Self-Monitoring of Blood Glucose in Type I Diabetic Patients: Comparison With Continuous Microdialysis Measurements of Glucose in Subcutaneous Adipose Tissue During Ordinary Life Conditions

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OBJECTIVE — To evaluate whether frequent self-monitoring of blood glucose (SMBG) sufficiently reflects the true diurnal glucose control during ordinary daily life in type I diabetic patients.

RESEARCH DESIGN AND METHODS — By using a microdialysis technique, continuous monitoring of adipose tissue glucose was performed in 24 type I diabetic patients during ambulatory conditions. A microdialysis probe was implanted subcutaneously and perfused by a portable microinfusion pump. Dialysate fractions were collected in 1- to 2-h samples during 3 consecutive days. The diurnal microdialysis glucose profiles were compared with those obtained by SMBG recordings performed seven times a day.

RESULTS — In seven patients, the SMBG profiles showed marked aberrations as compared to the continuous microdialysis glucose recordings; during the 3-day study period, 5–6 inconsistencies were registered. In only 4 patients (17%) did SMBG provide a valid reflection (0–2 inconsistencies) of the diurnal glucose profile, whereas in 13 patients the SMBG recordings paralleled the diurnal adipose tissue glucose profiles in an intermediate way (3–4 major inconsistencies). The inaccuracy of the SMBG data was due more often to the fact that wide glucose swings remained unrecognized, rather than to erroneous testing techniques ($P < 0.05$), and it was more evident during the night ($P < 0.05$).

CONCLUSIONS — In many type I diabetic patients, the true diurnal variability in glycemia is too great to be accurately reflected even by frequent self-monitoring of blood glucose.

Several prospective investigations have indicated that intensive insulin treatment and near-normoglycemia prevent or retard the development of microvascular complications in patients with type I diabetes (1–3). In these studies, the implementation of intensified insulin regimens has relied heavily on the patients' self-monitoring of blood glucose levels (SMBG). The data were used to assess daily glucose control, to facilitate decisions concerning clinical management and adjustment of insulin doses, and to help in the recognition of hypoglycemia.

While SMBG is generally thought to be a reliable indicator of diabetic control (4), the usefulness of the recordings depends on the patient's ability to accurately carry out the testing procedure and the frequency of the testing (5). Problems related to erroneous testing technique may be alleviated by giving patients adequate training (6). However, it is not known how frequently self-monitoring must be performed to determine the actual diurnal variations in blood glucose during ordinary daily life.

We have developed a microdialysis sampling technique (7) for continuous long-term monitoring of glucose in the interstitial water space of subcutaneous adipose tissue in type I diabetic patients (8,9). With this method, a dialysis tube is implanted in the tissue and slowly perfused with isotonic fluid. The glucose concentration in the outgoing microdialysate is determined and reflects the corresponding level in the extracellular water because of the diffusion of the substance across the semipermeable membrane (7). The concentration of glucose in the tissue dialysate is almost the same as that in venous plasma, and variations in tissue glucose levels closely parallel changes in plasma glucose with a time lag of <5 min (10). Moreover, with the use of a portable device, ambulatory monitoring of adipose tissue glucose became possible and was carried out continuously during 3 days, while the patients maintained their usual activities (9).

While not a primary objective of the previous investigation (9), preliminary findings indicated that in some type I diabetic patients, the true variations in glycemia may be too great to be detected by conventional SMBG. Therefore, in the present study, we have used this novel microdialysis glucose-monitoring technique to determine whether or not frequent self-recordings of capillary blood glucose provide sufficient information about the diurnal changes in glucose control, including detection of hypoglycemic events, under ordinary daily life conditions. Glucose concentrations in subcutaneous adipose tissue were recorded over a 75-h period in 24 type I diabetic patients during ambulatory conditions. The 24-h microdialysis glucose profiles were compared with those obtained by conventional SMBG, performed at least 7 times a day.

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Received for publication 12 March 1996 and accepted in revised form 2 August 1996.
MAGE, mean amplitude of glycemic excursions; SMBG, self-monitoring of blood glucose.

RESEARCH DESIGN AND METHODS

Patients

Twenty-four type 1 diabetic patients (9 women and 15 men), recruited from the diabetes outpatient clinic, participated in the study. They were aged 19–58 years (mean ± SD age, 36 ± 12 years), and the duration of their diabetes ranged between 3 and 41 years (18 ± 10 years). All patients were of normal weight (BMI 23.2 ± 2.6 kg/m^2). Their degree of glycemic control covered a wide spectrum, as evidenced by their glycated hemoglobin (HbA_{1c}) values, which ranged between 5.1 and 13.6% (mean value 8.7 ± 1.9%; normal range 3.4–5.0%). One patient was receiving continuous subcutaneous insulin infusion, and all the others were on intensive insulin-injection treatment (i.e., preprandial injections of regular insulin and an evening injection of intermediate or long-acting insulin). Their daily insulin dose averaged 0.69 ± 0.19 U · kg^{-1} · 24 h^{-1}. Six patients had background retinopathy, and three patients displayed preproliferative retinopathy. One patient had clinical diabetic nephropathy, that is, an albumin excretion rate >200 μg/min, and two patients had incipient diabetic nephropathy, defined as an albumin excretion rate between 20 and 200 μg/min. No one showed evidence of macroangiopathy. None of the patients displayed signs of autonomic neuropathy, and all patients said they could recognize symptoms of hypoglycemia. Before entering the study, all patients had regularly carried out SMBG, although with various frequencies. The study was approved by the Ethics Committee at Huddinge Hospital. The patients were given a detailed description of the study, and informed consent was obtained.

Microdialysis device

The principle of the microdialysis catheter (CMA Research, Stockholm, Sweden) has been described in detail elsewhere (8,9,11). Briefly, a tubular dialysis membrane (30 × 0.62 mm, 20,000 molecular wt cutoff) was glued to the end of a double-lumen catheter. The inlet tubing of the catheter was connected to a portable microinfusion pump (Minimed 504, Minimed Technologies, Sylmar, CA) and was perfused with Ringer's solution (contents in 1,000 ml water: 147 mmol sodium, 4 mmol potassium, 2.3 mmol calcium, 156 mmol chloride; osmolality 290 mOsm/kg). The perfusate entered the probe through the space between the outer inlet lumen of the catheter and the dialysis membrane. Thereafter, it left the catheter via the inner outgoing lumen from which it was collected in polyethylene test tubes.

Study protocol

The patients reported to the hospital at 7:30 A.M. in a nonfasting state. A microdialysis catheter was inserted percutaneously, under sterile conditions, into the subcutaneous adipose tissue in the periumbilical region with a steel cannula guide. No anesthesia was required for this procedure. The inlet lumen of the catheter was connected to the portable microinfusion pump (external size 51 × 86 × 21 mm) and was perfused at 0.5 μl/min with Ringer's solution. After a 15- to 30-min equilibration period, 60- or 120-min samples (see below) of the outgoing tissue microdialysate were collected manually for measurements of glucose using a routine enzymatic glucose-oxidase method (12). During the first 27 h, the patients were examined in the hospital; tissue dialysate was sampled over 60-min (7:00 A.M. to 9:00 P.M.) or 120-min (9:00 P.M. to 7:00 A.M.) periods. In the middle of each 1- to 2-h period, a venous blood sample was drawn simultaneously from an indwelling polyethylene catheter placed in a cubital vein for analyses of plasma glucose (12). In addition, self-monitoring of capillary blood glucose levels was carried out by the patients before and 1 hour after the main meals, and once in the evening before bedtime, using an in vitro enzymatic glucose sensor (ExacTech, MediSense, Cambridge, MA). The patients were asked to perform additional SMBG in connection with suspected hypoglycemic events. During the stay in the hospital, they followed their usual pattern of food intake, insulin injections, and physical activity.

On day 2 at 11:00 A.M., the patients were discharged from the hospital. They continued to collect the tissue dialysate samples and carry out SMBG by themselves, as often as described above. The dialysate samples were collected in prelabeled, capped test tubes and were returned to the laboratory for glucose measurements (12). Before analysis, each test tube was visually inspected and/or weighed (n = 14 patients) in order to verify appropriate sampling. SMBG values; insulin doses; timing of insulin injections, meals, and physical activity; and symptomatic hypoglycemic events were registered by the patients in a log book. On days 3 and 4, they visited the hospital between 8:00 A.M. and 11:00 P.M.; during this period the venous plasma glucose level was determined once an hour (8:30, 9:30, and 10:30 A.M.). During the time outside the hospital, the patients were either at home or at work (optional), and they were encouraged to maintain their usual daily activities. After completion of the study, the patients rated the degree of difficulty in performing their ordinary daily routines (such as participation in usual social activities, limitations at work, personal hygiene, etc.) during the recordings on a 100-mm visual analog scale (0 mm = no problems; 100 mm = impossible); the average rating value being 3 ± 1 mm. All patients reported that they could go back to sleep during the 2-h interval between each night sample collection.

In one patient, monitoring was stopped after 65 h because of an obstruction in the inlet lumen of the catheter. No other malfunctions of the device were encountered, and no local complications at the site of implantation were observed. However, in one additional patient the experiment had to be terminated after 55 h because of the acute onset of intercurrent gastroenteritis.

HbA_{1c} was determined by the hospital's clinical laboratory, using a monodisperse cation exchanger and commercially available microcolumns (Mono S HR 5/5, Pharmacia, Uppsala, Sweden).

Calculations

It has been shown repeatedly that the concentration of glucose in the adipose tissue interstitial fluid is almost identical with that in venous plasma (8,9,13,14). Thus, the relative recovery of glucose in the tissue dialysate was calculated as the ratio between dialysate glucose and plasma glucose × 100 (%).

The degree of similarity between the diurnal glucose profiles, as obtained from the continuous adipose tissue glucose monitoring and the patients' self-measurements of capillary blood glucose levels, was assessed independently by the three diabetologists in the study (J.B., P.A., and E.H.-T.). The reliability of the SMBG was evaluated by visually comparing each patient's three consecutive 24-h SMBG profiles with the corresponding microdialysis glucose-monitoring profiles: first, with regard to its inability to detect significant increases or decreases in glucose levels (i.e., missed information about glucose swings) and, second, by looking at large discrepancies in glucose readings (≥3 mmol/l) at comparable points of time between the two

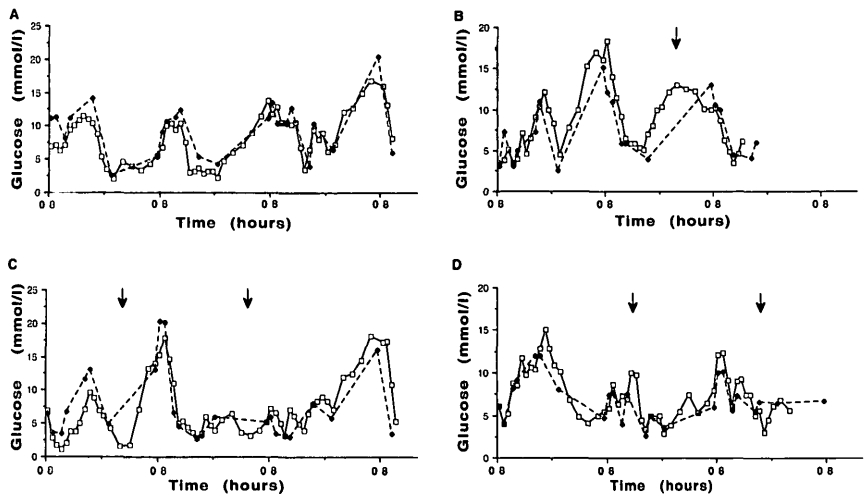

Figure 1—*SMBG (- - - -) and continuous microdialysis measurements of glucose in subcutaneous adipose tissue (——) over 3 days in four type I diabetic patients with high accuracy in home glucose monitoring. Arrows depict significant discrepancies between the two types of recordings.*

monitoring techniques (i.e., deviation in glucose determinations). By counting the total number of inconsistencies over the 75-h study period, the accuracy of the SMBG was rated as being high (0–2), intermediate (3–4), or low (≥5 inconsistencies). Among the three reviewers the rating was unanimous in 19 of the 24 patients. In the remaining five patients, one of the reviewers gave a different rating from the two others; in such cases the majority opinion was used for the evaluation.

The patients' ability to recognize hypoglycemic reactions was assessed by identifying episodes of manifestly low concentrations of glucose (≤3.5 mmol/l) in the tissue dialysate and then checking whether or not hypoglycemia had been verified by patient-derived SMBG data.

To assess the variability in the daily glucose control, *M* values were calculated from the microdialysis glucose-monitoring profiles and from the SMBG recordings, respectively, according to the formula developed by Schlichtkrull et al. (15):

$$M = \frac{\Sigma\,[10 \log_{10}(\frac{G}{\text{standard}})]^3}{n}$$

where *G* is the sample glucose concentration, "standard" is a chosen reference value, and *n* is the number of determinations. The standard glucose reference value was set at 4.4 mmol/l. In addition, the mean amplitude of glycemic excursions (MAGE) was calculated, according to Service et al. (16). The reported *M* values and MAGE values represent the respective average values during the three consecutive 24-h recordings in each patient.

Statistical analysis

The reported values are the means ± SE. Linear regression analysis was performed by the least-squares method. Positions of regression lines were compared by the *F* distribution test (17). Statistical evaluation of the data was performed by the sign test.

RESULTS — The absolute glucose concentrations in the adipose tissue dialysate were almost identical with those in venous plasma throughout the 3-day study period; the recovery of glucose in the 24 patients averaged 91 ± 2%. When the data from all patients were calculated together, a close correlation ($y = -0.58 + 0.94x$; $r = 0.90$, $P < 0.01$) was found between the glucose concentrations in venous plasma and in the tissue dialysate. A similar correlation ($y = 0.66 + 0.79x$; $r = 0.90$, $P < 0.01$) was registered between the SMBG recordings in capillary blood and venous plasma glucose concentrations. However, the slopes of the two regression lines differed significantly ($F = 3.98$, $P < 0.01$). The average within-patient correlation between the plasma glucose levels and the adipose tissue glucose levels was 0.89 ± 0.02; similar relationships were found between the glucose levels in plasma and in capillary blood (0.91 ± 0.02) as well as between the adipose tissue glucose concentrations and the capillary blood glucose concentrations (0.87 ± 0.02) in the individual patients. The mean tissue glucose concentration correlated positively with HbA_{1c} ($r = 0.56$, $P < 0.01$).

When comparing the individual patients' SMBG data with their corresponding microdialysis adipose tissue glucose profiles, only four patients had fewer than 3 inconsistencies (Fig. 1). In these patients, the diurnal pattern of glucose control was correctly reflected by their own SMBG recordings, and the two sets of profiles were almost superimposed most of the time. In 13 patients, the reliability of the SMBG was considered to be intermediate (i.e., 3–4 inconsistencies); individual profiles obtained from four representative

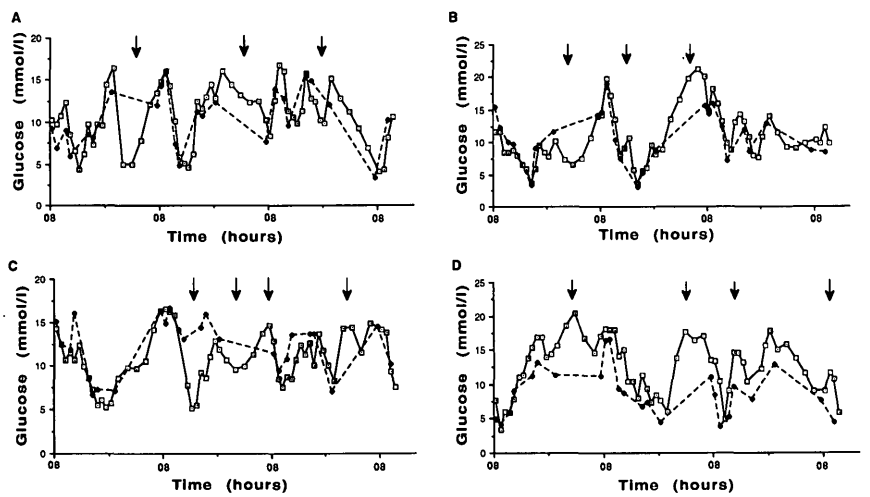

Figure 2—*SMBG (- - - -) and continuous microdialysis measurements of glucose (——) in subcutaneous adipose tissue. Glucose profiles obtained in 4 of 13 representative patients with intermediate accuracy in home glucose monitoring, are given. For further details, see legend to Fig. 1.*

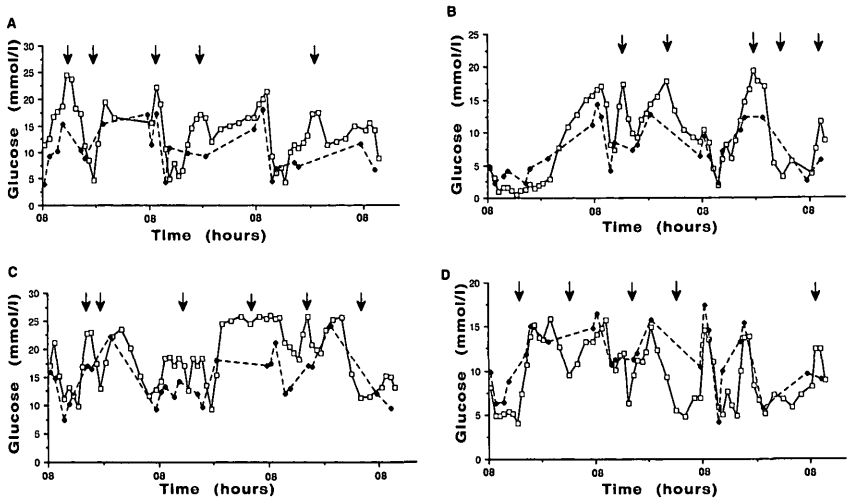

Figure 3—*SMBG (- - - -) and continuous microdialysis measurements of glucose (——) in subcutaneous adipose tissue. Glucose profiles obtained in four of seven representative patients, with low accuracy in home glucose monitoring are given. For further details, see legend to Fig. 1.*

patients in this group are depicted in Fig. 2. In seven patients, four of whom are shown in Fig. 3, the SMBG profiles showed marked aberrations as compared with the corresponding continuous adipose tissue recordings, the number of inconsistencies during the 75-h study period being 5–6. In the latter patients, most of the true diurnal variations in glucose control were totally unconfirmed by the SMBG recordings. Individual glucose profiles in the remaining nine patients in the intermediate group and the three remaining patients in the low-accuracy group are given as microprints in the APPENDIX.

Figure 4 depicts the principal causes (i.e., deviation in glucose determinations and missed information about glucose swings) of the inconsistencies between the SMBG recordings and the microdialysis glucose profiles in the individual patients. While both types of inconsistencies were recognized in most patients, inability to detect major glucose swings was the main cause in 17 of the 24 patients ($P < 0.05$). In half the patients, the latter phenomenon was observed during daytime and nighttime. However, on the whole it occurred more often during night hours (17 vs. 5 cases; $P < 0.05$). The number of inconsistencies was uniformly distributed over the 3-day study period, the number on day 1, 2, and 3 being 26, 32, and 29, respectively.

The *M* values in the 24 patients, as calculated from the microdialysis glucose-monitoring profiles, ranged between 26.5 and 254.6 (mean value 80.8 ± 10.7). The corresponding *M* values from the SMBG recordings ranged between 16.1 and 158.2 (mean value 69.2 ± 7.7, NS). The MAGE values calculated from the microdialysis data and the SMBG readings averaged 8.1 ± 0.4 mmol/l and 7.8 ± 0.5 mmol/l, respectively (NS). However, there was only a weak positive correlation between the respective *M* values calculated from the two different methods of glucose monitoring ($r = 0.50$, $P < 0.05$), and no statistically significant relationship was observed between the corresponding MAGE values ($r = 0.32$; NS). The *M* values from the microdialysis recordings and the SMBG data correlated positively with HbA_{1c} ($r = 0.58$, $P < 0.01$ and $r = 0.45$, $P < 0.05$, respectively). No significant correlations were found between the respective MAGE calculations and HbA_{1c} ($r < 0.2$). Neither HbA_{1c} nor the *M* values or MAGE values correlated with the number of undetected glucose swings or with the total number of inconsistencies between the SMBG recordings and the microdialysis glucose profiles ($r < 0.3$). Moreover, there were no significant correlations between the indexes of variability in the diurnal glucose control (i.e., the *M* and MAGE values) and age, diabetes duration, insulin doses or BMI.

In eight patients, 18 hypoglycemic events were registered during the study period. Twelve of these events were perceived by the patients and were documented by additional SMBG. Six hypoglycemic attacks, however, were not recognized by the patients. Four of them occurred in the afternoon, and the remaining two attacks occurred during the night. The hypoglycemic glucose nadir, as determined in the adipose tissue dialysate, in the 12 events perceived by the patients (2.6 ± 0.2 mmol/l) did not differ from that in the unperceived 6 events (3.0 ± 0.2 mmol/l, NS).

CONCLUSIONS — Self-monitoring of blood glucose levels is a mainstay in intensive insulin treatment in type I diabetes. However, this study shows that conventional SMBG recordings, even if performed very frequently, often may not sufficiently

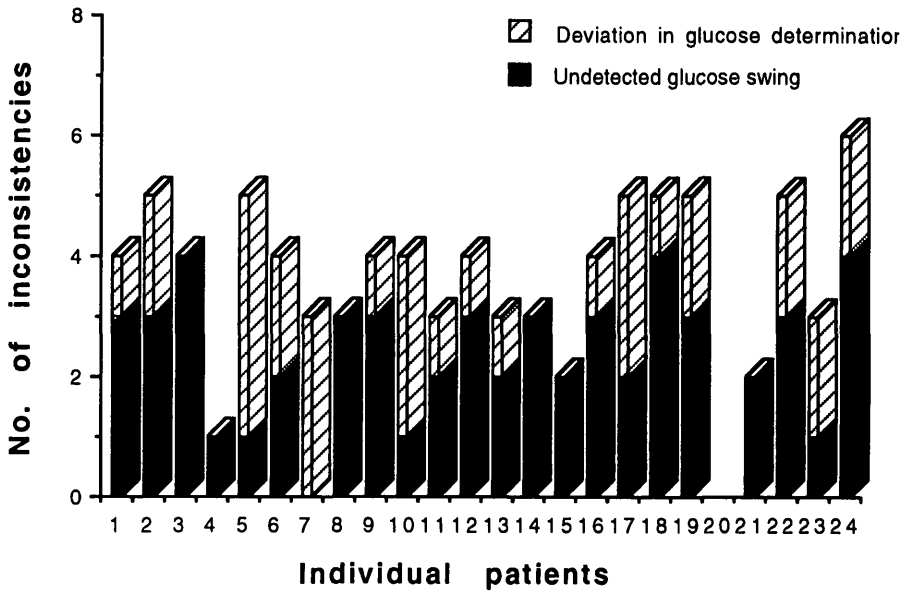

Figure 4—*Causes of significant discrepancies between SMBG and continuous microdialysis measurements of glucose in subcutaneous adipose tissue >3 days in 24 type I diabetic patients.*

reflect the characteristics of the individual patient's true diurnal blood glucose profile.

Previous investigations of SMBG have focused mainly on technical aspects (device-related and user-related accuracy) (6,18), reliability in data presentation (19–21), and patient compliance (22), but less attention has been paid to the optimal daily frequency of testing. Since a detailed description of the diurnal fluctuations in glucose levels necessitates variously timed blood glucose measurements (23), it has hitherto been difficult to evaluate individual glucose profiles without having to hospitalize the patients. On the other hand, in the present study a comparison between SMBG recordings and continuous diurnal glucose monitoring became possible for the first time in the ambulatory state, using microdialysis measurements of glucose in subcutaneous adipose tissue. As shown in previous investigations (8,9), and in the present one, it is possible with this method to determine the true glucose concentration in the tissue, which is nearly identical with that in the venous plasma. Although the resolution of the tissue glucose profile depends on the dialysate sampling frequency, it seems that the presently used sampling time (1 h during the day and 2 h at night) was sufficient to register the major glucose swings that occurred during the 3-day observation period. In addition, the mean tissue glucose level over this period as well as the *M* value correlated significantly with HbA_{1c}, which indicates that the ambulatory recordings were representative of the patients' average daily glucose control.

When comparing visually the glucose profiles provided by the patient's conventional SMBG recordings with those from the continuous microdialysis adipose tissue glucose determinations, we observed large discrepancies in most patients. Hence, in nearly one-third of the cases, the correspondence between the two types of glucose profiles was very poor, showing 1–2 major inconsistencies each day. In only four patients did home glucose monitoring provide a valid reflection of the actual diurnal glucose profile. In the remaining half of the patients, the self-recordings were acceptable at best. Our results also indicated that the inaccuracy of the SMBG mainly was due to failure to monitor frequently enough, rather than to erroneous glucose testing techniques. It should be noted that the inconsistency between the two types of glucose-monitoring profiles may be due to errors in SMBG readings, microdialysis glucose measurements, or both. However, the relationship between the dialysate glucose determinations and plasma glucose concentrations was closer to equality than that between the SMBG recordings and the venous plasma glucose measurements. Therefore, we may even have overestimated the difference in glucose readings between the SMBG and the microdialysis recordings. Hence, our findings indicate that even though the frequency of testing was high (i.e., at least seven times a day), the true variability in glycemia was too great to be correctly reflected by the SMBG recordings.

The limitations of the patients' SMBG profiles also included inadequate ability to prevent hypoglycemic events. This is particularly important when intensive insulin treatment is given, as it may increase several-fold the risk of hypoglycemia (3,24) and reduce the capability of recognizing and protecting against hypoglycemia (25,26). In this study, one-third of the hypoglycemic episodes were not perceived by the patients and were not recognized by the regular SMBG protocol. It might be argued that with our definition of hypoglycemia (tissue dialysate glucose $\leq$3.5 mmol/l), the glucose threshold was too high to ensure true hypoglycemia. However, the hypoglycemic glucose nadir was similar whether the hypoglycemic episodes were perceived by the patients or not.

At present, there is no general consensus regarding the daily frequency of SMBG. A recent survey in the U.S. showed 20% of patients with type I diabetes never tested their own blood glucose, and only 15% tested it at least three times a day (27). This is in contrast to the finding that home glucose monitoring does not improve the long-term glycemic control, unless it is performed at least five times daily (28). The findings in our study indicate that SMBG must be carried out even more frequently to identify in detail the true diurnal variations in glycemia. The intensive insulin therapy regimen in the Diabetes Control and Complications Trial also included testing once a week (3,24) at night (3:00 A.M.). The latter seems to be well advised, as the shortcomings of the SMBG protocol in this study were especially evident during the night.

There is now strong evidence that intensive insulin therapy to normalize glycemia is both desirable and feasible in type I diabetic patients (3). However, the more intensive the therapeutic regimen, the more important the detailed information concerning the diurnal glucose control is. The ultimate goal is the continuous recording of glucose levels. This study shows that microdialysis of subcutaneous adipose tissue offers great potentials for this purpose, although the present methodology with manual sampling cannot be used for routine care. However, automated and continuous monitoring of adipose tissue glucose with microdialysis is being developed in our laboratory. Other methods for glucose sensing are also being explored (29). With these technical improvements, continuous glucose monitoring in the near future may become a clinical reality.

Acknowledgments — This study was supported by the Swedish Medical Research Council (19X-01034-21B, 14X-35774-16A, and 19P-10166-02), the Swedish Diabetes Association, Karolinska Institute, CMA Research AB, and the Novo Nordic Foundation, Novo Nordisk Pharma, Hierta, Bergvall, Trygg-Hansa and Osterman Foundations.

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APPENDIX

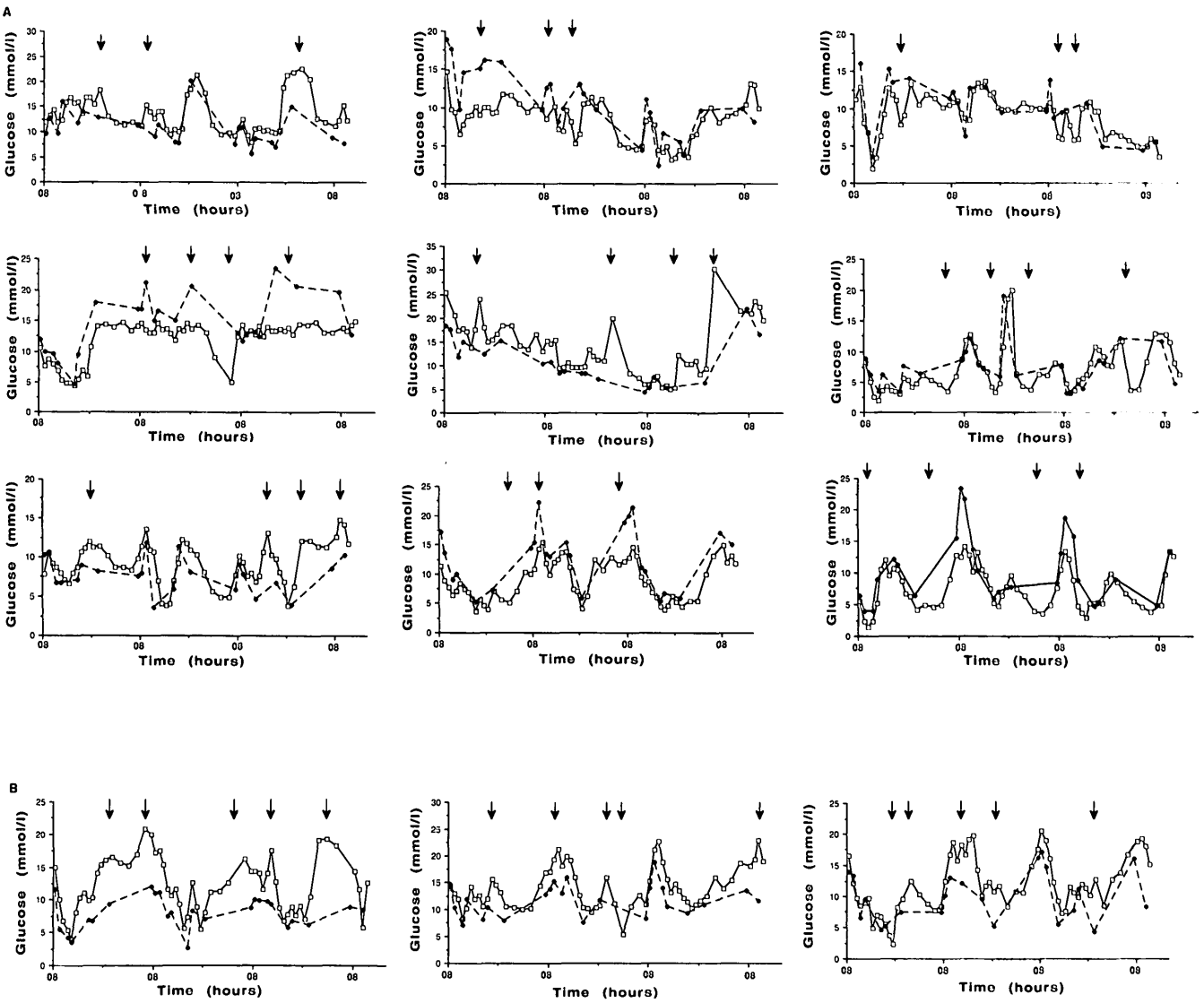

Figure A1—*Self-monitoring of blood glucose (- - - -) and continuous microdialysis measurements of glucose in subcutaneous adipose tissue (——). Glucose profiles obtained in the remaining nine type I diabetic patients with intermediate accuracy in home glucose monitoring are shown in A, and the three remaining patients with low accuracy in self-monitoring of blood glucose are given in B. Arrows depict significant discrepancies between the two types of recordings.*

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