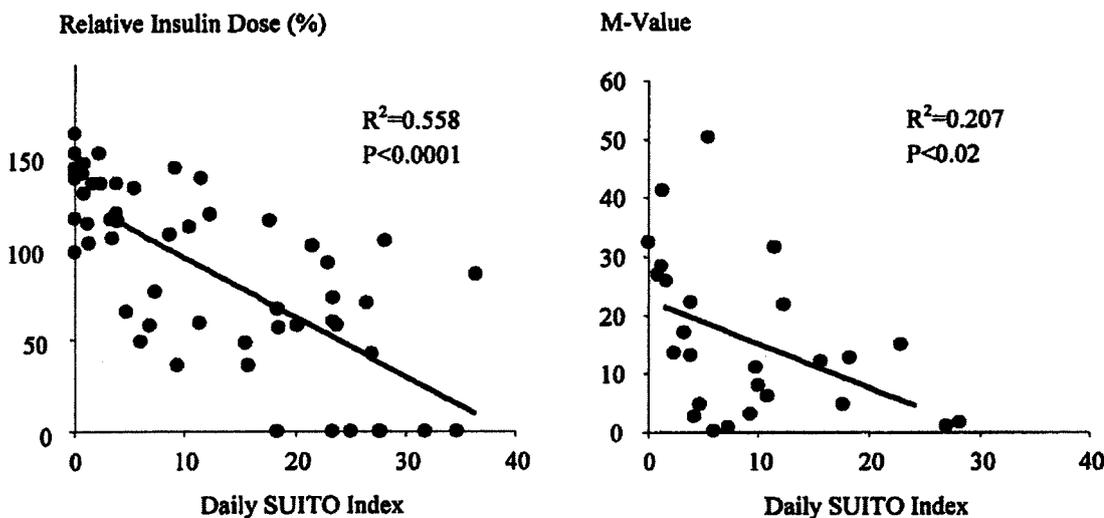


Figure 3. Relationships between the daily SUITO index versus the relative insulin dose (left) and M-values (right). The daily SUITO index strongly correlated with the relative insulin dose and weakly correlated with M-values.

meticulously regulate blood glucose, irrespective of the amount of external insulin injected. Even small amounts of engrafted islets were helpful for improving glycemic control and this fact is important to support the concept of single donor islet transplantation for brittle type 1 diabetes. The average M-value did not correlate with either the SUITO index or islet yield/body weight. This also indicated that even a small amount of engrafted islets could maintain excellent glycemic control, irrespective of the amount of external insulin injected.

Next, we compared the daily SUITO index with the daily relative insulin dose and daily M-values. We selected M-values instead of MAGE. MAGE requires 2-day blood glucose measurements (15) and therefore cannot be used as a daily indicator. The daily SUITO index strongly correlated with the daily relative insulin dose and weakly correlated with M-values. Because the SUITO index reflected engrafted islet mass, it seems reasonable that it correlates with the daily relative insulin dose.

Interestingly, the average relative insulin dose was

more than 100% when the SUITO index was less than 10. This means the patients needed more insulin compared to the dose of insulin before transplantation. In such cases, patients still improved glycemic control after islet transplantation even though more insulin was required, evaluated by improved HbA_{1c} and fewer events of hypoglycemic unawareness. A possible explanation is that after islet transplantation, alpha cells in the transplanted islets may secrete glucagon to counteract the overdose of the insulin injection that can stabilize glucose levels. In addition, use of tacrolimus might increase glucose levels, which might result in high insulin dosage.

The daily SUITO index weakly correlated with M-values. This suggested that even small amounts of engrafted islets help to maintain excellent glycemic control. Consequently, larger amounts of engrafted islets might maintain glycemic control more efficiently. However, there was no significant difference in the M-values between the group with a SUITO index of less than 10 and the group with a SUITO index equal to or more than 10. This also indicated that a relatively small number of islets can work to stabilize glycemic control.

In conclusion, the SUITO index was an excellent predictor of clinical outcomes, especially to predict the necessary insulin dose. We recommend using this simple index for assessing engrafted islet mass and function.

Table 3. SUITO Index Correlates With Insulin Dose and M-Value

| SUITO Index | Relative Insulin Dose (%) | M-Value |
|-------------|---------------------------|-----------------|
| <10 | 117.1 ± 5.9 | 18.3 ± 3.8 |
| ≥10 | 55.4 ± 8.4 | 11.5 ± 3.0 |
| | <i>p</i> < 0.0000001 | <i>p</i> = 0.21 |

M-value: average absolute blood glucose over day.

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REFERENCES

1. Faradji, R. N.; Monroy, K.; Messinger, S.; Pileggi, A.; Froud, T.; Baidal, D. A.; Cure, P. E.; Ricordi, C.; Luzi, L.; Alejandro, R. Simple measures to monitor beta-cell mass and assess islet graft dysfunction. *Am. J. Transplant.* 7:303–308; 2007.
2. Ichii, H.; Sakuma, Y.; Pileggi, A.; Fraker, C.; Alvarez, A.; Montelongo, J.; Szust, J.; Khan, A.; Inverardi, L.; Naziruddin, B.; Levy, M. F.; Klintmalm, G. B.; Goss, J. A.; Alejandro, R.; Ricordi, C. Shipment of human islets for transplantation. *Am. J. Transplant.* 7:1010–1020; 2007.
3. Liu, X.; Matsumoto, S.; Okitsu, T.; Iwanaga, Y.; Noguchi, H.; Yonekawa, Y.; Nagata, H.; Kamiya, H.; Ueda, M.; Hatanaka, N.; Miyakawa, S.; Kobayashi, N.; Song, C. Analysis of donor- and isolation-related variables from non-heart-beating donors (NHBDs) using the Kyoto islet isolation method. *Cell Transplant.* 17:649–656; 2008.
4. Matsumoto, S.; Noguchi, H.; Naziruddin, B.; Onaca, N.; Jackson, A.; Hatanaka, N.; Okitsu, T.; Kobayashi, N.; Klintmalm, G.; Levy, M. Improvement of pancreatic islet cell isolation for transplantation. *Baylor University Medical Center Proceedings* 20:357–362; 2007.
5. Matsumoto, S.; Noguchi, H.; Yonekawa, Y.; Okitsu, T.; Iwanaga, Y.; Liu, X.; Nagata, H.; Kobayashi, N.; Ricordi, C. Pancreatic islet transplantation for treating diabetes. *Expert Opin. Biol. Ther.* 6:23–27; 2006.
6. Matsumoto, S.; Okitsu, T.; Iwanaga, Y.; Noguchi, H.; Nagata, H.; Yonekawa, Y.; Yamada, Y.; Fukuda, K.; Shibata, T.; Kasai, Y.; Maekawa, T.; Wada, H.; Nakamura, T.; Tanaka, K. Successful islet transplantation from non-heart-beating donor pancreata using modified Ricordi islet isolation method. *Transplantation* 82:460–465; 2006.
7. Matsumoto, S.; Okitsu, T.; Iwanaga, Y.; Noguchi, H.; Nagata, H.; Yonekawa, Y.; Yamada, Y.; Fukuda, K.; Tsukiyama, K.; Suzuki, H.; Kawasaki, Y.; Shimodaira, M.; Matsuoka, K.; Shibata, T.; Kasai, Y.; Maekawa, T.; Shapiro, A. M. J.; Tanaka, K. Insulin independence after living-donor distal pancreatectomy and islet allotransplantation. *Lancet* 365:1642–1644; 2005.
8. Matsumoto, S.; Qualley, S.; Goel, S.; Hagman, D. K.; Sweet, I. R.; Poutout, V.; Strong, D. M.; Robertson, R. P.; Reems, J. A. Effect of the two-layer (University of Wisconsin solution-perfluorochemical plus O₂) method of pancreas preservation on human islet isolation as assessed by the Edmonton isolation protocol. *Transplantation* 74:1414–1419; 2002.
9. Matsumoto, S.; Rigley, T. H.; Qualley, S. A.; Kuroda, Y.; Reems, J. A.; Stevens, R. B. Efficacy of the oxygen-charged static two-layer method for short-term pancreas preservation and islet isolation from nonhuman primate and human pancreata. *Cell Transplant.* 11:769–777; 2002.
10. Matsumoto, S.; Yamada, Y.; Okitsu, T.; Iwanaga, Y.; Noguchi, H.; Nagata, H.; Yonekawa, Y.; Nakai, Y.; Ueda, M.; Ishii, A.; Yabunaka, E.; Tanaka, K. Simple evaluation of engraftment by secretory unit of islet transplant objects (SUITO) for living donor and cadaveric donor fresh or cultured islet transplantation. *Transplant. Proc.* 37:3435–3437; 2005.
11. Ricordi, C.; Gray, D. W.; Hering, B. J.; Kaufman, D. B.; Warnock, G. L.; Knetman, N. M.; Lake, S. P.; London, N. J.; Soggi, C.; Alejandro, R. Islet isolation assessment in man and large animals. *Acta Diabetol. Lat.* 27:185–195; 1990.
12. Sassa, M.; Fukuda, K.; Fujimoto, S.; Toyoda, K.; Fujita, Y.; Matsumoto, S.; Okitsu, T.; Iwanaga, Y.; Noguchi, H.; Nagata, H.; Yonekawa, Y.; Ohara, T.; Okamoto, M.; Tanaka, K.; Seino, Y.; Inagaki, N.; Yamada, Y. A single transplantation of the islets can produce glycemic stability and reduction of basal insulin requirement. *Diabetes Res. Clin. Pract.* 73:235–240; 2006.
13. Schlichtkrull, J.; Munck, O.; Jersild, M. The M-value, an index of blood-sugar control in diabetics. *Acta Med. Scand.* 177:95–102; 1965.
14. Shapiro, A. M. J.; Lakey, J. R.; Paty, B. W.; Senior, P. A.; Bigam, D. L.; Ryan, E. A. Strategic opportunities in clinical islet transplantation. *Transplantation* 79:1304–1307; 2005.
15. Shapiro, A. M. J.; Lakey, J. R. T.; Ryan, E. A.; Korbitt, G. S.; Toth, E.; Warnock, G. L.; Knetman, N. M.; Rajotte, R. V. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N. Engl. J. Med.* 343:230–238; 2000.
16. Toso, C.; Shapiro, A. M. J.; Bowker, S.; Dinvari, P.; Paty, B.; Ryan, E. A.; Senior, P.; Johnson, J. A. Quality of life after islet transplant: Impact of the number of islet infusions and metabolic outcome. *Transplantation* 84:664–666; 2007.
17. Yamada, Y.; Fukuda, K.; Fujimoto, S.; Hosokawa, M.; Tsukiyama, K.; Nagashima, K.; Fukushima, M.; Suzuki, H.; Toyoda, K.; Sassa, M.; Funakoshi, S.; Inagaki, N.; Taniguchi, A.; Sato, T.; Matsumoto, S.; Tanaka, K.; Seino, Y. SUIT, secretory units of islets in transplantation: An index for therapeutic management of islet transplanted patients and its application to type 2 diabetes. *Diabetes Res. Clin. Pract.* 74:222–226; 2006.

