

Accuracy of an Electrochemical Sensor for Measuring Capillary Blood Ketones by Fingertick Samples During Metabolic Deterioration After Continuous Subcutaneous Insulin Infusion Interruption in Type 1 Diabetic Patients

BRUNO GUERCI, MD, PHD¹
MURIEL BENICHO, MD¹
MICHÈLE FLORIOT, MD¹
PHILIP BOHME, MD¹

SEBASTIEN FOUGNOT, MD¹
PATRICIA FRANCK, MD²
PIERRE DROUIN, MD¹

OBJECTIVE — This study was designed to test the accuracy of capillary ketonemia for diagnosis of ketosis after interruption of insulin infusion.

RESEARCH DESIGN AND METHODS — A total of 18 patients with type 1 diabetes treated by external pump were studied during pump stop for 5 h. Plasma and capillary ketonemia and ketonuria were determined every hour from 7:00 A.M. (time 0 min = T0) to 12:00 P.M. (time 300 min = T300). Plasma β -hydroxybutyrate (β -OHB) levels were measured by an enzymatic end point spectrophotometric method, and capillary β -OHB levels were measured by a semiquantitative test (Ketodiastix). Positive ketosis was defined by a value of ≥ 0.5 mmol/l for ketonemia and ≥ 4 mmol/l (moderate) for ketonuria.

RESULTS — After stopping the pump, concentrations of β -OHB in both plasma and capillary blood increased significantly at time 60 min (T60) compared with T0 ($P < 0.001$), reaching maximum levels at T300 (1.30 ± 0.49 and 1.23 ± 0.78 mmol/l, respectively). Plasma and capillary β -OHB values were highly correlated ($r = 0.94$, $P < 0.0001$). For diagnosis of ketosis, capillary ketonemia has a higher sensitivity and negative predictive value (80.4 and 82.5%, respectively) than ketonuria (63 and 71.8%, respectively). For plasma glucose levels ≥ 250 mg/dl, plasma and capillary ketonemia were found to be more frequently positive (85 and 78%, respectively) than ketonuria (59%) ($P = 0.017$). The time delay to diagnosis of ketosis was significantly higher for ketonuria than for plasma ketonemia (212 ± 67 vs. 140 ± 54 min, $P = 0.0023$), whereas no difference was noted between plasma and capillary ketonemia.

CONCLUSIONS — The frequency of screening for ketosis and the efficiency of detection of ketosis definitely may be improved by the use of capillary blood ketone determination in clinical practice.

Diabetes Care 26:1137–1141, 2003

.....

From the ¹Service de Diabétologie, Maladies Métaboliques & Maladies de la Nutrition, CIC-INSERM, Hôpital Jeanne d'Arc, Nancy, France; and the ²Laboratoire de Biochimie, Hôpital Central, Nancy, France.

Address correspondence and reprint requests to Dr. Bruno Guerci, Service de Diabétologie, Maladies Métaboliques & Maladies de la Nutrition, CIC-INSERM/CHU Nancy, Hôpital Jeanne d'Arc, Centre Hospitalo-Universitaire de Nancy, B.P. 303, 54201 Toul Cedex, France. E-mail: b.guerci@chu-nancy.fr.

Received for publication 31 July 2002 and accepted in revised form 23 December 2002.

P.D. is deceased.

Abbreviations: β -OHB, β -hydroxybutyrate; CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; MDI, multiple daily injections.

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

The Diabetes Control and Complications Trial (DCCT) has demonstrated that intensive diabetes management, multiple daily injections (MDI) in two-thirds of cases, and continuous subcutaneous insulin infusion (CSII) in one-third of cases could reduce the risk of development and progression of long-term complications of type 1 diabetes (1). CSII provides the most physiological pattern of insulin delivery currently available (2). However, it is now clearly established that CSII is associated with a substantial increase in risk of diabetic ketoacidosis (DKA) compared with MDI (3,4). In a meta-analysis of 14 studies, odds ratios (95% CI) were 7.20 (2.95–17.58) for exclusive use of insulin pumps compared with 1.13 (0.15–8.35) for MDI (4). Technical problems with CSII (pump failure, catheter occlusion, skin infection) may reduce insulin delivery or insulin absorption and cause DKA (5). Currently, the use of short-acting insulin analogs in external pumps is becoming more widespread because some studies have shown that the use of such analogs provides better glycemic control and stability than regular insulin (6–8). Considering the pharmacokinetic characteristics of these analogs, a short interruption of their infusion in CSII is associated with an earlier and greater metabolic deterioration, probably due to a limited insulin depot in subcutaneous adipose tissue (9). In a previous unpaired study, this was not the case after nighttime insulin interruption (10).

Consequently, reliable self-monitoring of ketone body levels has become a priority in detecting insulin infusion interruption. Urinary ketone levels in type 1 diabetic patients are classically used to screen for impending DKA, because delays in the diagnosis and treatment of

DKA are associated with an increase in morbidity and mortality (11,12). However, commercial tests for detecting urinary ketones are associated with well-known difficulties in their role as diagnostic and management tools for DKA (13). Recently, inexpensive quantitative tests of β -hydroxybutyrate (β -OHB) levels have become available for use with small blood samples, offering new options for monitoring and treating diabetes. Previous studies (14,15) have evaluated the accuracy of this new electrochemical sensor for measuring capillary blood β -OHB in comparison to reference plasma ketonemia determination.

The aim of the present study was to determine whether use of capillary blood ketonemia was superior to that of ketonuria for detection of ketosis in terms of delayed diagnosis in patients treated by pump after deliberate interruption of CSII.

RESEARCH DESIGN AND METHODS

Patients

The study comprised 18 patients with type 1 diabetes, diagnosed according to American Diabetes Association criteria (16), who were C-peptide negative (<0.3 nmol/l, 6 min after intravenous administration of 1 mg glucagon). The patients were treated with infusion of insulin via an external pump (MiniMed Infusor 507, 507C, or 508; MiniMed Technologies, Northridge, CA) and a disconnectable catheter, either the Tender catheter (Disetronic Medical Systems, Burgdorf, Switzerland) or the Sofset QR (MiniMed). The type of insulin used in the pumps was velosulin (Velosulin HM, U-100; Novo-Nordisk, Boulogne-Billancourt, France) in eight patients and lispro (Humalog U-100; Lilly France, Saint-Cloud, France) in the other 10 patients. No randomization was performed, and the patients in the study were selected from 245 type 1 diabetic patients treated by CSII at our outpatient clinic. All these patients had received CSII for >1 year, had hypoglycemia awareness, and had good compliance with self-monitoring of blood glucose (more than four times per day). The patients were regularly followed (every 3 months) by the same investigator to evaluate metabolic control and to make insulin dose adjustments. Some patients declined to participate in the study for

reasons of insufficient time and/or demands of the experimental protocol. Insulin was infused into the abdomen, for which the infusion site was changed every 3 days. None of the patients had experienced any recent episode of DKA or required a daily insulin dose >1.5 units \cdot $\text{kg}^{-1} \cdot \text{day}^{-1}$. Patients with hyperlipidemia, thyroid or liver disease, diabetic or nondiabetic renal disease, urinary tract infection, pregnancy, or acute or chronic inflammatory syndrome were excluded from the study. None of the patients had proteinuria or microalbuminuria, macrovascular complications, retinopathy, or hypertension. Finally, patients were instructed to follow a weight-maintenance diet (15% of calories as protein, 35% as fat, and 50% as carbohydrate) taken as three main meals and one to three snacks per day.

Study protocol

Patients arrived at the Clinical Research Center (CIC/INSERM-CHU de Nancy) the day before the interruption of CSII, at 8:00 P.M., for a calibrated meal. The design of the protocol was similar to that previously described (9). No hypoglycemia episode was tolerated during the 24 h before interruption of CSII. Patients fasted for 11 h, until 7:00 A.M. (no breakfast), at which time the pump was stopped and the catheter was disconnected. Every hour from 7:00 A.M. (time 0 min = T0) to 12:00 P.M. (time 300 min = T300), plasma glucose levels and ketonemia as well as capillary blood glucose levels and ketonemia were measured, along with ketonuria. The pump of each patient was then reactivated at 12:00 P.M. (T300) at the patient's usual basal rate, at which time the patients ate a calibrated lunch and activated their usual pre-lunch insulin boluses. Additional insulin boluses were also given each hour, according to blood glucose levels, until the disappearance of ketosis.

Informed written consent was obtained from all patients. The study protocol was approved by the Ethics Committee of The Center Hospitalier Universitaire de Nancy (France).

Biochemical determinations

Plasma glucose was measured by the glucose oxidase method (Beckman Glucose Analyzer, Beckman, Fullerton). HbA_{1c} was measured by high-performance liquid chromatography on Biorex resins

(BioRad, Richmond, CA) with a normal range of 4–6%.

Blood samples for determination of ketone bodies were collected and placed on crushed ice. Plasma was immediately obtained by centrifugation at 4°C. The concentration of 3-hydroxybutyrate was determined by an enzymatic end point spectrophotometric method using 3-hydroxybutyrate dehydrogenase (3-HBDH), normal range of 0.06–0.17 mmol/l (KONE Delta Automatic Analyzer). This method was used as the reference method. The intra-assay coefficient of variation was 4.9% (17).

Capillary plasma glucose was measured using a Medisense Optium meter (MediSense/Abbott Laboratories, Abingdon, U.K.), which is a combined glucose and ketone sensor that produces an electrical current proportional to blood β -OHB concentration. The Optium strips were plasma calibrated on a YSI reference glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH).

For determination of capillary blood ketone levels, an electrochemical strip was inserted into the sensor to which 5 μ l of capillary blood was applied. The β -OHB, in the presence of hydroxybutyrate dehydrogenase, was oxidized to acetoacetate with the concomitant reduction of NAD^+ to NADH. The NADH was reoxidized to NAD^+ by a redox mediator, such that the current generated was directly proportional to the 3-hydroxybutyrate concentration. After 30 s, the 3-hydroxybutyrate concentration in a sample was displayed. This system is accurate for 3-hydroxybutyrate levels from 0 to 6 mmol/l. On three different levels of β -OHB (low at the mean of 0.43, moderate at 1.08, and high at 3.55 mmol/l), the intra-assay coefficients of variation (calculated on three determinations for each sample) were 10.5, 5.5, and 3.2%, respectively.

Urine ketone bodies were measured by a semiquantitative test (Ketodiastix; Bayer Diagnostics, Stoke Poges, Slough, U.K.; trace to ≥ 16 mmol/l [large]). Positive ketosis was defined as values ≥ 0.5 mmol/l for capillary blood ketonemia and ≥ 4 mmol/l (moderate) for ketonuria (18).

Statistical analyses

Results are expressed as means \pm SD. The distribution of variables was tested for approximation to a Gaussian distribution

(normality) using the Kurtosis and Skewness test. Data were compared using the nonparametric Wilcoxon's test for two paired groups (plasma versus capillary determinations) and versus the value recorded at 7:00 A.M. (T0).

Univariate linear regression was used to calculate the correlation coefficients and equations for the regression slopes. The frequency of positive ketosis was checked by χ^2 test.

For determination of the accuracy of the electroenzymatic method, we analyzed the results by calculating the specificity and sensitivity of the capillary and urinary methods to correctly detect ketone bodies by comparison with the plasma 3- β hydroxybutyrate concentration determined by the spectrophotometric method for all time points from T0 to T300. With regard to the positive ketosis criteria defined above, we assigned for each of the sensor and urinary values the term of true positive (TP), false positive (FP), true negative (TN), or false negative (FN), according to the plasma ketone body value simultaneously measured higher or lower than 0.5 mmol/l. Sensitivity and specificity were defined by the following equations: sensitivity = TP/[TP + FN], and specificity = TN/[TN + FP].

Significance was implied at $P < 0.05$. StatView software (version V; St. Abacus Concepts, Brain Power, Calabasas, CA) was used for all calculations.

RESULTS

Clinical and metabolic characteristics of patients in the study

The main clinical and biological characteristics of the patients in the study are summarized in Table 1. The average age of the 18 patients (9 women and 9 men) and the duration of diabetes (mean \pm SE) were 41.1 ± 7.1 and 20.8 ± 9.6 years, respectively.

Glucose levels

Compared with T0, plasma glucose concentrations were increased significantly at T120 after the pump had been stopped (197 ± 68 vs. 149 ± 60 mg/dl, $P = 0.0012$) and reached a maximum at T300 (285 ± 68 mg/dl, $P = 0.0002$). Similarly, capillary plasma glucose levels were significantly increased at T120 compared with T0 (213 ± 76 vs. 166 ± 68 mg/dl, $P = 0.004$) and reached a maximum at

Table 1—Clinical and metabolic characteristics of patients in study

Sex ratio (men/women)	9/9
Age (years)	41.1 ± 7.1
BMI (kg/m^2)	24.8 ± 2.7
Duration of diabetes (years)	20.8 ± 9.6
Duration of CSII (months)	66.4 ± 44.2
Systolic blood pressure (mmHg)	132 ± 9
Diastolic blood pressure (mmHg)	74 ± 5
Serum creatinine ($\mu\text{mol}/\text{l}$)	105.5 ± 8.8
Anti-insulin antibodies (%)	32.6 ± 19
Total cholesterol (mg/dl)	201 ± 34
Triglyceride (mg/dl)	78 ± 41
LDL cholesterol (mg/dl)	126 ± 27
HDL cholesterol (mg/dl)	61 ± 12
HbA _{1c} (%; normal range 4–6%)	7.34 ± 0.99

Data are means \pm SD.

T300 (316 ± 79 mg/dl, $P = 0.0003$). The capillary plasma glucose levels were significantly correlated with venous plasma glucose levels ($r = 0.98$, $P < 0.0001$).

Ketone body levels

After stopping the pump, the concentration of plasma ketone bodies (determined by the reference enzymatic spectrophotometric method) was increased significantly at T60 compared with T0 (0.28 ± 0.26 vs. 0.18 ± 0.18 mmol/l, $P = 0.01$) and reached a maximum at T300 (1.30 ± 0.49 vs. 0.18 ± 0.18 mmol/l, $P = 0.0002$) (Fig. 1). Capillary blood ketone body levels were also increased significantly at T60 compared with T0 (0.13 ± 0.29 vs. 0.05 ± 0.15 mmol/l, $P = 0.05$); the maximum was reached at T300 (1.23 ± 0.78 vs. 0.050 ± 0.15 mmol/l, $P = 0.0003$). However, these levels remained signifi-

cantly lower than levels measured in the plasma from T0 to T240 (Fig. 1). Nevertheless, the capillary blood β -OHB levels were highly and significantly correlated with plasma β -OHB levels ($r = 0.94$, $P < 0.0001$). When we subdivided the patients according to the type of insulin used (velosulin or lispro), the kinetics of ketone body levels were very similar for capillary and plasma β -OHB levels (data not shown).

At T300, 16 of the 18 patients (89%) had a positive reading for plasma β -OHB levels (≥ 0.5 mmol/l), whereas 15 patients (83%) had a positive reading for capillary β -OHB levels (≥ 0.5 mmol/l). Conversely, ketonuria was negative in all patients at T0 and positive (≥ 4 mmol/l [moderate]) at T300 only in 13 patients (72%). Using the plasma β -OHB value as a reference, the sensitivity and negative predictive value of capillary blood ketonemia were higher than those of ketonuria (sensitivity 80.4 vs. 63%; negative predictive value 82.5 vs. 71.8, respectively) (Table 2). When we analyzed the data for capillary glucose values > 2.50 g/l only (the limit at which the detection of ketone bodies must be identified), we found that the sensitivity of capillary plasma ketonemia was increased (86.6%) and remained higher than the sensitivity of ketonuria (68.8%).

During CSII interruption, we recorded a total of 41 plasma glucose values ≥ 250 mg/dl, a level leading to the detection of ketone bodies in clinical practice. In these 41 cases of hyperglycemia, we compared the frequency of positive values for plasma ketonemia, capillary blood ketonemia, and ketonuria. Positive ketosis was more frequently observed with plasma ketonemia (85%, 35 of 41 pa-

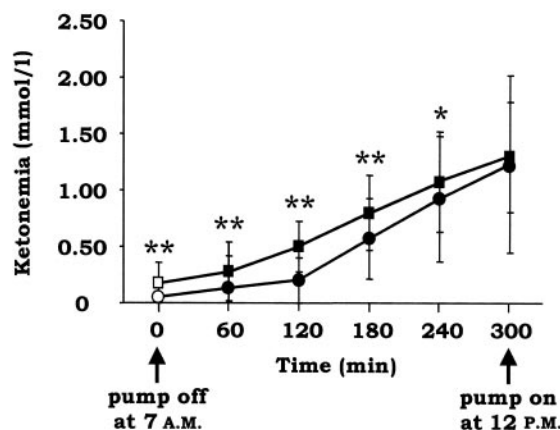


Figure 1—Changes in plasma (squares) and capillary blood ketonemia (circles) during a 5-h interruption of CSII (from T0 to T300). Results are shown as means \pm SD. * $P < 0.05$, ** $P < 0.001$ between plasma and capillary ketonemia; $P < 0.05$ – 0.001 versus 7:00 A.M. (T0).

Table 2—Sensitivity, specificity, and positive and negative predictive values of capillary ketonemia and ketonuria

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Ketonuria	63	100	100	71.8
Capillary blood ketonemia	80.4	100	100	82.5

tients) and capillary blood ketonemia (78%, 32 of 41 patients) than with ketonuria (59%, 24 of 41 patients) ($P = 0.017$).

When we compared the time delay to confirm the diagnosis of ketosis (as defined by a β -OHB value ≥ 0.5 mmol/l or ketonuria ≥ 4 mmol/l [moderate]), we found a significant difference in the mean time between the three methods of detection ($P = 0.0089$). This was due to a significant difference in time for measurement of ketosis according to plasma ketonemia compared with that of urinary ketone bodies (140 ± 54 vs. 212 ± 67 min, $P = 0.0023$). Conversely, no significant difference between plasma and capillary ketonemia was noted for the mean time to observe ketosis positivity (140 ± 54 vs. 180 ± 60 min). After restarting the pump, the resolution of ketosis was marked and rapid; all patients returned to an β -OHB value < 0.5 mmol/l or ketonuria < 4 mmol/l within 180 min of insulin infusion. Although the mean time to confirm ketosis resolution seemed longer for ketonuria (113 ± 58 min) than for plasma ketonemia bodies (93 ± 37 min) and for capillary ketonemia bodies (87 ± 37 min), we were unable to find any significant difference between the three methods of ketosis detection ($P = 0.19$).

CONCLUSIONS— In this study, we have examined the accuracy of the capillary blood method compared with the plasma venous method for diagnosing ketosis in patients treated by pump infusion of insulin as a function of time after deliberate interruption of CSII for 5 h. We demonstrated that the sensor method for measuring capillary blood ketone body levels gave results similar to the spectrophotometric method used to measure plasma ketone body levels and that capillary blood β -OHB levels were highly and significantly correlated with plasma β -OHB. We also showed that the ketone sensor has a higher sensitivity and provided an earlier diagnosis of ketosis than

measurement of ketosis according to ketonuria.

The development of inexpensive quantitative tests of capillary blood β -OHB levels was recently motivated by the unreliability of the urinary ketone tests in their role as DKA diagnosis and management tools (19,20). Indeed, several difficulties are associated with urinary ketone tests. First, patients perceive urinary ketone testing to be an unpleasant and time-consuming experience, particularly in this era of promoting blood glucose monitoring. Consequently, the rates of noncompliance are exceedingly high (13). Second, these urinary tests can provide misleading information in the diagnosis and management of DKA or impending DKA, because they detect only acetoacetate (AcAc) but not β -OHB, which is the predominant ketone body produced in the case of DKA. Furthermore, urinary ketone tests have been reported to give false-positive results in the presence of drugs containing sulfhydryl groups such as the antihypertensive drug captopril, as well as mesna, *N*-acetylcysteine, dimercaprol, and penicillamine (21). False-negative readings also have been reported when test strips have been exposed to air for an extended period of time or when urine specimens are highly acidic, such as after the ingestion of large quantities of ascorbic acid (22). Health care professionals should be aware that currently available urine ketone tests are not reliable for diagnosing DKA or in monitoring its treatment. Consequently, the American Diabetes Association recommends the use of blood ketone testing methods rather than urine ketone testing for diagnosis and monitoring of DKA (23).

The use of a capillary blood ketone sensor seems to have many advantages over ketonuria testing. Its ease of use, small sample volume, short test time (30 s), automatic timing, and digital display make the ketone sensor a simple method that may increase patient compliance for

ketone testing. However, its routine use requires that normal values be distinguished from pathological values and that a threshold of ketosis positivity be defined. Levels of circulating ketone bodies vary across populations of normal individuals, even after controlling for age and duration of fasting, presumably as a result of variations in basal metabolic rate, hepatic glycogen stores, and differences in the mobilization of amino acids from muscle proteins (18). Most investigators agree that normal levels of ketone bodies are < 0.5 mmol/l; hyperketonemia is defined as levels > 1 mmol/l, and DKA is defined as levels > 3 mmol/l (18). We have thus applied these levels of positivity in the present work.

Our study demonstrated clearly that the hand-held ketone sensor accurately measures capillary blood β -OHB with a strong correlation between the sensor values and those measured by the venous plasma method. Available evidence suggests that this test could be helpful in detection of underinsulinization and recognition of impending DKA delayed by failure of urinary ketone reagent strips (22).

The sensitivity and negative predictive value of capillary ketonemia measured here were higher than those of ketonuria. It is worth noting that for plasma glucose values ≥ 250 mg/dl, the main situation in which the presence ketone bodies must be identified, ketosis positivity was more frequently reported with capillary ketonemia than with ketonuria. Likewise, the mean time of positive detection for ketonuria was significantly longer than for plasma ketonemia, suggesting an increased risk in the delay of diagnosis of ketosis. Therefore, similar to the fact that self-monitoring of blood glucose by fingerstick has replaced urine glucose testing, it is tempting to speculate that fingerstick determinations of β -OHB levels might increase patient compliance with recommendations for ketone testing. In this way, patients would have an earlier warning mechanism for detecting the development of metabolic deterioration, which should theoretically bring about a reduced incidence of DKA observed in diabetic patients treated by external pump. This could provide substantial savings in health costs for patients, particularly those treated by pump (4).

A previous study showed that ketone body measurements using a reflectance

meter (Stat-Site meter; GDS Diagnostics) could enhance the management of DKA (24). When acidosis had resolved, all patients had β -OHB levels <0.5 mmol/l, whereas more than half of the patients had positive ketonuria for up to 24 h after correction of DKA, suggesting that ketonuria fails to detect the overall improvement and may lead to unnecessary and potentially dangerous increases in insulin dose delivery.

In conclusion, the accuracy of ketosis screening and frequency of ketosis detection definitely may be improved by the use of this capillary blood ketone determination method in clinical practice.

Acknowledgments—This study was supported by Abbott France-Division Medisense for the distribution of electrochemical strips.

We thank the staff of the Center d'Investigation Clinique du CHU de Nancy for their clinical help and technical assistance.

This study is dedicated to Professor Pierre Drouin, deceased 21 October 2002.

References

1. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977–986, 1993
2. Bode BW, Steed RD, Davidson PC: Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type I diabetes. *Diabetes Care* 19:324–327, 1996
3. Diabetes Control and Complications Trial Research Group: Implementation of treatment protocols in the Diabetes Control and Complications Trial. *Diabetes Care* 18:361–376, 1995
4. Egger M, Davey Smith G, Stettler C, Diem P: Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med* 14: 919–928, 1997
5. Peden NR, Braaten JT, McKendry JB: Diabetic ketoacidosis during long-term treatment with continuous subcutaneous insulin infusion. *Diabetes Care* 7:1–5, 1984
6. Zinman B, Tildesley H, Chiasson JL, Tsui E, Strack T: Insulin lispro in CSII: results of a double-blind crossover study. *Diabetes* 46:440–443, 1997
7. Melki V, Renard E, Lassmann-Vague V, Boivin S, Guerci B, Hanaire-Broutin H, Bringer J, Belicar P, Jeandidier N, Meyer L, Blin P, Augendre-Ferrante B, Tauber JP: Improvement of HbA_{1c} and blood glucose stability in IDDM patients treated with lispro insulin analog in external pumps. *Diabetes Care* 21:977–982, 1998
8. Renner R, Pflutzner A, Trautmann M, Harzer O, Sauter K, Landgraf R: Use of insulin lispro in continuous subcutaneous insulin infusion treatment: results of a multicenter trial. German Humalog-CSII Study Group. *Diabetes Care* 22:784–788, 1999
9. Guerci B, Meyer L, Salle A, Charrie A, Dousset B, Ziegler O, Drouin P: Comparison of metabolic deterioration between insulin analog and regular insulin after a 5-hour interruption of a continuous subcutaneous insulin infusion in type I diabetic patients. *J Clin Endocrinol Metab* 84: 2673–2678, 1999
10. Attia N, Jones TW, Holcombe J, Tamborlane WV: Comparison of human regular and lispro insulins after interruption of continuous subcutaneous insulin infusion and in the treatment of acutely decompensated IDDM. *Diabetes Care* 21:817–821, 1998
11. Lebovitz HE: Diabetic ketoacidosis. *Lancet* 345:767–772, 1995
12. Singh RK, Perros P, Frier BM: Hospital management of diabetic ketoacidosis: are clinical guidelines implemented effectively? *Diabet Med* 14:482–486, 1997
13. Laffel L: Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes Metab Rev* 15:412–426, 1999
14. Byrne HA, Tieszen KL, Hollis S, Dorman TL, New JP: Evaluation of an electrochemical sensor for measuring blood ketones. *Diabetes Care* 23:500–503, 2000
15. Laffel L, Brink S, Kaufman F, Bergenstal R, Fineberg SE, Jenkins M: Frequency of elevation in blood β -hydroxybutyrate (β -OHB) during home monitoring and association with glycemia in insulin-treated children and adults (Abstract). *Diabetes* 49 (Suppl. 1):A92, 2000
16. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
17. McMurray CH, Blanchflower WJ, Rice DA: Automated kinetic method for D-3-hydroxybutyrate in plasma or serum. *Clin Chem* 30:421–425, 1984
18. Mitchell GA, Kassoovska-Bratinova S, Boukaftane Y, Robert MF, Wang SP, Ashmarina L, Lambert M, Lapierre P, Potier E: Medical aspects of ketone body metabolism. *Clin Invest Med* 18:193–216, 1995
19. Sulway MJ, Malins JM: Acetone in diabetic ketoacidosis. *Lancet* 2:736–740, 1970
20. Foster DW, McGarry JD: The metabolic derangements and treatment of diabetic ketoacidosis. *N Engl J Med* 309:159–169, 1983
21. Csako G: Causes, consequences, and recognition of false-positive reactions for ketones. *Clin Chem* 36:1388–1389, 1990
22. Rosenbloom AL, Malone JI: Recognition of impending ketoacidosis delayed by ketone reagent strip failure. *JAMA* 240: 2462–2464, 1978
23. American Diabetes Association: Tests of glycemia in diabetes. (Position Statement). *Diabetes Care* 25:S97–S99, 2002
24. Umpierrez GE, Watts NB, Phillips LS: Clinical utility of β -hydroxybutyrate determined by reflectance meter in the management of diabetic ketoacidosis. *Diabetes Care* 18:137–138, 1995