

## Treatment and Prevention of Diabetic Ketoacidosis in Children and Adolescents

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### Introduction

Ketoacidotic coma remains an important cause of mortality in children and adolescents with diabetes mellitus<sup>1</sup>. Despite this, it is preventable by educating patients and their attendants, except at first onset of the disease<sup>2</sup>. The management of ketoacidotic coma is important not only in patients with type 1 diabetes, but also with type 2 diabetes (so-called 'soft drink ketosis')<sup>3,4</sup>.

This review discusses aspects of the causes, the pathophysiology, the clinical features, the treatment and the prevention of diabetic ketoacidosis (DKA).

### Causes

Precipitation factors leading to DKA are newly presented type 1 diabetes with  $\beta$ -cell depletion, so-called abrupt onset type 1 diabetes, omitted or decreased doses of insulin, and sick day (a febrile illness, acute stress from trauma or severe psychological stress that increase counter-regulatory hormone) (Table 1). Since urine glucose mass screening has been conducted in schools in Japan, the number of abrupt onset patients has decreased, which has contributed to the decrease in the number of deaths from DKA at onset in Japan<sup>5</sup>.

### Pathophysiology

Kitabchi et al.<sup>6</sup> described the pathogenesis of DKA

Table 1 Causes of DKA

- |  |
|--|
| 1) Newly presented type 1 diabetes with $\beta$ -cell depletion (abrupt onset) |
| 2) Incorrect insulin dosage (omitted or decreased)                             |
| 3) Sick day  |

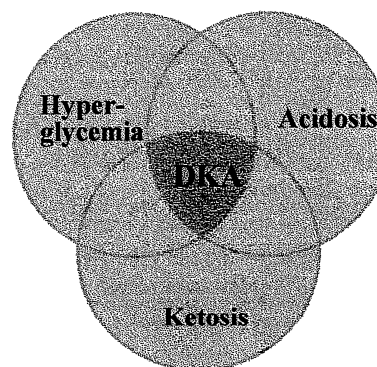


Fig. 1 Pathophysiology (1)—Diagnostic triad

simply as a diagnostic triad (Fig. 1). DKA is a metabolic derangement consisting of 3 concurrent abnormalities, which are high blood glucose, high levels of ketone bodies, and metabolic acidosis.

DKA is characterized by severe alterations in carbohydrate, lipid, and protein metabolism, mainly as a result of a lack of, or ineffectiveness of insulin, with concomitant elevations of counter-regulatory hormones (such as growth hormone, glucagon, glucocorticoid, catecholamines) due to stress (Fig. 2).

#### 1) Carbohydrate pathway

First, in the carbohydrate pathway decreased insulin leads to increased glucose production and

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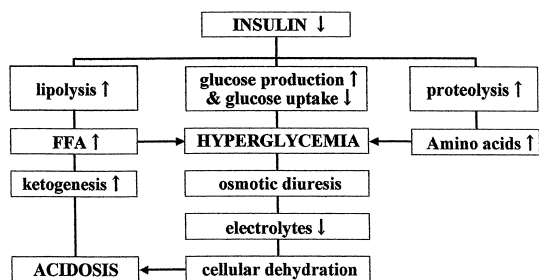


Fig. 2 Pathophysiology (2)—Carbohydrate, lipid and protein pathway

Table 2 Clinical features of DKA

- 1) Symptoms  
polyuria, thirst, polydipsia, weight loss, abdominal pain, weakness, vomiting, air hunger, visual disturbance, confusion
- 2) Signs  
lethargy, dehydration, Kussmaul respiration, smell of ketones on breath, disordered consciousness or unconscious

decreased glucose uptake that results in hyperglycemia. Hyperglycemia then causes osmotic diuresis, loss of electrolytes and cellular dehydration.

**2) lipid pathway**

Second, in the lipid pathway increased lipolysis leads to increased free fatty acid, which stimulates gluconeogenesis and ketogenesis. These ketoacids are buffered by extracellular and cellular buffers, and generate endogenous bicarbonate, resulting in metabolic acidosis.

**3) protein pathway**

Third, in the protein pathway increased proteolysis leads to increased amino acids, which serve as major substrates for gluconeogenesis.

**Clinical features**

Based on this pathophysiology, the clinical features of DKA are shown in **Table 2**. The symptoms are: polyuria, thirst, polydipsia, weight loss, abdominal pain, weakness, vomiting, air hunger, visual disturbance and confusion. The signs are: lethargy, dehydration, Kussmaul respiration, smell of ketones on breath and disordered consciousness or unconsciousness<sup>7</sup>.

Table 3 Treatment of DKA (1)—Therapeutic goals

- 1) Improve circulatory volume and tissue perfusion
- 2) Correct electrolyte imbalances
- 3) Decrease serum glucose
- 4) Clear the serum and urine of ketoacids at a steady rate

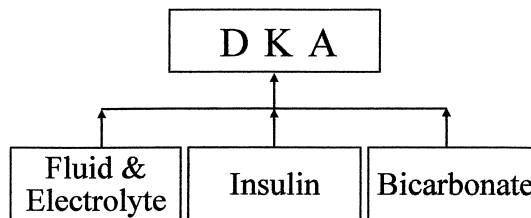


Fig. 3 Treatment of DKA (2) —Three kinds of replenishment

**Treatment**

The therapeutic goals of the treatment of DKA are: to improve circulatory volume and tissue perfusion, to correct electrolyte imbalances, to decrease serum glucose, and to clear the serum and urine of ketoacids at a steady rate (**Table 3**). Therefore, the treatment of DKA should involve 3 kinds of replenishment, which are fluid and electrolyte, insulin, and bicarbonate (**Fig. 3**). Vital signs and laboratory evaluation should be checked hourly.

**1) Fluid and electrolyte management (Table 4)**

The fluid replacement volume is the sum of half the losses and the maintenance volume. It is important to check any acute weight loss of the patient for the assumption the degree of dehydration, which ranges from 5 to 20%, usually 10% in shocked patients. The maintenance dose is 60 ml/kg/24 hours. So, when a patient weighs 20 kg and has 10% acute weight loss, his replacement fluid volume for 24 hours will be 2,200 ml, which is 1,000 for half the losses plus 1,200 for the maintenance.

In the first 1 to 3 hours, normal saline should be given for immediate restitution of blood volume. This effectively removes the patient from the immediate consequences of potential or overt shock.

Table 4 Fluid and electrolyte management

1) Volume
Half the fluid losses (% of acute weight loss) + maintenance (60ml/kg/24 hours)
2) Composition
a) First: normal (0.9%) saline for 1—3 hours
b) Next: half-normal (0.45%) saline
c) After first urination: add 30 mEq/l of K
d) When BG falls below 250 mg/dl: add 5% dextrose
3) Infusion rate
a) First 8 hours: Half of the 24 hour volume
b) Next 16 hours: The other half

Treatment with hypotonic fluids and overload initially increases the extracellular PH more rapidly than intracellular PH, activating the sodium proton pump and transporting sodium and water into the cell, leading to risks of cerebral edema<sup>8,9</sup>. Approximately 0.4~1% of children and adolescents with DKA develop cerebral edema with a high mortality/morbidity<sup>10</sup>.

Afterwards, normal saline is changed to half-normal saline with 30 mEq/l of potassium on confirmation of the patient's first urination. Despite a total body potassium deficit, most patients with DKA have a serum potassium level at or above the upper limits of normal. These high levels occur because of a shift of potassium from the intracellular to the extracellular space due to acidemia, insulin deficiency, and hypertonicity<sup>11</sup>. Half of the potassium should be given as potassium chloride (15 meq/liter KCL) and the other half as potassium phosphate (15 meq/liter K<sub>2</sub>HPO<sub>4</sub>). If there is any doubt about renal function, an electrocardiogram should be checked for peaked T-waves before potassium is given.

When blood glucose level falls approximately 250 mg/dl by insulin, 5% dextrose should be added, since both insulin and glucose are required to reverse glycogenolysis and ketogenesis.

Regarding the infusion rate, a half dose of 24 hours should be infused in the first 8 hours and another half in the next 16 hours.

## 2) Insulin therapy (Table 5)

Generally, blood glucose falls by approximately 10

Table 5 Insulin therapy

1) Intravenous low dose regular insulin infusion
a) Prepare 100 units (U) of regular insulin/100 ml of normal saline
b) Give 0.1 U/kg of regular insulin as bolus
c) Start 0.1 U/kg/hour of regular insulin by continuous infusion
2) Subcutaneous regular insulin injection:
Start 0.25 U/kg of regular insulin 3 times a day before meals when the patient is offered food by mouth

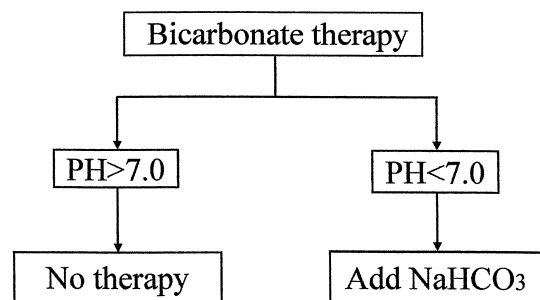


Fig. 4 Bicarbonate therapy

% per hour once the initial "dehydrated" blood glucose value is corrected with rehydration. So, intravenous low dose regular insulin infusion has become the standard method of treating DKA<sup>12</sup>.

The protocol is: prepare 100 units of regular insulin/100 ml of normal saline, give 0.1 units/kg of regular insulin intravenously as bolus, and start 0.1 units/kg/hour of regular insulin intravenously by continuous infusion. Subcutaneous regular insulin injection is started before meals, 3 times a day at a dose of 0.25 units/kg, when the patient is offered food by mouth.

When patients start complaining that they are hungry, it is usually prudent to begin refeeding. This is usually after the blood glucose falls to less than 250 mg/dl.

## 3) Bicarbonate therapy (Fig. 4)

Since acetoacetate and betahydroxybutyrate are metabolizable anions, restoration of serum bicarbonate concentration will follow insulin administration in the absence of treatment with alkali containing solutions (Ketone bodies are converted to bicarbonate). Treatment with sodium

bicarbonate should be restricted to patients with severe metabolic acidosis as indicated by an arterial PH of less than 7.0. When sodium bicarbonate is used, a 7% solution should be given at 1 ml/kg by slow intravenous infusion over several hours<sup>13</sup>. Potential dangers of bicarbonate include acute

exacerbation of hypokalemia, tissue hypoxia due to reduced dissociation of oxyhemoglobin, sodium overload and increasing CSF acidosis.

**Prevention**

So, how do we prevent DKA, especially recurrent DKA?

**1) Self-monitoring blood glucose (SMBG)**

First, I emphasize the importance of forming a habit of self-monitoring blood glucose (SMBG) at least 2 times a day, before breakfast and before dinner. If possible, I also recommend SMBG before lunch and before sleep, a total of 4 times a day. And once a month, SMBG should be done 7 times a day, including the above-mentioned times plus 2 hours after each meal.

**2) Predicting blood glucose levels before SMBG**

Second, before SMBG, patients should practice predicting their blood glucose level from their physical condition. The difference between predicted

平成10年2月:血糖値(mg/dl)

	朝前	後	昼前	後	夕前	後	寝前	深夜
1	10 <sup>30</sup> 141	(120)			16 <sup>30</sup> 125		23 <sup>30</sup> 213	(250)
2	6 <sup>30</sup> 82				81		45	①1.5
3	107	(100)			62	(70)	113	
4	103				82		146	(130)
5	72	(100)			86	(90)	70	
6	67	(90)			67	(100)	108	(130)
7	121				138		203	(190)
8	142	(190)			126		152	(200)
9	112	(110)			130		146	(180)
10	7 <sup>30</sup> 115	(100)			125		119	
11	98	(130)	12 <sup>30</sup> 135	(120)			258	(300)
12	188	(150)			131	(160)	112	(140)
13	103				86		128	(180)
14	108	(120)	120		148	(180)	110	
15	10 <sup>30</sup> 160	(130)			153		167	(180)
16	6 <sup>30</sup> 124				122	(150)	136	(120)

FRA	μmol/L	GA	%
1.5AG	μE/ml	HbA1c	7.5%
		氏名	

Fig. 5 SMBG note

Table 6 Symptoms of mild/moderate hyperglycemia

- 1) A heavy feeling, a hot feeling, malaise
- 2) Thirst, polydipsia, polyuria
- 3) Headache, nausea, abdominal pain

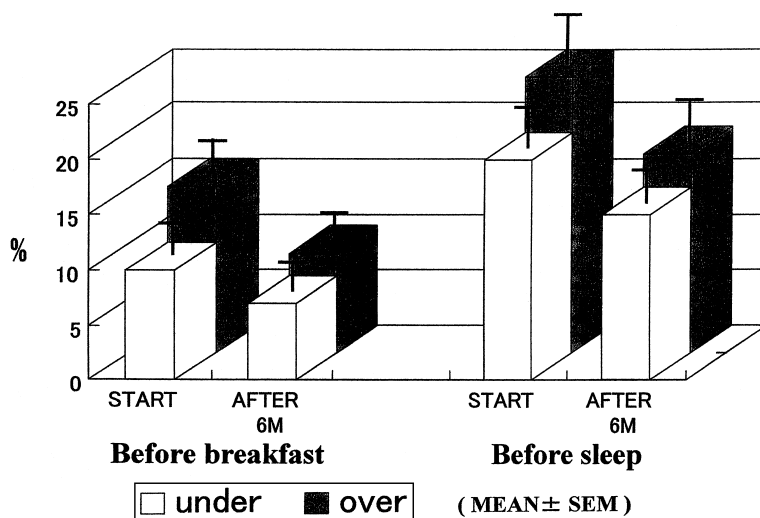


Fig. 6 Effect of 6 months' training in blood glucose prediction

and measured values will decrease with practice.

**Fig 5** shows the SMBG note of a 13-year-old boy whose HbA1c is 7.5%. These Japanese 'Kanji' mean before breakfast, lunch, dinner and before sleep from left to right. He does SMBG 3 times a day-before breakfast, dinner and sleep. The numbers on the left are the actual measured values of blood glucose and those on the right in parentheses were predicted by the patient before SMBG. The 2 values are sometimes very close and sometimes differ. So, how do patients predict their blood glucose levels? The symptoms of hypoglycemia are well known, but those of mild to moderate hyperglycemia in which blood glucose levels are between 250 to 500 mg/dl depend on the person.

The most common symptoms of mild to moderate hyperglycemia are feeling heavy, feeling hot and malaise. Next are thirst, polydipsia, and polyuria. The patient sometimes has headache, nausea, and abdominal pain (**Table 6**). These symptoms are very important for prediction of hyperglycemia.

The mean difference between the actual blood glucose values and predicted values in 7 patients who kept records for 6 months before breakfast and before sleep is shown in **Fig. 6**. The records were divided into 2 groups, underestimated values and overestimated values, because if these groups were mixed, the data would offset each other and the error would become smaller. White bars are underestimated percentage to measured blood glucose values, and black bars are overestimated percentage. For instance, for the first 1 month the extent of underestimation was 10%, which means when measured blood glucose was 100 mg/dl, the predicted one was 90.

It is effective for correcting predicted values if the patient knows the trends and characteristics of the previous prediction. You can see in **Fig. 6** that the differences decreased after 6 months for both under- and overestimated predicted values, and both before breakfast and before sleep.

Thus, it is very effective for patients to practice predicting their blood glucose level before SMBG based on their physical condition. The difference between predicted and measured values will

decrease with more practice and this might be effective for preventing DKA.

I presented part this review at a lecture in a symposium at the 22<sup>nd</sup> International Congress of Pediatrics (Amsterdam, 1998).

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