Assessment of the Severity of Hypoglycemia and Glycemic Lability in Type 1 Diabetic Subjects Undergoing Islet Transplantation

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Currently, the major indications for solitary islet transplantation are recurrent severe hypoglycemia and labile glucose control. Quantifying these problems remains subjective. We have developed a scoring system for both hypoglycemia and glycemic lability, established normative data, and used them in patients who have undergone islet transplantation. A composite hypoglycemic score (HYPO score) was devised based on the frequency, severity, and degree of unawareness of the hypoglycemia. In addition, using 4 weeks of glucose records, a lability index (LI) was calculated based on the change in glucose levels over time and compared with a clinical assessment of glycemic lability. A mean amplitude of glycemic excursions (MAGE) was also calculated based on 2 consecutive days of seven readings each day. These scores were determined in 100 randomly selected subjects with type 1 diabetes from our general clinic to serve as a control group and in patients before and after islet transplantation. The mean age of the control diabetic subjects was 38.4 ± 1.3 years (±SE), with a duration of diabetes of 21.5 ± 1.1 years. The median HYPO score in the control subjects was 143 (25th to 75th interquartile range: 46–423). The LI in the diabetic control subjects was 223 (25th to 75th interquartile range: 130–329 mmol/l^2/h · week^{-1}). The LI correlated much more closely than the MAGE with the clinical assessment of lability. A HYPO score of ≥1,047 (90th percentile) or an LI ≥433 mmol/l^2/h · week^{-1} (90th percentile) indicated serious problems with hypoglycemia or glycemic lability, respectively. The islet transplant patients (n = 51) were 42.1 ± 1.4 years old, with a duration of diabetes of 25.7 ± 1.4 years. Islet transplant patients had a mean HYPO score of 1,234 ± 184 pretransplant, which was significantly higher than that of the control subjects (P < 0.001), which became negligible posttransplantation with the elimination of hypoglycemia. The median LI pretransplant was 497 mmol/l^2/h · week^{-1} (25th to 75th interquartile range: 330–692), significantly higher than that of control subjects (P < 0.001), and fell to 40 (25th to 75th interquartile range: 14–83) within a month after the final transplant. In those who had lost graft function, the LI rose again. The HYPO score and LI provide measures of the extent of problems with hypoglycemia and glycemic lability, respectively, complement the clinical assessment of the problems with glucose control before islet transplantation, and will allow comparison of selection of subjects for transplants between centers.
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Patients with type 1 diabetes have to balance the risks of long-term hyperglycemia and its consequences versus the acute risk of hypoglycemia. The Diabetes Control and Complications Trial has confirmed that achieving strict glycemic control is worthwhile but comes with the price of a threefold increased risk of severe hypoglycemia (1). In addition to long-term consequences (2), such hypoglycemia comes with costs in the short term as evidenced by the interruption in day-to-day living, employment, and routine tasks such as driving. In patients with severe problems with lability or hypoglycemia, islet or pancreas transplantation has offered correction of these problems (3–5)

However, it has been difficult to quantify hypoglycemia. The standard definition of severe hypoglycemia is that outside help is required to treat the occurrence (6,7). There are estimates of the fear of hypoglycemia (8), but quantitative or qualitative measures of the magnitude of the problem for an individual are not routinely used. An objective system to quantify the degree and severity of hypoglycemia would be helpful in standardizing the assessment of patients undergoing solitary pancreas or islet transplantation.

Simple measures of glycemic lability have also been elusive. Older studies have suggested the use of the mean amplitude of glycemic excursions (MAGE) (9) or the M value of Schlichtkrull et al. (10), but these have not been tested for validity in a large group of patients. The recent report from Kessler et al. (11) with a continuous glucose monitoring system used the absolute glucose level minus 5.5 mmol/l as a measure of variability over a limited 3-day observation period. However, subjects can have longer periods of stable and unstable glucose control. Patients

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HYPO score, hypoglycemic score; LBGI, low–blood glucose index; LI, lability index; MAGE, mean amplitude of glycemic excursions.

may have wide oscillations in their glucose values and, when severe, especially if associated with disruption of lifestyle, may be labeled "brittle," but there has been difficulty in the definition of this term (12). HbA_{1c} is often only slightly elevated because the low glucose values offset the high numbers. In fact, the finding of a normal HbA_{1c} in this setting may be indicative of frequent unrecognized hypoglycemic reactions. It would be helpful to have a uniform measure of lability in assessing subjects who present for transplantation.

We have developed a new scoring system of both hypoglycemia and lability to assist in quantifying these problems in patients being considered for islet transplantation. To establish normative data in this study, we asked 100 patients from our general type 1 diabetes clinic who were not considering islet transplantation to keep detailed records of their glucose readings for 4 weeks, note details of each hypoglycemic event, record the number of occurrences of hypoglycemia, and complete a questionnaire about the frequency of severe hypoglycemic reactions over the previous year. From these records we developed a system for a hypoglycemic score (HYPO score) to allow quantification of the extent of the problem with hypoglycemia. In addition, we developed a lability index (LI) based on the changes in glucose over time to provide a measure of glucose lability in everyday practice. We then utilized these scores in patients before and after islet transplantation.

RESEARCH DESIGN AND METHODS

As there were no previous data available to make a power and sample size calculation, we estimated that 100 patients was a suitable number to establish normative data. The primary entry criteria for these control subjects was the presence of type 1 diabetes, and thus a total of 877 type 1 diabetic subjects in our clinic were listed in random order. These patients had attended our diabetes educational program at least once and were cared for by either community physicians or our diabetes clinic staff. We tried to contact the first 339 subjects on this list in order to enroll 100 subjects. Of these 339, we could not contact 95 and 16 did not meet entry criteria. Of the 228 remaining subjects, 29 declined to participate and 28 had already applied for an islet transplant. From the remaining 171 subjects who were then contacted and mailed study sheets, 110 records were returned. Of these, 10 records were not used; 9 because of inadequate frequency of monitoring (less than two readings a day) and 1 because on review it was felt that the subject had type 2 diabetes. One hundred returned records were adequately completed, and these are the basis of the normative data in this report. In addition, the patients completed a written informed consent form and returned it before any of the results were used. The study was approved by the Health Research Ethics Board of the University of Alberta.

The mean age of the 100 subjects (51 women) who completed the reports was 38.4 ± 1.3 years (mean ± SE), with a duration of diabetes of 21.5 ± 1.1 years. All patients were judged to have type 1 diabetes based on two or more of the following self-reported details: onset of diabetes under the age of 40, lean body habitus at the time of diagnosis, started insulin at the time of diagnosis, or a history of diabetic ketoacidosis. The group of subjects ($n = 61$) who did not return completed records were younger (age 32.0 ± 1.4 years, $P = 0.002$) and had a slightly shorter duration of diabetes (17.7 ± 1.3 years, $P = 0.035$) compared with that of the 100 subjects who completed records.

The subjects were asked to continue their usual monitoring of their glucose levels with a minimum of two capillary glucose readings a day. No specific testing times were requested. The patients recorded all measured glucose values and details about hypoglycemic occurrences over a 4-week period on sheets provided (online appendix 1*A* and *B* [available at http://diabetes.diabetesjournals.org). On any occasion that glucose was recorded as <3.0 mmol/l, the subjects were asked to describe the details of the event on the questionnaire (online appendix 1*B*). In particular, emphasis was placed on which symptoms occurred and whether outside help from a third party was obtained to either recognize or treat the hypoglycemic reaction. A reaction was considered severe if the individual had lost control of the situation and required outside help to treat the hypoglycemic event. In addition, all patients were asked to complete 2 days of seven capillary glucose readings a day for calculation of the MAGE (9). These 2 days could be at any time during the 4 weeks of recorded monitoring.

A general questionnaire about previous episodes of hypoglycemia occurring in the last year was included in the package sent to subjects. This questionnaire requested details on the number of hypoglycemic reactions that occurred per month and how many of the reactions were felt or were not felt, how many times outside help was required to either recognize or treat the reaction, whether an ambulance was called, or whether glucagon was administered. Patients were also asked to rank how they perceived the stability of their diabetes on a scale of 1–5, with 1 being very stable and 5 indicative of severe instability. Details of the insulin regimen used and information about concurrent medications were also recorded.

Islet transplantation subjects. Fifty-one subjects (29 women) with type 1 diabetes who had percutaneous intrahepatic islet transplantation up to 1 June 2003 were included in this retrospective analysis. The mean age was 42.1 ± 1.4 years (P = NS versus control subjects), with a duration of diabetes of 25.7 ± 1.4 years ($P = 0.015$ versus control subjects). Subjects completed 4 weeks of glucose monitoring, with details of symptoms or lack thereof for every glucose value <3 mmol/l. Subjects were not instructed as to how often to test their capillary glucose, rather just to continue with their routine frequency because noting the adequacy of glucose monitoring was part of the assessment for an islet transplant. At the initial clinic visit, details about the number of severe hypoglycemic reactions over the last year were recorded. After the islet transplantation, similar details were recorded as well as glucose-monitoring values.

Analysis

Hypoglycemia. A HYPO score was generated based on a combination of scores from the 4 weeks of readings and the patients' self-reported episodes over the previous year using the scoring system found in online appendix 2 (available at http://diabetes.diabetesjournals.org). The record sheets returned by the patients were analyzed for the number of episodes of glucose values recorded as <2.5 mmol/l and between 2.5 and 2.9 mmol/l. Points were awarded if symptoms were absent or were neuroglycopenic rather than autonomic (13–15). If autonomic symptoms occurred that gave adequate warning of the event, then no extra points were given other than for the occurrence. Thus the more severe the problem with hypoglycemia, the higher the score.

If subjects noted a glucose value of <3.0 mmol/l, had no symptoms, and dealt with the hypoglycemia themselves, then points were awarded only for the occurrence and the fact that no symptoms were felt. If the episode was recorded as "low" but no absolute glucose value was provided, then no points were allotted. However, if outside help was required for such an episode, then it was counted as an episode of hypoglycemia <2.5 mmol/l that required outside help to treat. From the 4-week records, a score was obtained and then multiplied by 13 to provide a 1-year value. Points were given for prior episodes of severe hypoglycemia (7) in the past year, with a greater number of points allocated if an ambulance was called or glucagon administered. The scores for the self-reported episodes over the previous year were then added to the 1-year score derived from the 4 weeks of documented episodes, giving a final score per year.

Lability. The values and times of glucose determinations were noted from the 4 weeks of glucose records returned. An LI for each of the 4 weeks was developed based on calculating the following sum for each week of the 4-week period.

$$\text{LI mmol/l}^2/\text{h} \cdot \text{week}^{-1} = \sum_{n=1}^{N} \frac{(Gluc_n - Gluc_{n+1})^2}{(h_{n+1} - h_n)}$$

where $Gluc_n$ (in millimoles per liter) is the nth reading of the week taken at time h_n (rounded to the nearest hour). N is the total number of readings in a week (e.g., Monday morning to the following Monday morning). The minimum and maximum time intervals used are 1 and 12 h, respectively. For the normative data portion of the study, the mean of the 4 individual weeks was calculated for each patient's set of records. For the islet transplant subjects, the meters were electronically downloaded and then exported to a spreadsheet for rapid calculation of the LI.

To have a clinical comparison, each patient's weekly records were independently reviewed by two diabetologists (E.A.R. and M.-C.V.), who were blinded to the LI score and classified each week's record on a scale of 0–10 according to degrees of lability from perfectly stable (score 0) to extremely labile (score 10). These two scores from the diabetologists were combined to form an average clinical score since they correlated closely with each other ($r = 0.869$, $P < 0.0001$, y intercept of -0.1). To validate the LI score, the mean of the 4-week combined clinical assessment of lability was then compared with the LI. The MAGE was calculated from 2 consecutive days of seven capillary glucose readings a day (9).

TABLE 1
The frequency of hypoglycemic events

	Median number of events (%-iles)/4 weeks/patient	
	Control	Pre–islet transplant
From record sheets		
n	100	23
Glucose values 2.5–2.9 mmol/l	2 (1.0–4.0)	3 (2–5)
Glucose values <2.5 mmol/l	1 (0.0–3.0)	2 (1–5)*
Severe hypoglycemic reactions	0 (0–0)	1 (0–2)†
	Median number of events (%-iles)/month/patient	
	Control	Pre–islet transplant
From questionnaire		
n	100	48
Number of reactions (glucose values <3 mmol/l)	4 (1.0–8.0)	13 (6.5–20.8)†
Hypoglycemic reactions for which outside help was provided	0 (0–0)	1 (0.0–2.8)†

*$P = 0.02$; †$P < 0.001$. %-iles, 25th to 75th interquartile range.

Statistics. Results are expressed as means ± SE or median and 25th and 75th interquartile range. Student's *t* test was used to assess differences between groups and the Mann-Whitney rank-sum test when the normality test failed. ANOVA was used when comparing multiple groups. Spearman's rank-order correlation analyses were performed using Sigma-Stat from Jandel Scientific (San Rafael, CA).

RESULTS

Diabetic control subjects. Of the 100 diabetic control subjects who completed the forms, the mean daily dose of insulin was 0.73 ± 0.02 units/kg. All of these patients were taking insulin two or more times a day (61% four times a day, 22% three times a day, and 16% twice a day; one subject took insulin five times a day). Subjects usually monitored their capillary glucose values three or four times a day (80% three or more times a day and 52% four or more times a day). Table 1 shows the frequency of episodes of hypoglycemia observed during the 4 weeks of recordings for capillary glucose values 2.5–2.9 and <2.5 mmol/l. The total number of episodes of hypoglycemia was 5.1 ± 0.6 per patient per 4 weeks, with the number of severe reactions being 0.1 ± 0.04 per 4 weeks. From the historical questionnaire sheet, the number of reactions reported by the control patients was 5.7 ± 0.6 episodes per month and the number of severe reactions recalled was 0.27 ± 0.07 per month. Of the 100 subjects, 85 had at least one hypoglycemic event over the study period. Seventy-nine had an event with a glucose value of 2.5–2.9 mmol/l within the 4 weeks, and 49 had a hypoglycemic reaction with a glucose value of <2.5 mmol/l in the 4 weeks. In the 85 subjects, there were 287 hypoglycemic events with glucose values in the range of 2.5–2.9 mmol/l and 224 more severe hypoglycemic events, with a glucose value of <2.5 mmol/l over the 4 weeks.

A HYPO score was calculated for each patient as described above, and the frequency distribution is shown in Fig. 1. The median HYPO score was 143 (25th to 75th interquartile range: 46–423). A HYPO score of ≥1,047 (90th percentile) indicated that the patient had serious problems with hypoglycemia. The 10 patients with a HYPO score >1,047 had recalled 73 severe reactions over the last year and required glucagon or an ambulance on seven occasions. Scores between 423 and 1,046 were indicative of subjects who had moderate problems with hypoglycemia, and a score of <423 indicated that hypoglycemia was unlikely to be a major clinical concern. In the 75 subjects with a score <423, there were 36 recalled severe reactions over the previous year, but in the 50 subjects with scores ≤223, the median, there were only 9 recalled severe reactions in the previous year. The HYPO score showed a correlation with the frequency of glucose monitoring ($r = 0.3$, $P = 0.003$) but did not correlate with patient age or duration of diabetes. There was also a correlation between the 4-week recorded and previous-year recalled components of the HYPO score ($r = 0.335$, $P < 0.0001$). Some of the patients with high scores had problems with the high frequency of hypoglycemia but had maintained awareness of hypoglycemia, whereas others had lost complete warning of hypoglycemia. Only three patients were on oral β-blocker medications. Twenty-five of the 100 subjects had at least one hypoglycemic reaction that was not felt over the 4 weeks and were considered to have decreased awareness. The HYPO score in this group with decreased

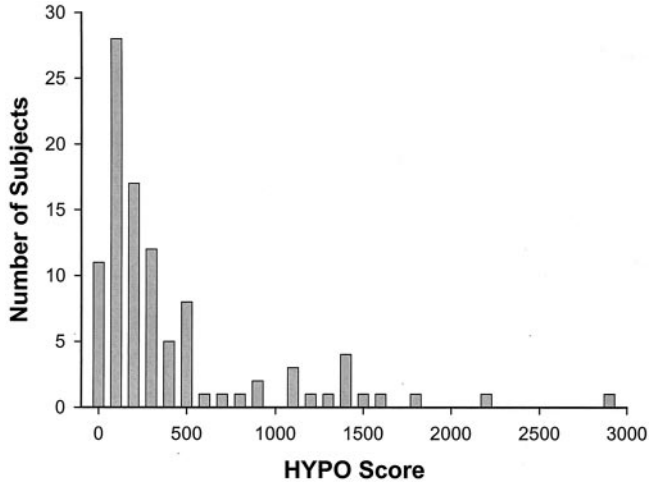

FIG. 1. Frequency distribution of the HYPO score for the 100 type 1 diabetic control subjects. The HYPO score was based on the frequency and severity of the episodes of hypoglycemia during the 4 weeks of records and the patient's recall of episodes of severe hypoglycemia over the last year (online appendix 2 [available at http://diabetes.diabetesjournals.org]).

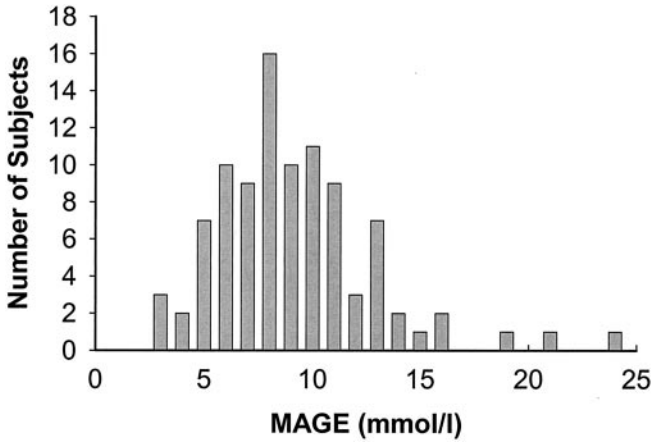

FIG. 2. Frequency distribution of the MAGE score for 95 type 1 diabetic control subjects. The MAGE was based on 2 days of capillary glucose readings (seven per day) (9).

awareness was 850 (25th to 75th interquartile range: 485–1,228), much higher than the group who did not record an episode of unawareness, which was 91 (25th to 75th interquartile range: 23–203) ($P < 0.001$). This group with diminished awareness compared with the remainder with fully intact hypoglycemic awareness had 8.0 (25th to 75th interquartile range: 5–12) vs. 2.0 (25th to 75th interquartile range: 1–5) reactions per patient per 4 weeks ($P < 0.001$), respectively, and 0.4 ± 0.07 vs. 0.0 severe reactions per patient per 4 weeks, respectively.

The MAGE results are shown in Fig. 2. The median MAGE was 8.1 (25th to 75th interquartile range: 6.2–10.5). In reviewing the MAGE results, it was clear that a patient could have a gradual decline in glucose from 22.0 to 2.0 mmol/l over the 2-day period and have a very high MAGE reading, but not have major problems with lability. The MAGE correlated with the clinical scoring of the lability by the diabetologist ($r = 0.328$, $P = 0.001$) and with the calculated LI ($r = 0.291$, $P = 0.004$).

Figure 3*A* shows the frequency distribution of the LI for the subjects. The LI was 223 mmol/l^2/h · week^{-1} (25th to 75th interquartile range: 130–329). This provided much better discrimination than the MAGE of the subjects who would be judged to be labile, as evidenced by the strong correlation between the clinical classification of the lability of the patients and the LI score ($r = 0.868$, $P < 0.0001$) (Fig. 3*B*). Patient perception of the stability of their diabetes correlated weakly with the LI ($r = 0.254$, $P = 0.012$). The LI correlated with the frequency of glucose testing ($r = 0.654$, $P < 0.0001$), duration of diabetes ($r = 0.275$, $P = 0.006$), and weakly with the age of the subject ($r = 0.197$, $P = 0.049$). Based on the clinical evaluation, an LI value of ≥433 mmol/l^2/h · week^{-1} (90th percentile) indicated problematic lability.

Islet transplant subjects. The most frequent indications for an islet transplant were problems with hypoglycemia (88%) and/or glycemic lability (55%), but in many instances, both were present to some extent. On the assessment sheets, the subjects usually monitored their capillary glucose values three or four times a day (90% three or more times a day and 81% four or more times a day), and these frequencies were greater than those in the control subjects ($P = 0.005$ and $P < 0.001$, respectively). At the first clinic visit, the number of reactions noted by history per month was significantly greater than that reported by the control subjects as well as the number of severe reactions (Table 1). The HYPO score in the pre–islet transplant subjects was 722 (25th to 75th interquartile range: 432–1,980) ($n = 30$), significantly higher than that of the control subjects ($P < 0.001$). Posttransplant problems with hypoglycemia resolved as long as islet function was maintained, and this is reflected in the HYPO score (Fig. 4*A*). The LI in the pre–islet transplant subjects was 497 (25th to 75th interquartile range: 330–692), significantly higher than that of the control subjects ($P < 0.001$). Figure 4*B* shows the LI in subjects pretransplantation, after the first transplant, and 1 month and 1 year after the final transplant. A clear improvement is evident after the first transplant ($P < 0.05$), and by 1 month after the final transplant, the LI was 40 mmol/l^2/h · week^{-1} (25th to 75th interquartile range: 14–83). Four subjects lost graft function and became C-peptide negative. The LI in these subjects pretransplantation was 584 ± 155, shortly after the final transplant was 20 ± 4, and the most recent value since graft function was lost was 300 ± 63 mmol/l^2/h · week^{-1} ($P < 0.05$). The progression in LI for a subject

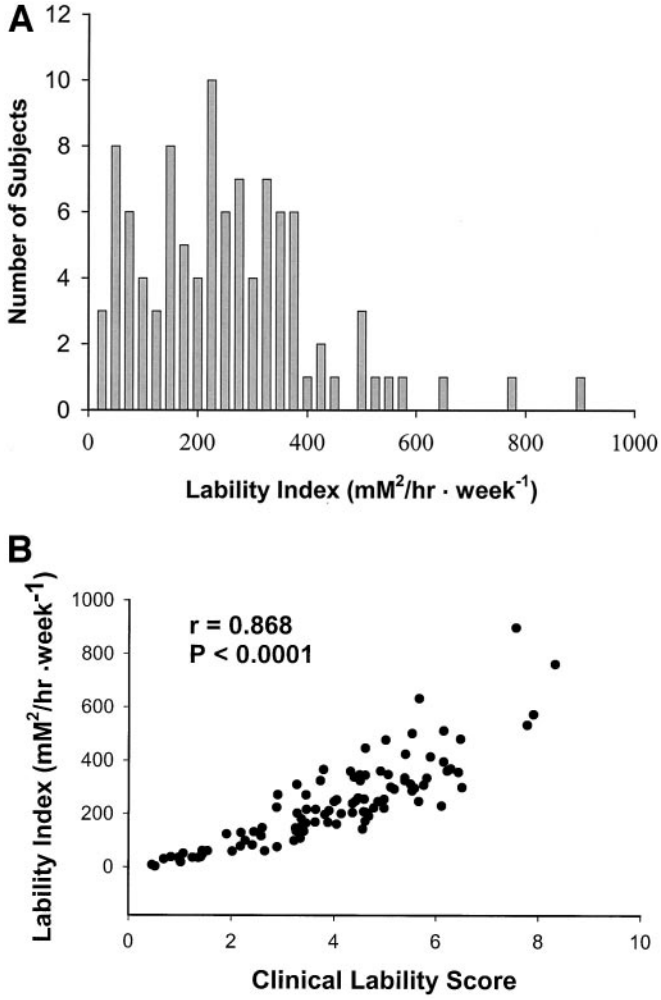

FIG. 3. *A*: Frequency distribution of the LI for the 100 type 1 diabetic control subjects. The LI was calculated for each week as described in the Analysis section of RESEARCH DESIGN AND METHODS and the mean of the 4 weeks taken. *B*: Relationship of the clinical judgement of the lability of the glucose (based on 0 = very stable and 10 = extremely labile) and the LI. Each point represents the mean of four individual week's glucose readings.

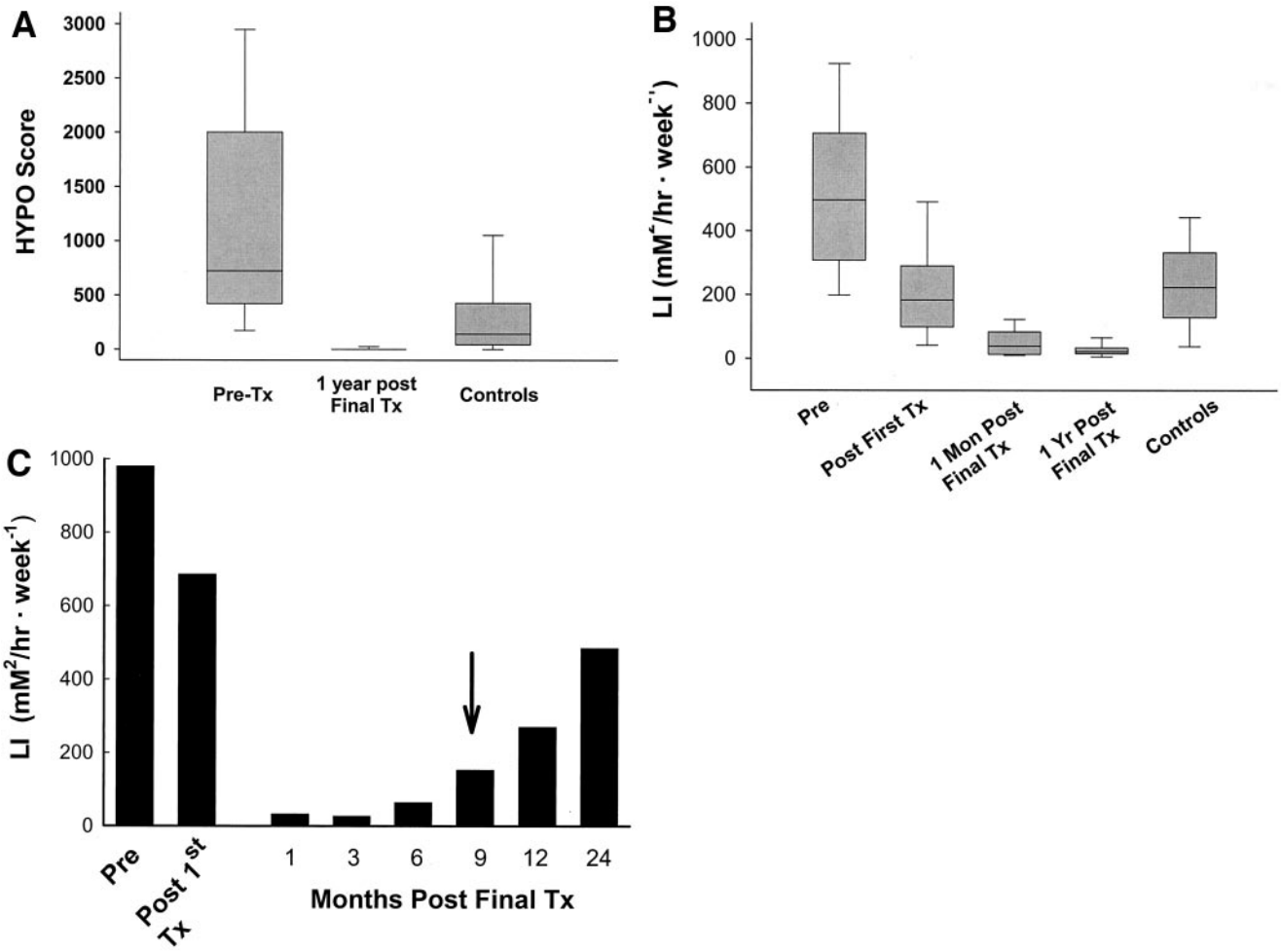

FIG. 4. *A*: **The HYPO score in patients who underwent islet transplantation. Values shown are for pretransplant patients (Pre-Tx) (n = 30) and for those off insulin 1 year after the final transplant (1 Year Post Final Tx) (n = 18). The HYPO score from the general type 1 diabetic clinic subjects (n = 100) is also shown. There was a significant improvement in the HYPO score from pretransplant to 1 year after the final transplant. The box plot shows the median and 25th to 75th interquartile range and the bars the 10th to 90th interquartile range.** *B*: **The LI score in patients who underwent islet transplantation. Values shown are for pretransplant (Pre) (n = 42), after the first transplant (Post First Tx) (n = 44), 1 month (1 Mon Post Final Tx) (n = 34), and 1 year after the final transplant (1 Yr Post Final Tx) (n = 25). The LI score from the diabetic control subjects (n = 100) is also shown and is significantly lower than the values from the pre–islet transplant subjects (P < 0.001). There was a significant improvement in the LI from pretransplant to after the first transplant and from the first transplant to after the final transplant.** *C*: **The LI score in a patient who underwent successful islet transplantation that subsequently failed. Values shown are for pretransplant (Pre), 1, 3, 6, and 9 months after transplant, and at 1 and 2 years after the final transplant. Insulin was restarted at 9 months after the final transplant when (arrow) C-peptide secretion was completely lost.**

who had an islet transplant and then lost islet graft function is shown in Fig. 4*C*. With loss of C-peptide, there is clear deterioration in the LI.

DISCUSSION

Assessing the risk-to-benefit ratio for solitary islet transplantation is a challenge and has to be individualized. The risks associated with the procedure have been documented (3,4,16), but assessing the indications of problematic hypoglycemia and glycemic lability has been subjective. Some patients cope well with recurrent hypoglycemia or erratic glucose levels that would be disabling for others. Some perspective on the severity of the problem compared with the general diabetes clinic population would be helpful for the physician and patient, and standardization of the assessment of islet transplant patients across various sites would be beneficial. There is a similar need for the assessment of subjects for solitary pancreas transplant.

The frequency of severe hypoglycemia in the Diabetes Control and Complications Trial was 0.61 episodes per patient per year (6). Allen et al. (17) reported that one-third of patients with type 1 diabetes, mainly younger and with a duration of diabetes of 4–6 years, had two reactions per week and 4% had a severe reaction with loss of consciousness in a year. Pramming et al. (18) found that the symptoms of hypoglycemia waned with increasing duration of diabetes. They reported a frequency of 1.8 episodes of hypoglycemia per patient per week, with the frequency of severe hypoglycemia being 1.4 episodes per patient per year (18), which is similar to other reports (19). The overall frequency of hypoglycemia in the current study of subjects from a general type 1 diabetes clinic is similar to that of other reports. Thus the magnitude of the problem of hypoglycemia is considerable but there is little in the way of quantification.

Some scales measuring hypoglycemia have been tried but are not in general use. The low–blood glucose index

(LBGI) proposed by Kovatchev et al. (20) predicts the occurrence of severe hypoglycemia. The LBGI is a summary statistic extracted from a series of self-monitored blood glucose readings that increases when the frequency and/or extent of hypoglycemic episodes increase. The LBGI provided some prediction of future severe hypoglycemia (R^2 = 40%). However, the LBGI does not quantify hypoglycemia in terms of awareness, which is important in determining the risk for severe hypoglycemia (7,21). Clarke et al. (22) have described a survey tool that helps identify those with unawareness and who have more episodes of hypoglycemia. Thus the degree of hypoglycemia awareness is an important factor and likely related to hypoglycemia-associated autonomic failure (23). Our HYPO score does inherently give extra weight to neuroglycopenic symptoms and the loss of autonomic symptoms. Continuous glucose monitoring can also detect hypoglycemia over a short period of time but gives no sense of the disruption of daily lifestyle caused by the hypoglycemia (11). It would be helpful when a patient is assessed for either solitary islet or pancreas transplantation to have a measure of the severity of the problem.

We have developed a composite hypoglycemia score based on the frequency, severity, and degree of unawareness of hypoglycemia. In this population, the HYPO score appears to be a reasonable discriminator of the severity of the problems that occur with hypoglycemia. It is a composite based on both frequency and severity of hypoglycemia as recorded over a 4-week period and the recalled episodes over a year. A score of ≥433 was representative of problematic hypoglycemia, and a score ≥1,047 was indicative of very serious concerns. When problems with hypoglycemia exist, there were some patients who simply had very frequent hypoglycemic reactions but had full capability of recognizing them. Some of these subjects were striving for excellent glycemic control and by monitoring their glucose frequently were able to tolerate the recurrent episodes of hypoglycemia. Others had truly severe hypoglycemia unawareness and regularly needed outside help to deal with major hypoglycemic reactions. The HYPO score would be beneficial in identifying both groups of patients. The former group may well respond to adjustments of insulin therapy, especially if they are willing to aim for slightly higher target glucose values. The latter group is more difficult to manage in that the decreased awareness of hypoglycemia and frequent hypoglycemia may well be a manifestation of a vicious cycle (23). The management of hypoglycemia unawareness is challenging (24,25), and short of a pancreas or islet transplant, avoidance of episodes of hypoglycemia appears to carry the best chance of regaining some sensation of hypoglycemia (26–28). The islet transplant patients had high scores that corrected with the transplant procedure and only in those who have lost graft function has the score risen again.

The way the records were gathered in the control group could potentially be of concern. The records were manually recorded, and thus the accuracy of the results was predicated on the true reporting of the events. It is possible that with electronic downloading of meters more complete measurements could be made, but this by itself would miss the more descriptive component of the hypoglycemia scoring system. Secondly, we used a 4-week period detailed record and extrapolated this for a year. This is a weakness in that a particular month may not be representative, though the results of the recalled and recorded frequency of hypoglycemia were similar (Table 1). Although the history of hypoglycemia was a reasonable correlate of the result we obtained from the 4-week record (r = 0.335, $P < 0.0001$), we feel that both the recalled and recorded components contribute to the overall assessment of the degree of difficulty associated with the hypoglycemia. A third potential concern is that the control patients who completed the records may have inherently had more problems with hypoglycemia. The younger age of the group that did not return completed records may support such a contention. It should be recalled that patients who applied to our islet transplant program were a priori excluded from the control group, i.e., those who typically have the most severe problems with hypoglycemia or lability. In addition, the fact that we had a total of 100 subjects, the majority of whom had no major problems with hypoglycemia, suggests that our results are representative of the general type 1 diabetic population. Finally, the control subjects did not monitor their glucose as frequently as the patients being considered for an islet transplant, and some episodes of hypoglycemia may have been missed. However, 80% of control subjects were monitoring their glucose at least three times a day and the majority had hypoglycemic awareness, so it is unlikely that we missed many occurrences of hypoglycemia.

Measuring lability is always difficult, it has even been suggested that the simple measure of the thickness of the patient chart provides an indication of the patient with brittle diabetes (12). Health care professionals who routinely deal with type 1 diabetes can judge if someone has labile diabetes, but quantifying it is a challenge. The MAGE recordings have not been well validated previously, but our results lend some support to its use. The median was 8.1 mmol/l, with a 75th percentile of 10.5 mmol/l, which is close to the level of 11.0 mmol/l previously considered to be the threshold for diagnosing labile diabetes. The MAGE did not discern the number of oscillations of blood glucose levels. The concept that amplitudes >1 SD be used is reasonable, but if only one major decline or rise occurred over 48 h, a very high MAGE reading resulted. The MAGE did not show a strong correlation with the clinical assessment of lability (r = 0.328, P = 0.001). We initially created some theoretical models of glucose profiles and used a variety of indexes to assess lability. We felt that any index should be based on the change in glucose over time and that the assessment should be for a duration that was representative and not just 2 days, such as the case for MAGE (9). A measure of the change in glucose over time $(Gluc_n - Gluc_{n+1})/(h_{n+1} - h_n)$ was adequate if sampling occurred only four times a day but became distorted with more frequent measurements. The formula described in RESEARCH DESIGN AND METHODS worked well in the model independent of the number of tests available. The correlation of the LI and the frequency of testing is a testimony to the fact that those with more labile diabetes tested more often rather than a feature of the formula. Frequent testing will result in a higher LI if the glucose is labile but will not skew it by much. Testing 12 times a day for a week with

variations of glucose of only 2 mmol/l between readings only gives an LI of 84 mmol/l^2/h · week^{-1}. Thus the LI provides an advantage in that any week's set of glucose recordings can be used for the LI determination. The LI can also be used by those who do not have years of diabetes experience or as a way of comparing subjects at different sites and can be quickly calculated from a simple electronic download of memory glucose meter readings to a spreadsheet file.

Because there is no gold standard, two experienced diabetologists reviewed each file and graded lability before knowing what LI value had been assigned. The LI gave a good measure of glycemic lability when compared with the clinical assessment ($r = 0.868$, $P < 0.0001$). Health care providers experienced in diabetes management can identify the patient with labile diabetes but previously had no measure for comparative purposes. The LI may fill this void. Newer methods of continuous glucose monitoring may also be of assistance, but they are currently restricted to measurements over 3 days only (11) and as yet have no simple measure to quantify lability other than looking at the profiles. The changes in both the LI and HYPO scores after islet transplantation (Fig. 4), which mirror the clinical situation, help confirm their validity.

Solitary islet or pancreas transplant is becoming recognized as a viable option for the management of difficult diabetes (29). The indications are primarily problems with hypoglycemia and glycemic lability. Individual care providers can judge these problems, but there is a lack of uniformity between sites and countries (30). Our scoring system provides a measure that may be helpful in the assessment of such patients. A high score provides reassurance that the particular patient has problems more severe than the norm for subjects with type 1 diabetes, provides a measure of improvement after transplantation, and allows comparison from site to site. In the islet transplant patients, the HYPO score and LI were elevated, and there was a prompt improvement seen after the transplant that was maintained for a prolonged period of time. Only if the transplant failed was there a rise in the score.

In conclusion, assessing difficult diabetes with a view toward islet transplantation remains a challenge, but the HYPO score and LI described here do give an objective indication of the severity of the problems being encountered. Both scores allow quantification of the extent of the problem, give a metric to compare with other groups, and document improvement in the context of islet transplantation. These scores should complement the clinical assessment for either solitary whole pancreas or islet transplantation and remove some of the subjectivity from the decision.

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