

Continuous Subcutaneous Glucose Monitoring in Diabetic Patients

A multicenter analysis

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OBJECTIVE — To evaluate the accuracy of a new subcutaneous glucose sensor (Glucoday; A. Menarini Diagnostics) compared with venous blood glucose measurement in type 1 and type 2 diabetic patients.

RESEARCH DESIGN — A multicenter study was performed in 70 diabetic patients. A microdialysis fiber was inserted subcutaneously into the periumbelical region and perfused with a buffer solution. Glucose concentrations in the dialysate were then measured every 3 min by the glucose sensor over a 24-h period, during which nine venous blood samples were also collected throughout the day.

RESULTS — Both the insertion of the fiber and the wearing of the device were well tolerated by the patients. Subcutaneous glucose levels were well correlated with venous glucose measurements ($r = 0.9$, $P < 0.001$) over a wide range (40–400 mg/dl) for up to 24 h, with a single-point calibration. An analysis of 381 data pairs showed a linear relationship between the GlucoDay and serial venous blood glucose levels, and 97% of the data fell in the A and B regions of the error grid analysis. Percentage bias between the GlucoDay and the blood venous levels was -2.0% in the hypoglycemic range (<70 mg/dl), 6.9% in the euglycemic range (70–180 mg/dl), and 11.2% in the hyperglycemic range (>180 mg/dl).

CONCLUSIONS — The GlucoDay system demonstrated high reliability and reported values that closely agreed with venous blood glucose measurements. The system was well tolerated and thus constitutes a relatively easy method to monitor glucose excursions in diabetic patients.

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

The benefits of strict metabolic control on microvascular complications of both type 1 and type 2 diabetes have been well established (1,2). In the last decade, self-monitoring of blood glucose levels has been the only available measure for diabetic patients to achieve a good metabolic control; however, glucose fluctuations during the day are often missed with this technique (3), and only continuous glucose measurements over prolonged periods can ensure optimal blood glucose management. Recently, minimally invasive techniques have been proposed for continuous monitoring of subcutaneous glucose in both normal and diabetic patients. Microdialysis of subcutaneous adipose tissue has been shown to identify glucose variations in vivo that closely mimic blood glucose patterns observed in patients on intensified insulin therapy. A monitoring system that provides automatic and frequent determinations would therefore identify the glycemic excursions and typical glucose trends in diabetic patients in a manner that is not possible even with frequent blood glucose meter readings. The ability to detect such fluctuations during the day, and particularly during the night, would enable appropriate changes in diabetes management in order to achieve the goal of optimal metabolic control in diabetic patients.

We documented the efficacy of a new glucose sensor and its accuracy in monitoring glucose levels in type 1 and type 2 diabetic patients recruited in a multicenter study. The GlucoDay is composed of a subcutaneous microdialysis probe connected to a portable unit. The system takes a glucose measurement every second and stores an average value every 3 min, for a total of 480 measurements per day. Data can be visualized continuously through an infrared communicating port and downloaded on a personal computer; thus, individual glucose profiles can be observed over a 24-h continuous monitoring period.

Table 1—Descriptive statistics of population under study

Characteristic	
<i>n</i>	70
Type 1 diabetes	43 (61.4)
Sex (male)	38 (54.3)
BMI (kg/m ²)	24.9 ± 3.2
Age (years)	47.03 ± 15.2
Systolic blood pressure (mmHg)	127 ± 13
Diastolic blood pressure (mmHg)	78 ± 8

Data are *n* (%) and means ± SD.

RESEARCH DESIGN AND METHODS

Diabetic patients

A total of 70 diabetic patients (43 type 1 and 27 type 2 diabetic patients, 38 women and 32 men, mean age 47 ± 17 years, BMI 24.9 ± 3.2 kg/m²) from seven different centers participated in this study (Table 1). Among the chronic diabetic complications, retinopathy was present in 43% of patients, nephropathy in 15%, and neuropathy in 34%. Mean systolic blood pressure was 127 ± 13 mmHg, and diastolic blood pressure was 78 ± 8 mmHg.

This study was approved by the local ethics committees, and subjects gave their written informed consent. Patients were admitted to each clinical center on the night before the study, and a small polyethylene catheter was inserted into an antecubital vein for blood sampling.

Study protocol

A microdialysis fiber assembled by Medica (Medulla, Italy), using 2 cm of hollow fiber (regenerated cellulose with an internal diameter of 0.17 mm and a molecular weight cutoff of 18,000 Dalton), was glued to a nylon tube and sterilized for in vivo use with ethylene oxide gas; it was then inserted subcutaneously in the periumbelical region, without local anesthesia, using a 18-gauge Teflon catheter as a guide, as previously described (4). For the 24-h monitoring, the fiber was then connected to a portable apparatus that weighs 245 g and is powered by a 9-V battery; the apparatus uses a wall-jet flow cell composed of a platinum electrode (diameter 0.4 mm) covered by three membranes (cellulose acetate, enzyme membrane, and polycarbonate membrane) housed in a Teflon tube. Glucose-oxidase enzyme (immobilized on a nylon net through a bovine serum albumin and glutaral-

dehyde solution) and two plastic bags (one for the buffer reservoir and the other for waste products) complete the apparatus, which is contained in a small wearable pouch and worn with a belt. A perfusion buffer (Dulbecco's solution, containing sodium-benzoate as preservative) was introduced at a rate of 10 μ l/min by means of a programmable peristaltic pump (5,6), as schematically represented in Fig. 1.

Glucose was determined every 3 min in the dialysate with the glucose-oxidase method, and results were stored. Nine venous blood samples were collected during the 24-h period as follows: 1 h after the insertion, usually performed in the morning; before lunch; 1, 2, and 3 h after lunch; before dinner; 2 h after dinner; and at 3:00 A.M. and at 7:00 A.M. on the next morning. During their stay in the hospital, patients followed their usual pattern of food intake, insulin injections, drug therapy, and physical activity, and diagnostic procedures were performed as scheduled.

Venous blood samples were stored in fluoride tubes for subsequent glucose determination, using the reference standard method (Beckman, Fullerton, CA). The sensitivity of the biosensor was verified in vitro before the experiments using standard glucose solution, and it was calibrated in vivo ~ 120 min after probe

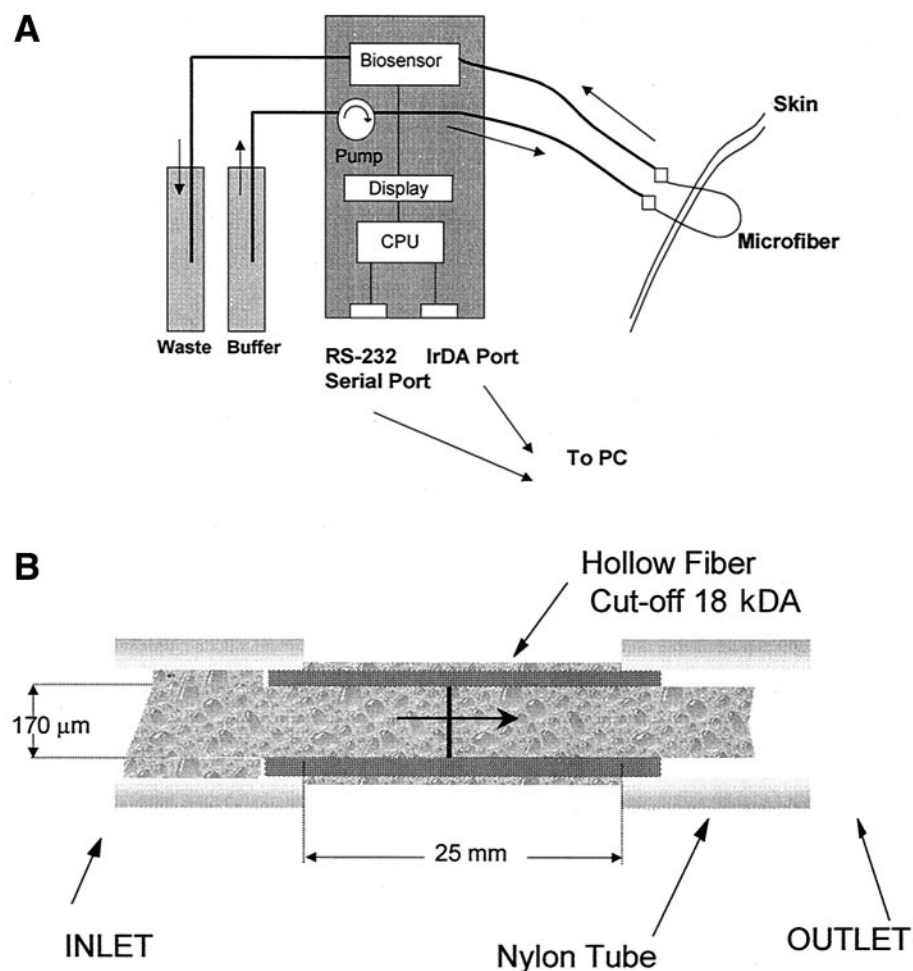


Figure 1—Schematic representation of the GlucoDay apparatus and the microdialysis fiber. A: Basic principle. B: Microdialysis catheter.

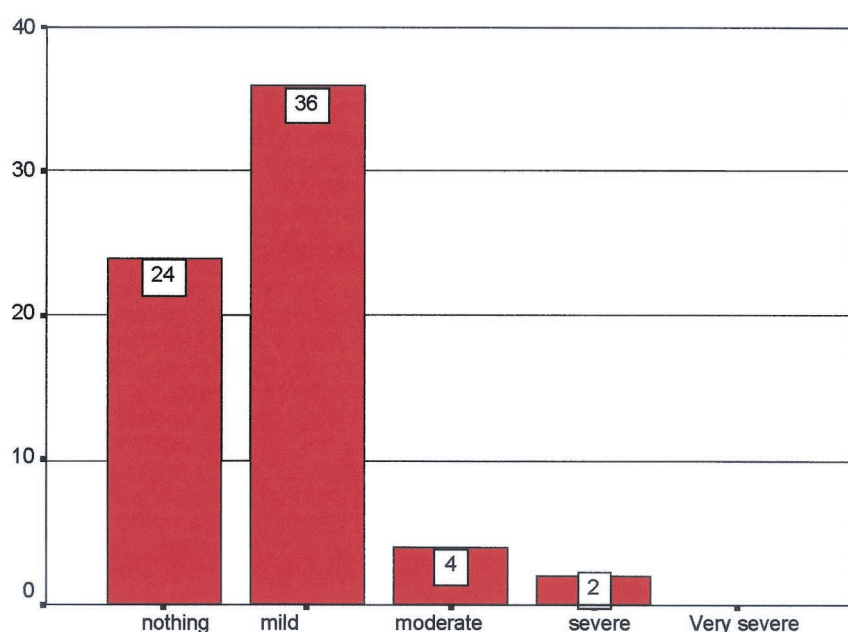


Figure 2—Patients' pain sensation during fiber insertion.

insertion by venous plasma glucose measurements. The lag time between subcutaneous glucose values and venous plasma glucose concentration has been estimated in vivo to be <3 min. At the end of the study, patients were asked to complete a questionnaire, in which they ranked discomfort and pain during the monitoring period on a linear analogue scale (see Figs. 2 and 3).

Data were downloaded on a computer, values reported by the GlucoDay were converted into glucose values, and then those values were represented as a graph. Figure 4 shows two typical 24-h profiles obtained with this system.

In one patient, monitoring was interrupted after a few hours (due to a vagal reaction). In seven patients, data were not correctly transferred to the computer unit and could not be analyzed. In two patients, venous blood glucose samples were not collected. Therefore, among 70 diabetic patients, 60 successfully completed the 24-h monitoring, and their data were analyzed by an independent statistician. No complications at the site of implantation were observed.

Statistical analysis

Results are expressed as the means $\pm$ SD. Linear regression analysis was performed by the least squares method, and the F distribution test was used for statistical evaluation of the slopes of the regression

lines. The Clarke error grid approach was used to assess the clinical significance of differences between the GlucoDay and the venous blood glucose measurements (7). The method uses a Cartesian diagram, in which the values generated by the continuous monitoring device (GlucoDay) are displayed on the y-axis, whereas the values received from the reference

method (glucose oxidase; Beckman) are displayed on the x-axis. The diagonal represents the perfect agreement between the two, whereas the points below and above the line indicate, respectively, overestimation and underestimation of the actual values. Zone A (acceptable) represents the glucose values that deviate from the reference values by $\leq 20\%$ or are in the hypoglycemic range (<70 mg/dl), when the reference is also within the hypoglycemic range. The values within this range are clinically exact and are thus characterized by correct clinical treatment. Zone B (benign errors) is located above and below zone A; this zone represents those values that deviate from the reference values, which are incremented by 20%. The values that fall within zones A and B are clinically acceptable, whereas the values included in areas C–E are potentially dangerous, and there is a possibility of making clinically significant mistakes. Tests for equality of variance between GlucoDay and venous glucose tests were performed by χ^2 and covariance matrixes.

RESULTS— Both fiber insertion and the wearing of the device were well tolerated by all patients (Figs. 2 and 3). As shown in Fig. 5, subcutaneous glucose concentrations in this group of patients were well correlated with plasma levels

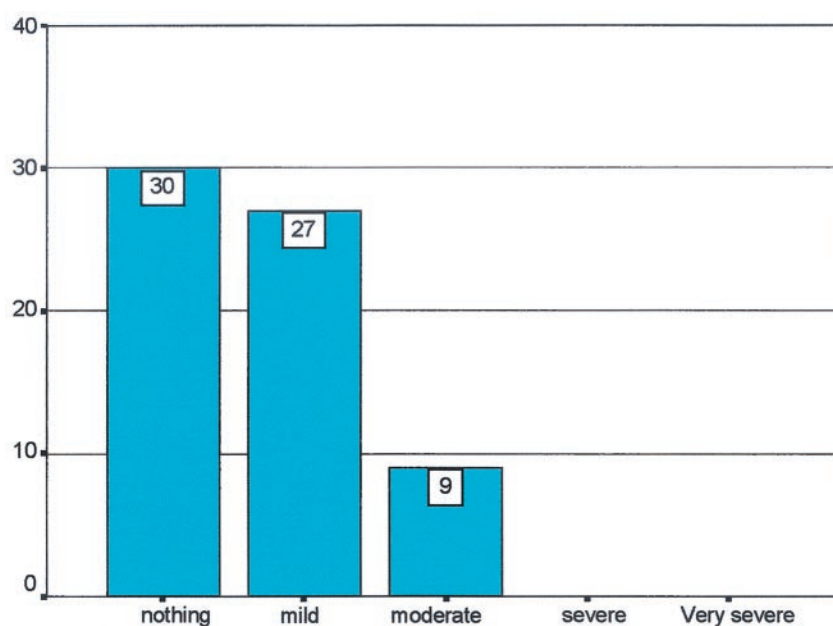


Figure 3—Patients' discomfort during normal daily activities throughout the 24-h monitoring period.

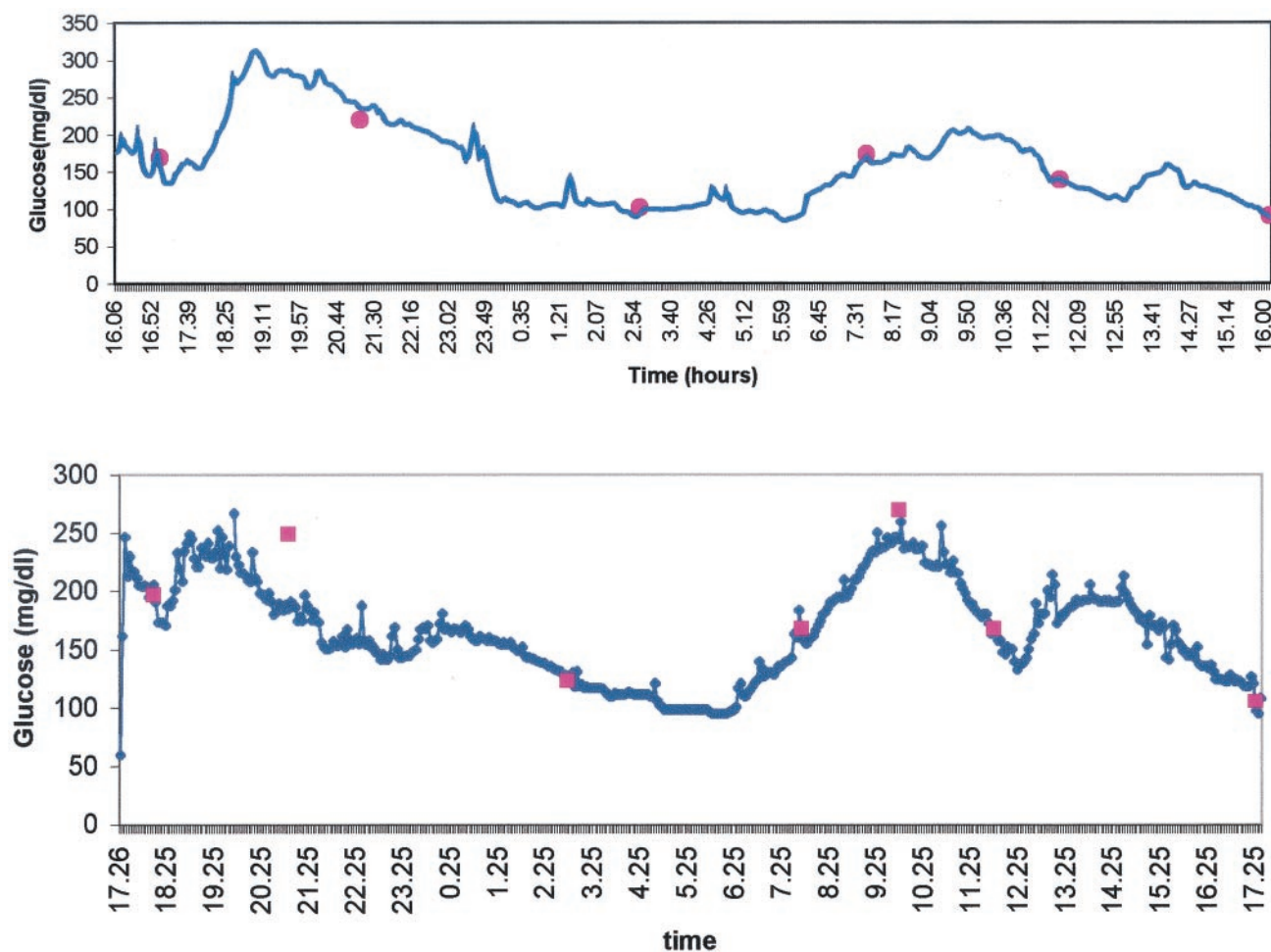


Figure 4—Two typical examples of 24-h monitoring with GlucoDay. Venous plasma measurements are represented as squares or circles in red.

($r = 0.9$, $r^2 = 0.817$, $P < 0.001$, slope = 1.15×-9.8 mg/dl). Analysis of venous blood measurement showed that 5.5% of values were in the hypoglycemic range (<68 mg/dl), 58.6% were between 68 and 180 mg/dl, and 36% were >180 mg/dl.

Error grid analysis of findings in 60 patients (Fig. 6) showed that 97% ($n = 381$) of the values were in zones A and B, and only 3% ($n = 9$) were in zone C, with a single value in zone D. No values in zone E were detected. Bias percentage from reference (Fig. 7) showed a difference of -2% in the hypoglycemic range (<68 mg/dl), 6.9% in the euglycemic range (>68 – 180 mg/dl), and 11.2% for the hyperglycemic range (>180 mg/dl).

For a more accurate evaluation of the relation between the glucose concentrations determined by two compared methods (GlucoDay vs. glucose-oxidase [Beckman] as the reference method), a χ^2

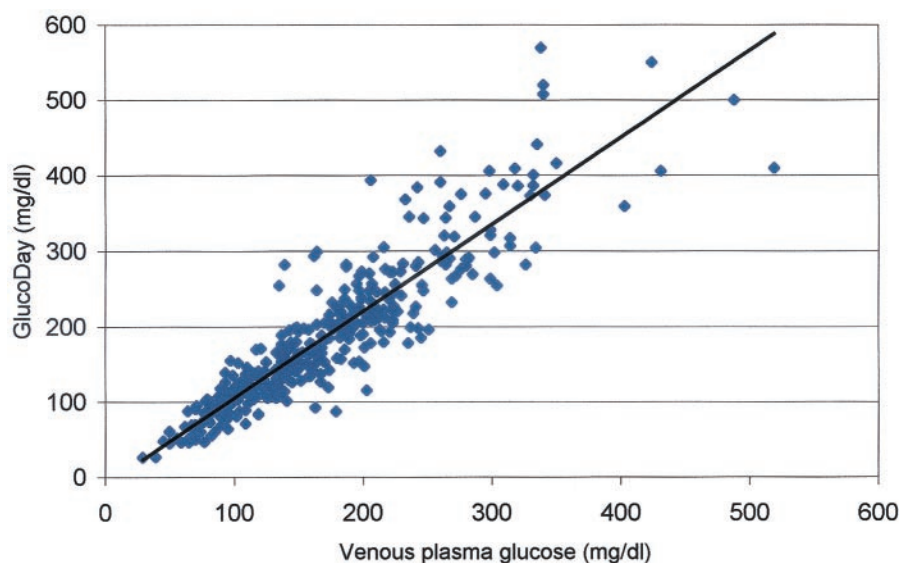


Figure 5—Correlation between the GlucoDay and venous glucose in the whole population under study ($n = 60$, $r = 0.9$, $r^2 = 0.817$, $P < 0.001$, slope = 1.15×-9.8 mg/dl).

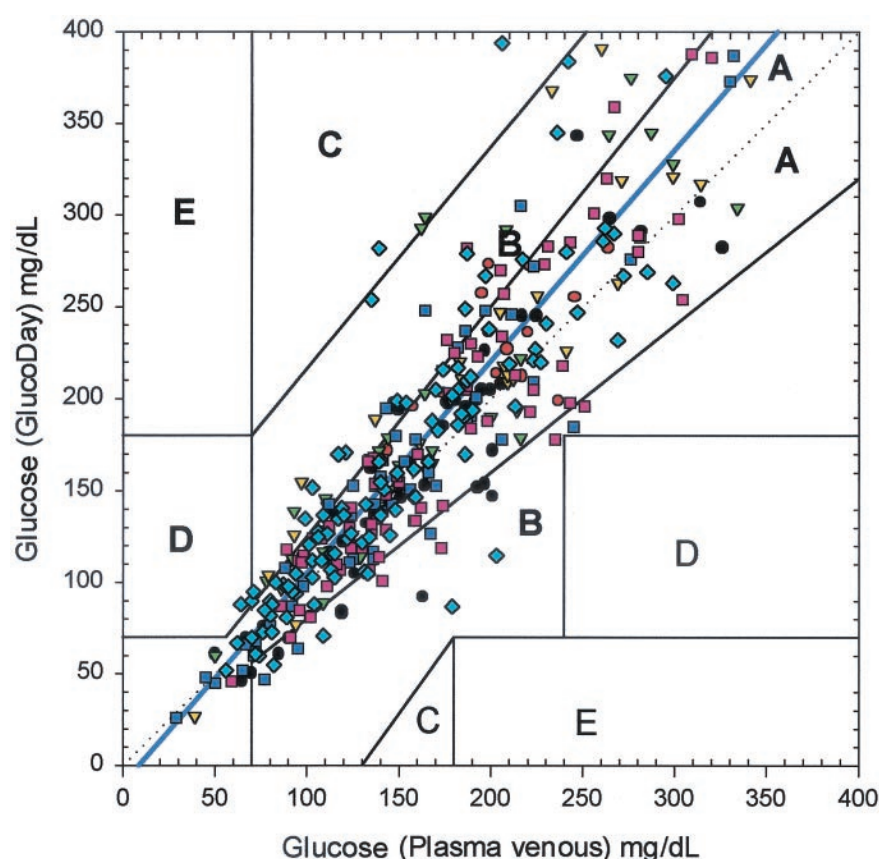


Figure 6— Clarke's error grid analysis for all determinations ($n = 391$). Altogether, 97% of the values fell in the clinically acceptable A–B zone, 3% fell in the C zone, and one fell value in the D zone.

analysis was performed. Three different areas of glycemia were identified: hypoglycemia area (<70 mg/dl), intermediate area (70 – 180 mg/dl), and hyperglycemia (>180 mg/dl). Among these three areas, there was a good correlation ($P < 0.001$) between the two methods, with none of the glycemic values reporting opposite coordinates.

CONCLUSIONS— Self-monitoring of blood glucose is a fundamental tool for type 1 diabetic patients on intensive insulin treatment. However, although performed very frequently, conventional self-monitoring of blood glucose recordings are often not sufficient to detect and reflect daily variations in the individual glucose profiles; therefore, trends can be missed unless continuous measurements are available. Moreover, the major patient complaints are the inconvenience and discomfort of finger-pricking and the high cost of the strips, all of which limit the number of measurements taken per day.

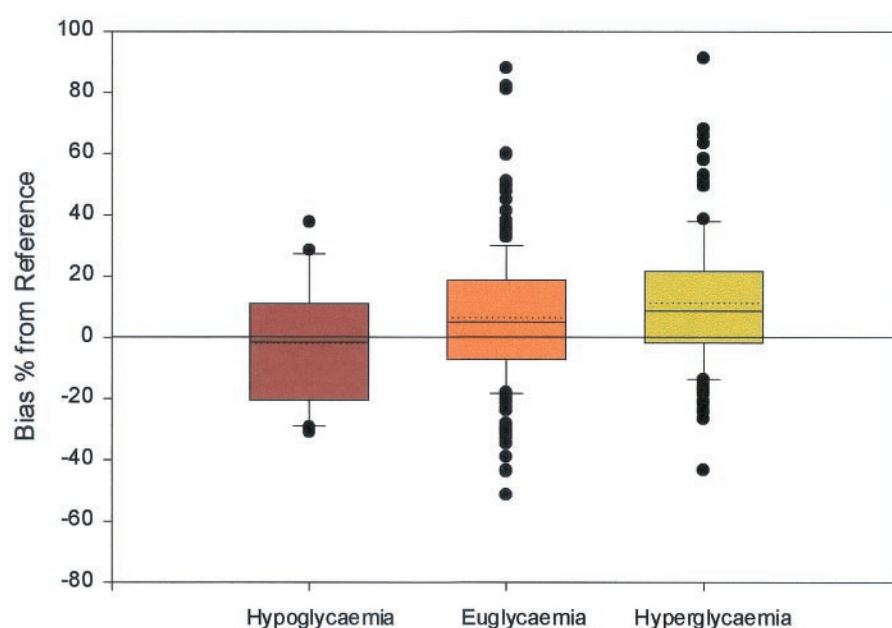


Figure 7— Box plots of bias in percentage between the GlucoDay and venous glucose measurements. Results demonstrated a mean absolute difference of -2% in the hypoglycemic range (<68 mg/dl), 6.9% in the euglycemic range (68 – 180 mg/dl), and 11.2% in the hyperglycemic range (>180 mg/dl).

During the last few years, several devices have been proposed for continuous subcutaneous glucose analysis in vivo (8–14). In this study, we evaluated a novel technique for continuous subcutaneous glucose monitoring in type 1 and type 2 diabetic patients. Our findings demonstrated that the GlucoDay system was accurate compared with conventional glucose determination and was associated with little or no discomfort for the patient. One of the advantages of this system is that subcutaneous glucose is recorded every 3 min; therefore, ~ 480 readings are available after a 24-h monitoring period.

In addition, because of the ability of the system to communicate with a computer through an infrared port, on-line glucose variations can be detected even at a patient's bedside in real time. After calibration with one single venous blood sample (120 min after probe insertion), the system was shown to correlate accurately with venous blood glucose levels determined by the reference method. A series of alarms are built into the system that allow the definition of low and high glucose thresholds, and thus the system can alert the patient to take appropriate action. Once calibration is performed and current values (in nanoamperes) are converted into glucose values, a large display

will show glucose variations continuously every second during the 24 h.

Moreover, when values fell in the low hypoglycemic range (<68 mg/dl), the system was extremely sensitive in identifying clinical hypoglycemia, which commonly occurs in insulin-treated diabetic patients. This aspect is important for the detection of unrecognized hypoglycemia, particularly during the night, when the patient is sleeping.

In conclusion, 24-h monitoring of subcutaneous glucose levels can provide extremely useful information about an individual's glucose pattern and fluctuations during the day. This is particularly useful for detecting overnight hypoglycemia episodes in intensively insulin-treated type 1 diabetic patients, as well as in other clinical settings (continuous subcutaneous insulin infusion, intensive care unit, pregnancy, and glucose profiles when a new drug treatment is started). Continuous glucose monitoring is an important adjunct to the overall care of the diabetic patient. By providing important information that may lead to therapeutic adjustments, the patient's glycemic control can be improved significantly, and the risk of acute hypoglycemia and long-term complications of the disease can be reduced.

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