Early detection of insulin deprivation in continuous subcutaneous insulin infusion-treated Patients with T1D

Population Study of Pediatric Ketoacidosis in Sweden: Predisposing Conditions and Insulin Pump Use

What Are Capillary Blood Ketone Levels in T1D Patients Using CSII in Normal Conditions of Insulin Delivery?

Hypoglycemia and Ketoacidosis with Insulin Pump Therapy in Children and Adolescents
Early detection of insulin deprivation in continuous subcutaneous insulin infusion-treated patients with Type 1 Diabetes.

Background

- Insulin bioavailability resulting from continuous subcutaneous insulin infusion (CSII) allows for a better metabolic control together with a reduced risk of hypoglycemia relative to conventional therapy, however:
  - The minimal amount of insulin available as a subcutaneous depot in the fasting state represents a relevant risk for diabetic ketoacidosis (DKA) in case of failure of the insulin system or increased metabolic needs
- DKA in CSII-treated patients might be insidious because sometimes not accompanied by a marked concomitant increase of blood glucose (BG), while it can be characterized by a fast increase of blood ketone bodies due to the clinical features of pump-treated patients (generally lean, highly insulin sensitive, physically active)
- Different studies have shown that capillary β-hydroxybutyrate (β-OHB) levels correlate with the degree of metabolic control as expressed by glucose and HbA1c values, indicating the utility of β-OHB as a marker of metabolic deterioration

Aim

To define the clinical relevance of early changes of capillary β-OHB for detection of metabolic deterioration before occurrence of overt DKA following interruption of CSII

Patients and methods

Eight patients with Type 1 diabetes (WHO criteria) on CSII therapy were included in this open clinical trial

<table>
<thead>
<tr>
<th>Time</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>8.00 am</td>
<td>T₀</td>
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<tr>
<td>T₀</td>
<td>Overnight fast</td>
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<tr>
<td>12.00 am</td>
<td>T₂₄₀ Deprivation phase</td>
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<td>T₂₄₀</td>
<td>CSII interruption</td>
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<tr>
<td>16.00 pm</td>
<td>T₄₈₀ Recovery phase</td>
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<td>T₄₈₀</td>
<td>CSII restoration*</td>
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<td>End of the study</td>
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* SC insulin bolus [calculated on the basis of metabolic deterioration taking into account levels of both BG and ketone bodies] followed by resumption of the usual basal insulin infusion

During the whole study session, assessment of:
- Venous and capillary β-OHB and BG, every 30 min
- Plasma insulin, every 60 min
- Urinary acetoacetate, every 2h
Results

- As expected, the interruption of CSII produced a rapid decline of plasma insulin levels and a parallel increase of BG, capillary β-OHB and ketonuria:
  - Although statistically significant at T_{120}, increment in BG was rather small in absolute terms and remained within ranges that can be considered compatible with fluctuations occurring in the patient’s daily life.
  - Increase in capillary β-OHB became statistically significant only at T_{150} (high inter-individual variability) but at T_{120} its increase was already more than twofold the basal value
- The restoration of CSII (and consequently of the plasma insulin levels) was able to correct metabolic deterioration as indicated by the reduction of BG and capillary β-OHB, while ketonuria remained elevated up to the end of the experiment
The rate of increase of capillary β-OHB was faster and significantly more relevant than that of BG (p < 0.05) throughout the insulin deprivation phase: at peak value (T270), capillary β-OHB showed a 614.3 ± 409.9% increase and BG a 73.1 ± 67.3% increase with respect to the basal values.

Similar results were observed during the insulin restoration phase with a faster and higher relative reduction for capillary β-OHB.

Conclusions

- The dynamic evaluation of changes of capillary β-OHB levels can represent a useful support to home BG monitoring in the event of CSII interruption, providing faster information on early metabolic deterioration due to insulin deprivation and allowing preventive action for avoiding the evolution towards overt DKA.
- After reintroduction of insulin infusion the monitoring of the faster recovery of β-OHB relative to BG can provide useful information for the prevention of late hypoglycemia due to insulin overinfusion.
- Urine ketones, because of their slow rate of appearance and disappearance, are not considered an appropriate parameter for early diagnosis and safe management of DKA (see also ADA and IDF guidelines).
Aim

To investigate triggering factors and insulin pump usage (continuous subcutaneous insulin infusion, CSII) in reported episodes of diabetic ketoacidosis (DKA) in the Swedish pediatric diabetes population.

Patients and methods

Data on episodes of DKA from 1999 and 2000 were collected retrospectively with the help of a questionnaire sent to pediatric diabetologists at all specialized centers in Sweden:

- In 1999, 7.4% of the pediatric diabetes population of 5168 subjects (age 0–20 yr) used insulin pumps.
- In 2000, 11% of the pediatric diabetes population of 5460 subjects (age 0–20 yr) used insulin pumps.

Results

142 episodes of DKA (defined as pH < 7.30) were identified in 115 children with established diabetes (DKA at onset not included) over the 2 years. 30 of 115 patients used insulin pumps.

Characteristics of the 115 patients at the time of DKA

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
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<tbody>
<tr>
<td>HbA1c (mean)</td>
<td>10.1 ± 2.0% (range 5.2–17.8%)</td>
</tr>
<tr>
<td>Age</td>
<td>14.6 ± 3.1 yr (range 1.5–19.9 yr)</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>6.6 ± 3.5 yr (range 0.4–17.7 yr)</td>
</tr>
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</table>

- One of the most common causes of DKA was insulin omission.

Reported causes of DKA:

- Missed insulin dose: 48.6%
- Gastroenteritis: 12.7%
- Technical pump problems: 13.4%
- Infection: 14.1%
- Social problems: 14.1%
- Unknown: 12.7%
- Not stated: 1.4%
**Discussion**

- This report highlights the risk of DKA in patients using insulin pumps (even if the total incidence of DKA in patients with established diabetes is low in comparison with other published reports).
- The high number of cases reported to be caused by gastroenteritis is alarming because this may reflect a misinterpretation of DKA symptoms (nausea or vomiting could be related to the increased levels of ketones).
- A lower HbA1c in pump users supports the view that the reason for having DKA is more about the technical handling of the pump, which has a learning curve, than a long-term mismanagement of insulin administration.
- Increased attention needs to be given to the prevention of DKA; measures could include:
  - Improved education: practical advice on how to handle the pump and recognize failure of insulin delivery.
  - Home measurement of blood β-hydroxybutyrate (β-OHB): with β-OHB rising approximately 0.2 mmol/L/h there should be enough time to take appropriate measures to avoid DKA in most cases of ketosis.
  - Adding a small dose of subcutaneous basal insulin in the evening.

**Overall incidence of DKA**

<table>
<thead>
<tr>
<th>Year</th>
<th>DKA Incidence /100 patients years</th>
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<tr>
<td>1999</td>
<td>3.2 (p&lt;0.021)</td>
</tr>
<tr>
<td>2000</td>
<td>3.6 (p&lt;0.0001)</td>
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</table>

**DKA episodes in pump users**

- HbA1c at DKA admission was lower for CSII users than patients who used injections (9.1 ± 1.5% vs 10.8 ± 2.2%, p < 0.01), but pH and age did not differ.

**DKA frequency in CSII users was approximately twice that of patients who used injections**

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**The median duration of CSII use at the time of DKA episode was 6 months, and 76.7% of the DKA episodes occurred within 1 year from pump start**

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- **Overall incidence of DKA**
  - Year: 1999, DKA Incidence: 3.2 (p<0.021)
  - Year: 2000, DKA Incidence: 3.6 (p<0.0001)

- **DKA episodes in pump users**
  - Year after pump start: 0, Age, years: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
  - DKA incidence /100 patients years: 0, 1, 2, 3, 4, 5
Background

- Continuous subcutaneous insulin infusion (CSII) improved quality of life of diabetic patients mainly by reducing the risk of long term complications
- Nevertheless, CSII is associated with an increased risk of diabetic ketoacidosis (DKA) because of pharmacokinetic property of the insulin used and pump related failures (catheter obstruction, needle dislodgement, leakage at the infusion site)
- Measurement of β-hydroxybutyrate in capillary blood allows an accurate analysis of this acute metabolic derangement (superiority of this method vs urine testing for early detection of ketosis)
- Currently accepted normal values of blood ketones [0.5 mmol/L] were determined by venous sampling in patients on multiple daily injections (MDI)
- Insulin pump provides a better physiological delivery of insulin than MDI; the level of normal capillary ketones in CSII patients should be theoretically lower than that encountered in MDI patients

Aim

To determine the normal level of capillary ketonemia in Type 1 diabetic patients on CSII

Patients and methods

- 36 Type 1 diabetic patients treated by external pump were studied for 2 to 3 weeks
- Patients were instructed to self-monitor capillary glucose and capillary ketone levels at least 4 times a day with a handheld dual glucose and ketone sensor. Surveillance of urinary ketones was also performed daily and any time blood glucose exceeded 250 mg/dL.
- Data were collected and analyzed for each period of time defined as the time interval between two changes of the infusion site. A period was considered normal when no problem causing any impairment in insulin delivery was detected

Results

- 186 periods of 2.1 ± 0.9 days were recorded; 119 were considered normal
- 1281 coupled values of glucose and β-hydroxybutyrate were analyzed during the so-called normal periods
3

What Are Capillary Blood Ketone Levels in Type 1 Diabetic Patients Using CSII in Normal Conditions of Insulin Delivery?

- 98% (1255/1281 measurements) of β-hydroxybutyrate values were less than 0.3 mmol/L

![Blood glucose and ketonemia during "normal periods"](image)

**Conclusions**

- In this study normal β-hydroxybutyrate capillary levels rank between 0.0 and 0.2 mmol/L independently of the time of measurement (fasting, pre- or postprandial)
- 2% of the cases had a level of β-hydroxybutyrate ≥ 0.3 mmol/L, out of which 0.9% had glucose level ≥ 250 mg/dL

**Discussion**

- In Type 1 diabetic patients on CSII, screening for ketonemia using a cut-off value of 0.3 mmol/L instead of the usual value of 0.5 mmol/L coupled with blood glucose measurement would allow earlier detection of impending ketosis with a low risk of false positive results
- Early detection of ketone bodies should be an integral part of the monitoring program for all Type 1 diabetic patients on CSII
Hypoglycemia and Ketoacidosis with Insulin Pump Therapy in Children and Adolescents.

Background

• Although insulin pump treatment has important advantages, serious acute complications have to be taken into account when prescribing such a treatment to children
• Hypoglycemia and diabetic ketoacidosis (DKA) are the two most serious side effects encountered with insulin pump therapy

![DKA risk](image)

Odds Ratio (95% Cl)

- Intensified treatment
  - Use of continuous subcutaneous insulin infusion (CSII): 7.20 (2.95-17.58)
  - Use of multiple daily injections (MDI): 1.13 (0.15-8.35)
  - Choice between CSII and MDI: 1.28 (0.90-1.83)

DKA

Incidence/epidemiology

- Population-based or retrospective clinical studies reported a low rate of DKA in pump users that was still a higher rate than those using injection therapy, at least in some countries
- In research settings and for patients with good compliance and adequate family support, the risk of DKA seems lower
- Younger children are more prone to ketosis; older children can withstand insulin interruption better
- Most episodes of DKA occur early after pump start, suggesting a learning curve occurs in all new forms of treatment
- Pump use seems to decrease the risk in patients who had recurrent DKA before pump therapy

β-hydroxybutyrate (β-OHB)

- Several studies examined the course of events after a pump stops: a rise of blood glucose and β-OHB was observed; timing and increase level depend on the type of insulin used. The use of regular insulin slightly decreases the risk of a quick metabolic decompensation but other advantages of rapid-acting insulin usually outweigh this in clinical setting
- In most studies, the rise of β-OHB after the pump was stopped seems to be nearly linear, suggesting that the level would be approximately 3 mmol/L after 15 h without insulin

Prevention

- Home monitoring of β-OHB decreases diabetes-related hospital visits when compared to urine ketone monitoring by the early identification and treatment of ketosis
- Blood β-OHB measurements may be especially valuable to prevent DKA in patients who use a pump because interrupted insulin delivery rapidly leads to ketosis

Hypoglycemia

• Although clinical follow-up studies reported decreased rates of severe hypoglycemia, randomized studies have not confirmed this, showing no difference between the pump and injection groups
• Less severe hypoglycemia (mild/moderate/symptomatic hypoglycemia) was found to be more common with pump use.
• Some patients have inadvertently dosed or overdosed while awake or during sleep, causing fatal outcomes in rare cases