

Insulin therapy during diabetic ketoacidosis in children

Francesca Cardella

Paediatrics Diabetology Unit – University of Palermo, Palermo, Italy

Abstract. Diabetic ketoacidosis is still today a medical emergency in pediatrics. Despite the latest great sensibilization of the population and the doctors, the risk of DKA has not yet been completely eliminated and this pathology is still occurring in 25 to 40% of diabetes onset cases, in already diagnosed patients with poor compliance, or in patients undergoing acute medical or surgical events. In affected patients, missed recognition can influence morbidity and mortality rates. Despite the improvement in DKA management and therapy, a lot of controversies have been encountered through a careful review of the most recent literature in the sector (guidelines in Pediatrics). Particularly as far as DKA pathophysiology and its complications (cerebral oedema) are concerned. In terms of insulin therapy the latest progress has underlined the advantages and disadvantages of the therapeutical choices that have modified in time. A wide consent exists on the need to use small doses of regular insulin for continuous intravenous administration as therapy of choice for pediatric DKA (0.1-0.05 U/Kg/h). The success of the treatment is nevertheless tightly connected to a correct management of rehydration, of metabolic acidosis and of electrolyte deficit replacement more than on insulin therapy, aimed at avoiding the most dangerous complication of DKA: cerebral oedema. (www.actabiomedica.it)

Key words: Pediatric ketoacidosis, insulin therapy, cerebral oedema

Diabetic ketoacidosis (DKA) consists in a serious acute metabolic complication of diabetes mellitus caused by both absolute or relative insulin-deficiency associated with elevated levels of counterregulatory hormones, that modify glucose, lipid and protein metabolism.

It is characterized by hyperglycemia (>250-300 mg/dls), dehydration with electrolyte deficit, metabolic acidosis (pH <7.3; NaHCO_3 <15 mEq/ltses) primarily due to an increase of acetoacetic and β -hydroxybutyric acid serum concentration (ketonemia) and presence of ketone bodies and glucose in the urines (glycosuria and ketonuria).

Ketoacidosis strikes more frequently patients with absolute insulin deficit, and therefore patients affected by Type 1 diabetes: around 30% of young diabetic patients suffers from an episode of DKA versus 10% of

adults. The incidence of DKA in diabetic patients (1) is between 4,6 and 8 episodes/1000 people/year. The mortality rate, although reduced by the introduction of insulin treatment, is not still entirely annulled: according to Hylary Byrne (2000) it passed from 44% in the '30s to 3-5% in the '80s, but still in the year 2000 has only changed a little (2-5%) (2).

Every delay in the diagnosis can be particularly severe for the prognosis of the patient: in babies and toddlers it can be confused with respiratory distress, in reticent or obese teen-agers, weight loss can be wrongly considered a therapeutical success.

DKA may occur in children at the onset of diabetes (25-40%; Fig. 1), during acute illnesses, and in already diagnosed non-compliant patients. In toddlers (0-3 years) it is twice more frequent than in the following ages and is characterized by the presence of

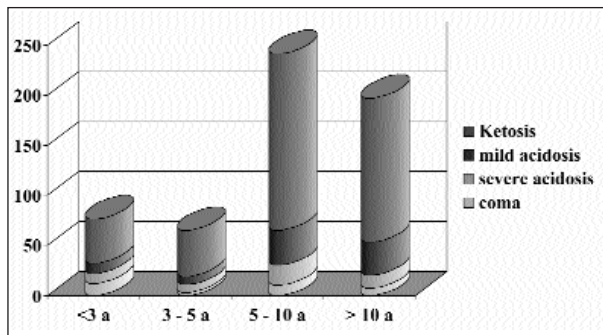


Figure 1. Pediatrics Diabetology Unit of Palermo - Type 1 Dm DDF for year and modality at onset

more serious clinical dehydration (>10%) and neurological signs (obnubilation 40%) (3). The other category at risk is represented by teen-agers, who may suffer from DKA at the moment of diabetes onset (scarce vigilance or reticence on the problems), or in the course of diabetes treatment when there is poor compliance (Fig. 2); furthermore in the puberty period the situation is also negatively conditioned by the fact that patients usually change doctor for their controls, passing from the pediatrician to the general physician. This can imply some risks in terms of follow-up and vigilance on the possible problems that can arise.

Pathogenesis (1, 4)

DKA is the result of an absolute or relative insulin deficit associated with overproduction of counter-regulatory hormones. Principal biochemical alterations are represented by:

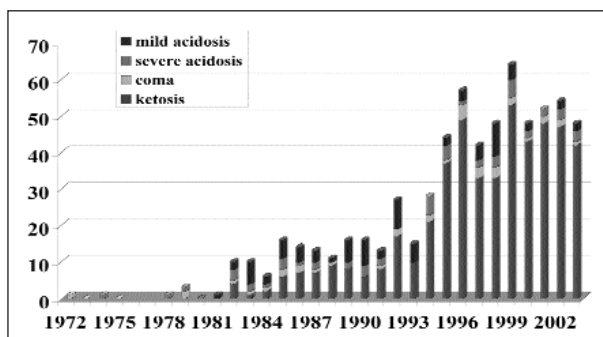


Figure 2. Pediatrics Diabetology Unit of Palermo - Type 1 Dm DDF for age and modality at onset

- 1) accelerated glyconeogenesis/glycogenolysis;
- 2) reduced extra-hepatic glucose uptake;
- 3) higher lipolysis with consequent increase of hepatic ketogenesis.

The combination of high glucose hepatic production and low peripheral uptake is at the basis of hyperglycemia: by overcoming the renal threshold for glucose, glycosuria can occur. Osmotic diuresis causes dehydration. Osmotic diuresis determines water (average 100 ml/Kg), sodium (7-10 mEq/kg) and potassium (5-7 mEq /Kg) loss.

Also the counterregulatory hormones interfere in the pathogenesis of DKA:

- 1) Glucagon level stimulates hepatic glyconeogenesis and glycogenolysis, muscular proteolysis and peripheral lipolysis.
- 2) Cortisol level favors proteolysis, providing substrata (Aminoacids) for glyconeogenesis.
- 3) Growth Hormone stimulates lipolysis, inhibits the transportation of glucose into adipose tissues and decreases peripheral lipogenesis.

Ketogenesis (4)

Under normal nutritional conditions ketone bodies (Acetoacetic and β -hydroxybutyric acids) hold a marginal role in metabolism. During fasting ketone bodies represent the most important alternative energetic source particularly for the brain (Owen 1967) that is not able to use free fatty acids (FFA) as energetic source.

Ketone bodies are produced in the hepatic mitochondria. Although their synthesis under fasting conditions is a protective mechanism of adaptation for the organism, excessive accumulation can induce severe metabolic acidosis treating strong organic acids.

Physiologically when the plasmatic ketone body concentration overcomes 4-6 mMol/l the mechanism regulating the mobilization of NEFA (not esterified fatty acids) is baited from the adipose tissues, through the stimulation of insulin secretion from the pancreas. The precursors of ketone bodies are long chain fatty acids, released by adipose tissues after lipolysis.

Hepatic and adipose metabolic changes are conditioned by glucagon/insulin ratio:

- a) low glucagon/insulin ratio (as in the post-prandial period) inhibits the release of fatty acids and makes inactive their β -oxidation;
- b) elevated glucagon/insulin ratio (fasting, diabetes Type 1) is associated to an increase of lipolysis and fatty acid β -oxidation in the hepatic mitochondria.

The level of Malonil-CoA (the first intermediary product in the synthesis of long chain fatty acids) is very important for the treatment of hepatic ketogenesis:

- a) a high concentration of Malonil-CoA reduces oxidation of fatty acids due to CPT1 inhibitions (carnitine-palmitoyl-transferase 1) and therefore reduces ketogenesis;
- b) a low concentration of Malonil-CoA involves CPT1 activation and increases ketogenesis.

Adipose tissues can be considered as a source of energetic substrata and the liver as the center of conversion mechanism of substrata into products (Fig. 3).

Treatment of DKA (1, 5-7)

The success of DKA treatment depends on the adequate correction of dehydration, hyperglycemia, ketoacidosis and electrolyte deficit.

Fluid therapy and electrolyte deficit reconstitution

Although numerous protocols on therapy are available in literature, the most recent reviews and the ADA position statement 2003 suggest an aware management of dehydration to avoid the risk of cerebral

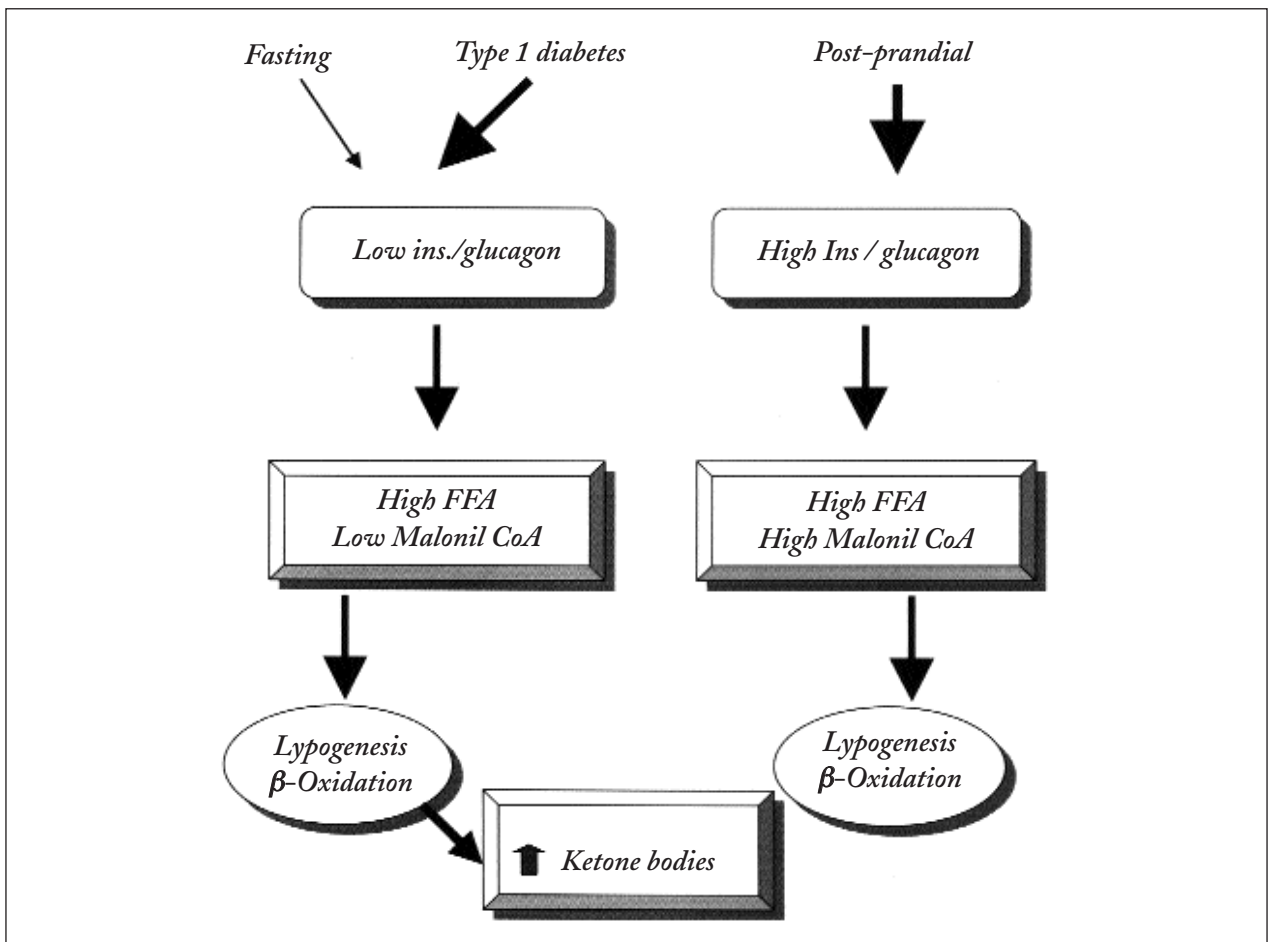


Figure 3. Ketogenesis

oedema, one of the most dangerous complications of ketoacidosis, that affects today still between 0.7 and 3% of patients and is associated with high rates of morbidity and mortality (5, 6, 8).

Cerebral oedema seems to be more frequent in patients with situations of more severe onsets, particularly in those with low paCO_2 and high levels of urea nitrogen, but seems to be correlated also to the rapid administration of fluids and to the inadequate use of NaHCO_3 (3, 8, 9).

For these reasons the most recent protocols for treatment of pediatric DKA underline the importance of a slow fluid reconstitution. Although Chiasson recommends for adult treatment to begin with 15–20 ml/Kg of physiological solution, for children the most recent recommendations are not to overcome 5–10 ml/Kg/h in the first two hours (max 250 ml/h: ISPAD 2000, ADA 2003) and to continue the hydration slowly calculating the body surface area of children so as not to exceed 3 lt/mq/die (average 2000–2500 ml/mq/die) (5, 6, 7, 10, 117).

The aware management of the therapy prevents abrupt osmotic variations that are at the basis of cerebral oedema. Careful controls of plasmatic electrolytes (opportune integrations particularly of potassium deficit: 20–40 mEq/lt, 50% of KCl + 50% of KPO₄) and of glycemia are suggested (to avoid too rapid falls: when glycemia <250mg/dl replace the sol. NaCl 0.9% N with mixed sol. constituted by 50% of sol. Glucose 10% and 50% of physiological sol.). The follow-up of clinical patient conditions and the EKG evaluation prevent rapid falls of kaliemia with well-known cardiac consequences (7).

Alcaly therapy

The use of bicarbonate is still controversial: it is only recommended under conditions of severe acidosis (pH <7) and suspended if pH >7.2 and $\text{HCO}_3^- > 10$ mEq/lts. It is administered in very limited quantities (1–1.5 mEq/Kg) only after initial hydration, it must be diluted to avoid osmotic impact and slowly infused (Sarah Laurence JAMC 2003). Careful controls of ketonemia (strips Optimum Medisense) and of EAB are essential to ensure a correct treatment management (5, 6, 12).

Insulin therapy for DKA (5-9, 12, 13)

The introduction of insulin therapy in the treatment of diabetic ketoacidosis has modified patient prognosis historically quoad vitam and quoad valetudinem. Moreover, today's available insulins have been improved in terms of purity and formulation, and besides this, other positive effects have been obtained by the adequate choice of the insulin type to administer (regular), and its administration way.

Up to the beginning of the years '70s large doses of regular insulin were administered with subcutaneous injections (previous bolus e.v.), this contributed inevitably to the onset of problems of management because of the unforeseeable absorption and accumulation in the site of administration, that often determined general unmanageable hypoglycemia and hypokaliemia.

The true revolution in insulin therapy goes up again in 1977 with the intuition from Alberti (1, 7, 12) who suggested to inject small insulin boluses in the muscle, considered that the insulin half-life administered in the muscle is around two hours, that could guarantee discreet stability of plasmatic insulinemia. The insulin dose was reduced from 0.25 to 0,1 U/Kg/h. The introduction of this administration regimen involved notable beneficial effects in the treatment of DKA:

- a) easy comprehension of the dose to administer by the staff;
- b) no need of complex devices for insulin administration;
- c) easy calculation of the dose to administer;
- d) low risks of late hypoglycemias and hypokaliemia;
- e) predictable fall of the serum lactate.

Nevertheless there were problems associated to the discomfort of the procedures for patients with the risk of hypotension if the management of rehydration wasn't well controlled, and to the unpredictable absorption if the patient was obese (buttocks, deltoid).

At the end of the seventies, today's therapy of choice for diabetic ketoacidosis was definitely introduced: continuous intravenous infusion of low doses of insulin (0.1 U/kg/h).

The pathophysiologic basis of this therapeutical approach was explained by De Fronzo (1988) that al-

so showed, through his studies, as the metabolic effect of insulin blood levels in adults is very close but extremely different: the administration of 1 U/h involved 100% inhibitions of lipolysis and 50% suppressions of hepatic gluconeogenesis with peripheral use of glucose equal to 13 g/h; increasing insulin infusion to 2 U/h involved a 90% suppression of glucose hepatic production and increased peripheral glucose metabolism to 21 g/h. In this way pathogenetic mechanism of hyperglycemia and ketogenesis could be interrupted. An increase of infusion up to 8 U/h increased the suppression of neo-glucogenesis only by 10% increasing the peripheral use of glucose up to 50 g/h and the potassium uptake, with the well known consequences (13).

In pediatrics, international guidelines have confirmed the utility of this therapeutical choice (ISPAD 2000; ADA 2003) according to which babies and toddlers, considering their particular insulin sensibility, begin the treatment with a dose of 0.05 U/Kg/h. A different administration is that suggested for hydration and it is possible to modify the dose during the follow-up (16). When glycemia goes down to under 250 mg/dl it is necessary to halve the dose of insulin, and modify the infusion solution.

The advantages of this approach consist in:

- a) correct therapeutical effect especially in terms of ketoacidosis control Vanelli (personal communication) has shown how good correlation exists between insulin requirement and EBA, ketonemia and glycemia in the first hours of diabetic pediatric ketoacidosis treatment;
- b) good hepatic and peripheral insulinization;
- c) reduction of the plasmatic osmotic fall;
- d) scarce onset of late hypoglycemia and hypokaliemia and possibility of correction;
- e) decreased risk of cerebral oedema;
- f) good acceptance of the patient;
- g) good choice of the insulin dose.

It is important nevertheless to underline how in case of use of sophisticated devices (infusion pumps), a detailed vigilance of their correct functioning is necessary, considered the rapid plasmatic absorption of the insulin administered through venous infusion (a few minutes), and the danger of suspending it without notice (7).

When the patient goes out of the metabolic maelstrom of DKA it is advised to begin an intensive therapy. Before completely interrupting infusion treatment, insulin has to be administered contemporarily in the subcutaneous way and in infusion.

The DCCT has confirmed how following an insulin therapy based on the continuous infusion of low doses is important to preserve the residual β -cell patrimony for a long time also after years from the clinical onset of the pathology (14). In the recommendations ADA 2003 the choice of this therapeutical approach is also suggested in case of mild ketoacidosis (6).

General consensus exists on the use of small doses of insulin in continuous intravenous administration (0.1-0.05 U/Kg/h) as a choice of treatment in pediatric diabetic ketoacidosis. The success of the treatment depends nevertheless also on the correct rehydration, on the adequate reinstatement of electrolyte deficit and on an accurate control of metabolic acidosis and plasmatic osmolarity to avoid the onset of the most dangerous complication in progress of treatment: cerebral oedema.

In consideration of the possible reoccurrence of episodes of DKA it is necessary to promote campaigns of information and vigilance underlying the risk of DKA not only at diabetes onset but also during follow-ups of already diagnosed patients, to underline once again as the diabetic patient is particularly complex to manage and needs to be followed for years without ever lowering the level of supervision.

References

1. Chiasson J, Jilwam NA, Bélanger R, et al. Diagnosis and treatment of diabetic Ketoacidosis and the Hyperglycemic Hyperosmolare. *Can Med Ass J April* 2003; 168 (7).
2. Byrne H, Kenneth L, Hollis S. Evaluation of an electrochemical sensor of measuring blood ketones. *Diab Care* 2000; 23: 500-3.
3. Glaser N, Barnett P, Mc Coslin I, et al. Risk factors for cerebral oedema in children with diabetic Ketoacidosis. *N Engl J of Med* 2001; 344 (4): 264-9.
4. Mc Garry JD, Foster DW. Ketogenesis. In the Ellenberg and Rifkin's: *Diabetes Mellitus*, vol. 1; 19; 1998.
5. Lines it drives for the management of the diabetes mellitus in children and in teen-agers Consensus Guidelines 2000. Pacini Ed. Med, 2000.

6. ADA position statement 2003. Hyperglycemic crises in patients with Diabetes Mellitus. *Diab Care* 2003; 26 Suppl. 1.
7. Brink SJ. Presentation and Ketoacidosis. In: Childhood and Adolescent Diabetes, and by C. Kelnar–Chapmann and Hall Medical, 1997.
8. Laurence S, Picaud D, Dean H, Lawson M, Daneman D. Pediatric Diabetic Ketoacidosis. *Can Med Ass J* 2003; 169 (4): 278-9.
9. Marcin J, Glaser N, P. Barnett P, et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis related cerebral oedema. *J Ped* 2002; 141: 793-97.
10. Felner EI, With PC. Improving management of diabetic ketoacidosis in children. *Pediatrics* 2001; 108 (3); 735-40.
11. Edge JA, Hawkins MM, Winter DL, Dunger DB. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. *Arch Dis Child* 2001; 85: 16-22.
12. Inward CD, Chamber TL. Fluid management in diabetic ketoacidosis. *Arch Dis Child* 2002; 86: 443-5.
13. Carlotti APCP, Bohn D, Alperin ML. Importance of timing of risk factors for cerebral oedema during therapy for diabetic ketoacidosis. *Arch Dis Child* 2003; 88: 170-3.
14. Wagner A, Brawls A, Brill HL, et al. Therapy of severe ketoacidosis: Zero mortalities under very-low dose insulin application. *Diab Care* 1999; 22, 5.
15. DCCT 1998. Effect of intensive therapies on residual β -cell function in patients with Type 1 diabetes in the DCCT. *Ann Med* 1998; 128: 517-23.
16. Ferrez Collett-Solberg P. Diabetic ketoacidosis in children. Review of pathophysiology and treatment with the use of the two bags system. *J Ped* 2001; 77 (1): 9-16.

Correspondence: Dr. Francesca Cardella
Pediatrics Diabetology Unit
University of Palermo
c/o Osp. Dei Bambini "G. Di Cristina"
Piazza Porta Montalto 1
90134 Palermo, Italy
E-mail: f.cardella@libero.it