

Reduction of Blood Glucose Variability in Type 1 Diabetic Patients Treated By Pancreatic Islet Transplantation

Interest of continuous glucose monitoring

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OBJECTIVE — To compare the glycemic profiles of patients with type 1 diabetes treated with either an implantable insulin pump or pancreas or islet transplantation by the means of the continuous glucose monitoring system (CGMS; Minimed, Sylmar, CA).

RESEARCH DESIGN AND METHODS — The CGMS enabled recording of subcutaneous glucose concentrations (range 2.2–22 mmol/l) over 72 h (288 measurements per day). Over 3 days, 26 patients with type 1 diabetes were connected to a CGMS: 10 patients were treated with intraperitoneal insulin infusion through an implantable pump (IPII), 9 patients were treated with simultaneous pancreas-kidney transplantation (SPK), and 7 patients were treated with pancreatic islet transplantation after kidney grafting (IAK). All SPK patients and four IAK patients were insulin independent, whereas three IAK patients had partial graft function and reduced exogenous insulin needs. Glucose control was evaluated by the mean glucose concentration, glucose variability, and the number and duration of hypoglycemic events (<3.3 mmol/l) over 3 days.

RESULTS — The mean glucose concentration and the glucose variability in SPK and IAK patients were significantly lower than those observed in patients treated with IPII: 5.38 ± 1.12 and 5.83 ± 0.81 vs. 7.81 ± 1.55 mmol/l ($P < 0.001$) and 1.40 ± 0.42 and 1.32 ± 0.53 vs. 3.47 ± 1.66 mmol/l ($P < 0.001$), respectively. Furthermore, the mean glucose concentration and the glucose variability were comparable between SPK and IAK patients. Over 3 days, no hypoglycemic events were observed in SPK patients and insulin-independent IAK patients. A total of 4.12 ± 1.66 hypoglycemic events were detected in the IPII patient group, whereas only 0.66 ± 0.57 events were observed in IAK patients with partial graft function ($P < 0.001$). The duration of the hypoglycemic events was significantly longer in IPII patients as compared with IAK patients: 64 ± 33 vs. 30 ± 15 min for the day period and 130 ± 62 vs. 30 ± 27 min for the night period ($P < 0.001$).

CONCLUSIONS — Use of subcutaneous CGMS confirms that islet transplantation can be as efficient as pancreas transplantation in restoring good metabolic control and reducing blood glucose variability. Metabolic improvement due to use of an implantable insulin pump requires insulin delivery by a closed loop.

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Abbreviations: CGMS, continuous glucose monitoring system; EIN, equivalent islet number; IAK, islet transplantation after kidney grafting; IPII, intraperitoneal insulin infusion through an implantable pump; MAGE, mean amplitude of glycemic excursion; SPK, simultaneous pancreas-kidney transplantation.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Keeping blood glucose levels under tight control represents the most effective way to either prevent the onset or reduce the progression of chronic complications in patients with type 1 diabetes. The Diabetes Control and Complications Trial (1) has shown that intensive insulin therapy can reduce HbA_{1c} and can significantly reduce the risk of microvascular complications. However, the intensive insulin therapy was associated with a threefold increased risk of severe hypoglycemia. Moreover, this treatment modality demands high patient compliance and can only be applied to a limited number of selected patients (2). Currently, two main therapeutic alternatives to intensive insulin therapy exist. First, intraperitoneal insulin infusion with implantable pumps (IPII) improves the metabolic control of labile type 1 diabetes and reduces hypoglycemic events (3–5). Second, simultaneous pancreas-kidney transplantation (SPK) can improve the quality of life because patients undergoing this procedure become insulin independent and, moreover, the life expectancy in type 1 diabetic patients with end-stage kidney failure increases (6,7). However, the significant surgical morbidity has been a limiting factor in pancreas transplantation in nonuremic type 1 diabetic patients (8–10).

Although the islet transplantation concept was initially believed to be simple and was expected to rapidly replace whole pancreas transplantation, its widespread clinical applicability was hampered by a variety of technical and biological obstacles. The results of islet transplantation, as reported by the International Islet Registry (11–13) in type 1 diabetic patients, remain insufficient in terms of insulin independence. Only 11% of the subjects were off insulin, whereas 41% produced C-peptide, allowing a 50% reduction in exogenous insulin needs along with normalization of HbA_{1c} level and decreased hypoglycemic events.

Table 1—Characteristics of type 1 diabetic patients treated with IPII, SPK, or IAK

Group	IPII	SPK	IAK	P
n	10	9	7	
Sex (M/F)	4/6	7/2	2/5	
Age (years)	48.5 ± 6.8	40.5 ± 7.5	42.6 ± 9.6	NS
BMI (kg/m ²)	24.9 ± 3.7	23.8 ± 2.3	22.5 ± 1.4	NS
Diabetes duration (years)	26.1 ± 9.6	22.5 ± 7.5	27.5 ± 9.6	NS
Pump duration (years)	6.7 ± 2.9	—	—	
Graft duration (years)		6.1 ± 3.5	1.8 ± 1.3	<0.01
HbA _{1c} (%) (4.4–6)	7.1 ± 0.7	5.2 ± 0.3	5.5 ± 0.4	<0.001

Similar results were also reported by the Swiss-French multicenter network (GRAGIL group) (14) in type 1 diabetic patients who had undergone kidney grafting. Recently, the Edmonton group (15) reported an improvement in islet transplantation in terms of insulin independence in labile, nonuremic type 1 diabetic patients using a steroid-free immunosuppressive regimen.

To date, evaluation of glycemic profiles of patients with diabetes does not allow analysis of glucose excursions, because the methods of glucose measurement such as HbA_{1c} and occasional blood capillary glucose levels give only limited information. In real-life situations, minute-to-minute blood glucose excursions cannot be monitored by glycemia auto-controls (16). The recent development of a continuous glucose monitoring system (CGMS) represents an improvement in the metabolic evaluation of patients with diabetes (17–19). Regarding the most promising treatment of type 1 diabetes, CGMS should allow more precise evaluation of the respective contribution of each treatment to glucose control. Therefore, by means of CGMS, we compared the subcutaneous glucose profiles of type 1 diabetic patients treated with an implantable pump, pancreas transplantation, or islet transplantation.

RESEARCH DESIGN AND METHODS

Continuous glucose monitoring

The CGMS (Minimed, Sylmar, CA) consists of a sterile disposable subcutaneous glucose-sensing device connected by a cable to a pager-sized glucose monitor (17). A communication device allows downloading and reviewing of the data on a personal computer. The needle-delivered transcutaneous sensor detects glucose

electrochemically in subcutaneous interstitial fluid due to its reaction with glucose oxydase. The system registers the glucose concentration every 10 s and stores an average value every 5 min. A total of 288 data points are collected each day (range 2.2–22 mmol/l). Four capillary blood glucose measurements per day are required for sensor calibration. The correlation between blood and subcutaneous glucose measurements is good ($r = 0.95$, $P < 0.001$) (20).

Subjects

From 1 March 1999 until 1 June 2002, a total of 10 IPII-treated patients consecutively admitted in our diabetologic unit with HbA_{1c} <7.5% were selected. Nine patients treated with SPK who had normal glycemic profiles during oral glucose tolerance testing and seven patients from the GRAGIL network who were treated with islet transplantation after kidney grafting (IAK) and who had plasma C-peptide levels >0.5 ng/ml were included in the study. All SPK patients and four IAK patients were insulin independent, whereas three IAK patients had partial graft function characterized by ongoing endogenous insulin production but persisting, although reduced, exogenous insulin needs. In these 26 C-peptide-negative type 1 diabetic patients in ambulatory care, the sensor was placed subcutaneously in the abdominal area for 3 days. The characteristics of study subjects are listed in Table 1. Diabetic patients in each group were comparable in terms of age, BMI, and duration of diabetes. HbA_{1c} was significantly higher in the IPII patients than in the patients who underwent pancreas and islet transplantation. There was no significant difference in HbA_{1c} between SPK and IAK patients.

Implantable insulin pump

In the IPII group, 10 patients received an implantable pump (Minimed Implantable Pump Model 2001; Minimed Technologies, Sylmar, CA), which delivered insulin intraperitoneally for a period of 6.7 ± 2.9 years (5). Pump catheters were made from silicone-coated polysulfone. The infused insulin was Hoechst's 21 PH neutral semisynthetic human insulin (Hoechst, Frankfurt, Germany) at a concentration of 400 IU/ml and stabilized by a glycol-polyethylene-polypropylene surface-active agent (Genapol; Hoechst). Refilling was performed under aseptic conditions every 6 weeks.

Simultaneous pancreas and kidney transplantation

Pancreas and kidney were harvested from heart-beating multiorgan donors. Simultaneous pancreas-kidney transplantation was performed intraperitoneally through a midline incision in nine uremic type 1 diabetic patients as previously described (10); the pancreas and kidney were placed in the right and left iliac fossae, respectively. The recipient's external iliac artery and vein were used for systemic drainage, whereas exocrine secretions from the pancreas graft were drained into the bladder through a side-to-side duodenocystostomy. Donor pancreas and kidney were selected on the basis of ABO blood group compatibility and a negative cross-match between donor and recipient.

Sequential quadruple immunosuppressive therapy was used for all recipients. This treatment comprised antilymphocyte serum (60 mg/day) for 7 days immediately after transplantation, prednisone (2 mg · kg⁻¹ · day⁻¹ decreasing to 0.15 mg · kg⁻¹ · day⁻¹ 1 year after transplantation), cyclosporin (8 mg · kg⁻¹ · day⁻¹ subsequently adjusted to obtain a cyclosporin trough level of 100–200 ng/ml), and azathioprine (1.5 mg · kg⁻¹ · day⁻¹). Continuous glucose measurements were performed 6 ± 3.5 years after transplantation.

Islet after kidney transplantation

Pancreata were harvested from heart-beating multiorgan donors. Islet isolation was started within 8 h after cross-clamping and was performed as described previously (21). Islets were counted on the day of injection and only the intact, dithizone-stained islets were taken into consideration. The equivalent islet num-

ber (EIN) was calculated by normalizing the islet to a standard islet of 150 μm in diameter. The islet preparation was collected in 50-ml syringes.

Islet transplantation was performed in seven type 1 diabetic patients having a functional kidney graft (creatinine clearance >60 ml/min) for ≥ 6 months. Before transplantation, islets of five patients were kept in culture for 2–10 days. After intravenous administration of 5,000 units of heparin, islets were injected into the portal vein under radiological control. A mean of $10,560 \pm 4,061$ EIN/kg was injected per recipient. The first patient was treated with a polyclonal antilymphocyte serum (Atgam; Pharmacia and Upjohn, Dubendorf, Switzerland), cyclosporin (Neoral; Novartis, Basel, Switzerland) with a trough level between 100 and 150 ng/ml, azathioprine (Imurek; Wellcome, Bern, Switzerland), and corticosteroids with rapid tapering to 5 mg of prednisone by the end of the third month after transplantation. Immunosuppression in the four other patients included the anti-interleukin-2-receptor antibody basiliximab (Simulect; Novartis, Basel, Switzerland) 20 mg intravenously at days 0 and 4. The protocol then consisted of oral cyclosporin (trough levels between 150 and 200 ng/ml during the first 3 months and 100 ng/ml thereafter), mycophenolate mofetil (Cellcept; Roche, Basel, Switzerland), and corticosteroids (methylprednisolone at a dose of 1 g intravenously on day 0 and 100 mg intravenously on day +1, followed by oral prednisone at dose of 20 to 0–5 mg/day until the end of the sixth month).

Islets were immediately transplanted after isolation in the two remaining patients. Two intraportal injections were needed to transplant 12,430 EIN/kg per recipient. Immunosuppression in these two patients included the anti-interleukin-2-receptor antibody basiliximab (Simulect; Novartis, Basel, Switzerland) 20 mg intravenously at days 0 and 4. The protocol then consisted of oral cyclosporin (Neoral; Novartis, Basel, Switzerland) with a trough level between 75 and 100 ng/ml and 300–500 ng/ml 2 h after oral administration during the first 3 months and a trough level between 50 and 75 ng/ml thereafter and rapamycin (RAD; Novartis) with trough level between 5 and 15 ng/ml.

In all seven cases, an adjuvant therapy was administered after islet injection: 2 g

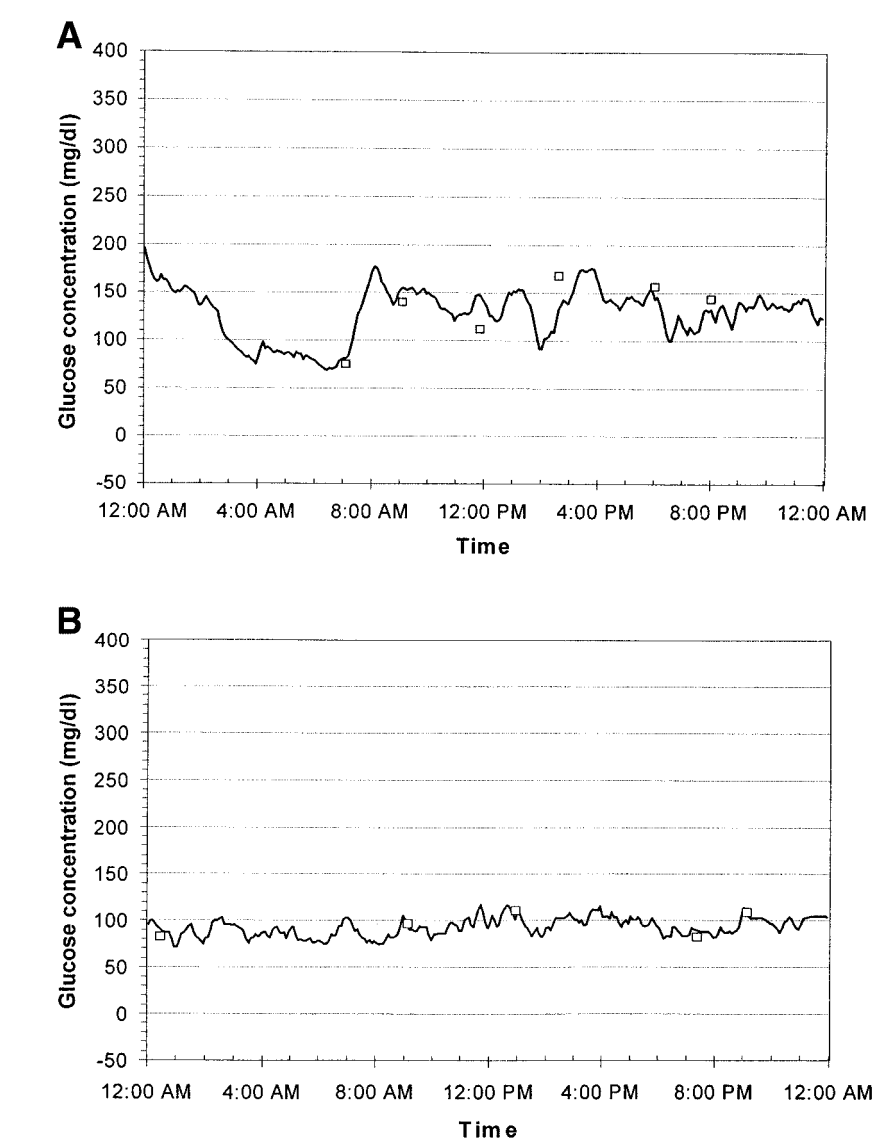


Figure 1—CGMS daily glucose profile of an IPII-treated patient (A) and an SPK-transplanted (B) patient. Squares identify the blood glucose capillary measurements used for the calibration.

nicotinamide (Nicobion; Merck), 800 units of vitamin E, and 1,200 mg of pentoxifylline (Trental; Hoechst-Marion-Roussel, Zurich, Switzerland) per day for a period of 1 month. Insulin therapy was maintained unless the patient experienced hypoglycemia. The study started 1.8 ± 1.3 years (0.5–5 years) after transplantation.

Glucose profile analysis

For each group, a qualitative analysis of the glucose profiles was performed from the graphical data of the CGMS daily analysis. After 3 days, glucose profiles of each group were analyzed quantitatively: the mean glucose concentration and the glucose variability. The latter was calculated

as the absolute value of measured glucose minus 5.5 mmol/l. In addition, the number and duration of hypoglycemic events (<3.3 mmol/l) were identified during the night and day periods.

Statistical analysis

Results are expressed as mean \pm SD. A one-way ANOVA followed by a multiple comparison procedure (least significant difference test) was used to compare each parameter between the groups.

RESULTS

Qualitative analysis

The CGMS daily glycemic profiles of the IPII patients are shown in Fig. 1A. A large

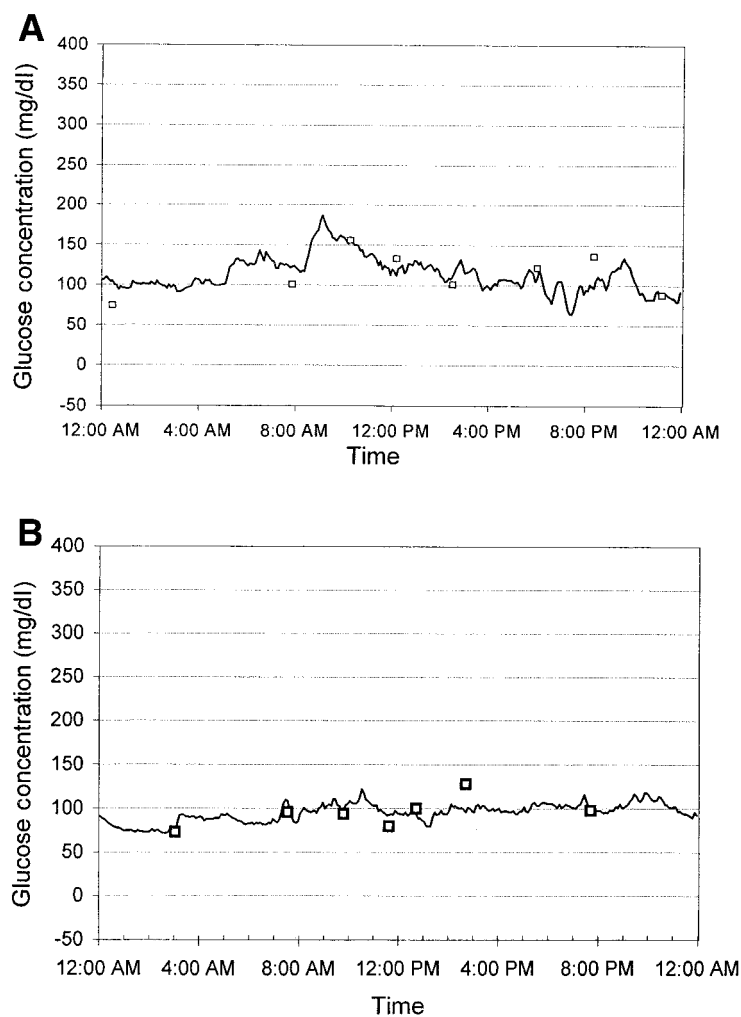


Figure 2—CGMS daily glucose profile of IAK-transplanted patients with partial graft function (A) or insulin independence (B). Squares identify the blood glucose capillary measurements used for the calibration.

amplitude of glucose excursion was shown, particularly during the night period. In contrast, after SPK transplantation, glucose values remained stable at ~ 5.5 mmol/l (Fig. 1B).

Among the IAK patients, the amplitude of glucose excursion was more important in patients having partial graft function than in insulin-independent patients (Fig. 2A and B).

Mean glucose concentration and glucose variability

During the 3-day period, the mean glucose concentration of IPII patients was significantly higher than that observed in SPK and IAK patients: 7.81 ± 1.55 vs. 5.38 ± 1.12 and 5.83 ± 0.81 mmol/l ($P < 0.001$) (Table 2). There was no

significant difference in the mean glucose concentration between SPK and IAK patients.

Glucose variability was comparable between SPK and IAK patients: 1.40 ± 0.42 and 1.32 ± 0.53 mmol/l. A significantly higher glucose variability was observed in IPII patients: 3.47 ± 1.66 mmol/l ($P < 0.001$) (Table 2).

Table 2—Mean glucose concentration and glucose variability in type 1 diabetic patients treated with IPII, SPK, or IAK

Group	IPII	SPK	IAK	P
Mean glucose concentration (mmol/l)	7.81 ± 1.55	5.38 ± 1.12	5.83 ± 0.81	<0.001
Glucose variability (mmol/l)	3.47 ± 1.66	1.40 ± 0.42	1.32 ± 0.53	<0.001

Number and duration of hypoglycemic events

During the 3 days, IPII patients had 4.12 ± 1.66 hypoglycemic events, whereas only 0.66 ± 0.57 events were observed in IAK patients with partial graft function ($P < 0.001$) (Fig. 3A). No hypoglycemia was observed in any of the SPK or insulin-independent IAK patients.

The duration of hypoglycemic events during daytime was significantly longer in IPII patients than in IAK patients with partial graft function: 64 ± 33 vs. 30 ± 15 min ($P < 0.001$). During the night, hypoglycemia persisted for 130 ± 62 min in IPII-treated patients, whereas in IAK patients with partial graft function, events of hypoglycemia lasted only 30 ± 27 min (Fig. 3B).

CONCLUSIONS— By using CGMS in type 1 diabetic patients, our study showed a significant improvement in glucose control after pancreas or islet transplantation as compared with intraperitoneal insulin infusion through an implantable insulin pump. After SPK or IAK transplantation, both the mean glucose concentration and the glucose variability were significantly lower than those observed in IPII patients. Furthermore, these two parameters were comparable between SPK and IAK patients. The number and duration of hypoglycemic events were reduced in IAK patients with partial graft function compared with IPII patients, whereas no hypoglycemia was observed in insulin-independent SPK or IAK patients.

In our study, the CGMS recording was performed in all subjects in ambulatory care over 3 days without any technical problems. The accuracy and reliability of CGMS have been tested under a variety of clinical and ambulatory conditions (17,22). CGMS provides accurate continuous measurement of interstitial glucose levels, correlating closely with blood glucose levels (21). The device collects many data points and detects glucose fluctua-

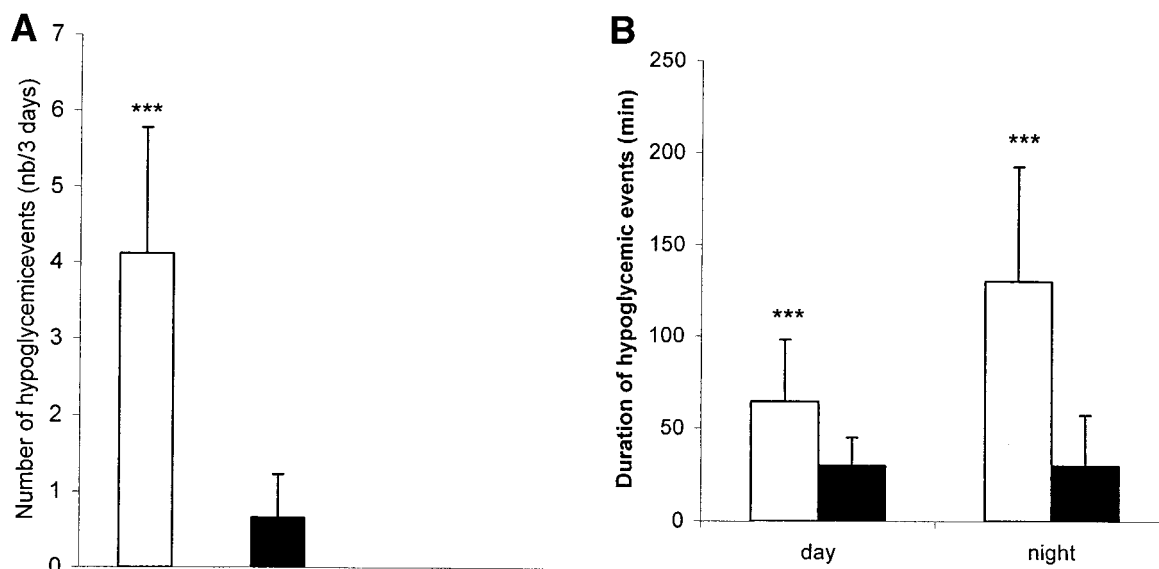


Figure 3—Number (A) and duration (B) of hypoglycemic events in IPII-treated □ and IAK-transplanted patients with partial graft function ■ during 3 days of CGMS registration (**P < 0.001).

tions during the day in a more detailed (288 measurements) but less accurate manner than those obtained with glucose self-monitoring. In agreement with several other groups, we found a modest difference between capillary blood and sensor glucose levels. Zung and Zadik (23) reported a total of 1,511 CGMS glucose values collected in a multicenter trial of 62 subjects. Of the 169 sensor readings in the low glucose concentration range, only 30% were confirmed by the capillary blood glucose measurements. In contrast, performance of CGMS was much better in the normal and high glucose concentration range. In addition, in a case report of a patient connected simultaneously with two CGMS devices, a slight difference between the two sensor values was observed, showing the limits of the CGMS system (24). The interpretation of an isolated data point on the CGMS graph must be considered with caution. Despite this limitation, the CGMS system allows better analysis of the duration of hypoglycemic and hyperglycemic events and glucose excursions than capillary blood glucose measurements. Recently, an improved sensor was used by us and other groups and resulted in more accurate glucose concentration measurements.

The glucose profile was analyzed by calculation of the mean glucose concentration, the glucose variability, and the number and length of hypoglycemic events. Among the different methods to

calculate diabetic instability, mean amplitude of glycemic excursion (MAGE) has been widely used in stable and unstable diabetic patients (25). MAGE is calculated by taking the arithmetic mean of blood glucose increases or decreases when both ascending and descending variation exceeds the value of 1 SD of the blood glucose concentration in 24 h. Consequently, the MAGE values are lower in normal subjects than in diabetic patients. However, the MAGE values are only significant for unstable patients with large amplitudes of glucose excursion (26). Because IPII treatment and pancreas and islet transplantation are known to potentially reduce the glucose excursions in diabetic patients, we have chosen to express the glucose variability as the absolute value of measured glucose concentration minus 5.5 mmol/l, instead of MAGE, allowing analysis of smaller amplitudes in glucose excursions and consequently the comparison between the groups in our study.

In terms of glycemic control, our study demonstrates the superiority of SPK and IAK transplantation over IPII. Indeed, both HbA_{1c} and mean glucose concentrations were comparable between pancreas- and islet-transplanted patients, whereas these values were significantly higher in IPII-treated patients. These results can be explained by the absence of a closed-loop insulin delivery system in IPII treatment. In addition, the glucose profile

of three healthy subjects (data not shown) analyzed by CGMS in our unit revealed that both mean glucose concentration and glucose variability were similar between healthy subjects and transplanted patients. Because of the small number of IAK patients, we have regrouped insulin-independent patients and patients with partial graft function. The glucose excursions expressed as MAGE index in the study by Ryan et al. (15) were significantly lower after islet transplantation. However, corticosteroids were included in our immunosuppressive therapy, except for in the latter two patients. Clinical symptoms together with a CGMS glucose value <60 mg/dl confirmed hypoglycemia. However, certain patients did not have symptoms of hypoglycemia. In these cases, a hypoglycemic event was taken into account when the glucose concentration was maintained at <60 mg/dl for >30 min. If capillary blood glucose measurements give only an indication of the number of hypoglycemia events, CGMS also integrates the duration of these events. Hypoglycemia events persisted for 2 h in IPII-treated patients. In our study, both the number and the length of hypoglycemic events were significantly lower in IAK patients than in IPII patients. During the 3 days of CGMS registration, a mean of four hypoglycemic events was observed in IPII patients, whereas SPK and insulin-independent IAK patients did not experience any hypoglycemic events.

Some authors reported hypoglycemia together with hyperinsulinism after pancreas transplantation, probably due to the systemic delivery of insulin (27). In our study, a longer CGMS analysis would probably be required to identify hypoglycemic events. The absence of hypoglycemia in insulin-independent islet-transplanted patients has also been reported by other groups (12–15). These results can be explained by the physiological portal delivery of insulin after islet transplantation. In agreement with several studies, islet-transplanted patients with persisting endogenous insulin production exhibited a reduced number and duration of hypoglycemic events (12–14). These results can be explained by the autoregulated endogenous insulin production of grafted islets. Ryan et al. (15) did not report hypoglycemia in patients with partial graft function. However, in their study, the analysis of the glucose profiles was based on the blood glucose auto-monitoring, which does not allow detection of asymptomatic hypoglycemic events.

In summary, CGMS is a useful tool to analyze precisely the glucose profile of type 1 diabetic patients under different investigational treatment modalities. Our results show that islet transplantation can be as efficient as pancreas transplantation in restoring good metabolic control and reducing blood glucose variability. To improve the implantable insulin pump treatment, the closed-loop insulin delivery system is required.

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APPENDIX

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