

Diabetic ketoacidosis in children

To the Editor

Dear Sir,

with great interest, I have read the recent review on diabetic ketoacidosis in children (1). However, in diabetic ketoacidosis are several controversial issues and, perhaps, it would be interesting for the readers of this journal if the authors could comment them more in detail.

1. On p 59, diabetic ketoacidosis is characterized by hyperglycemia >250 mg/dl, and later on the same page is mentioned hyperosmolar coma due to extreme hyperglycemia >1000 mg/dl without significant ketonuria. How is it possible to explain that one pathologic situation "hyperglycemia" has two quite different consequences "ketoacidosis and hyperosmolar coma without ketonuria"?

2. On p 60, the authors write "The hyperketonemia... determines metabolic ketoacidosis when the concentration of beta-hydroxybutyrate is about 6 mmol/L" and on p 63 "the normalisation of β -HBA levels may be used as a primary end-point for... the length of stay in the intensive care unit...". In patients with diabetic ketoacidosis, increased amounts of 36 organic acids have been observed (2): two of them are acetoacetic and beta-hydroxybutyric acids. The extent of increase of these 36 acids in very manifold: acidosis with blood pH of 6.85 has been observed in a diabetic girl without ketoacids (3). Is the level of beta-hydroxybutyrate always a reliable marker of the danger threatening the patient?

3. On p 64, the authors write "It is well known that the ketosis may persist for many hours after correction of hyperglycemia". Diabetic ketoacidosis has been observed also with normal glycemia (4, 5). The conclusion could be that ketoacidosis is glycemia-independent? What is the comment of the authors?

4. On p 65, the authors write "Metabolic acidosis

disappears spontaneously within 14.4 ± 8.2 hours using the scheme of treatment outlined". Earlier, on p 59, the authors write "mortality has not improved and has remained the same as that reported in the 1970s...". What is the cause of death if acidosis disappears spontaneously within 14.4 hours?

5. On p 66, the authors write "Bicarbonate may induce a paradoxical fall in cerebrospinal fluid pH", this being a negative effect. However, in their quotation 20 (Assal et al.) is written on p 411 "The data presented here support that abnormally low CSF pH values are not necessarily associated with a deterioration in clinical status". What is correct and what is incorrect?

Sincerely, yours

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The Author reply

We appreciate Dr. Rosival's (1) interest in our article (2) and the opportunity to respond to his comments.

About the first point of his remarks, the lack of significant ketogenesis in very young newly diagnosed diabetic patients as well as in diabetic children with brain disorders, extreme hyperglycemia, hyperosmolar coma and insignificant ketonuria may be explained by a couple of mechanisms: 1) hyperosmolar state has been shown to inhibit lipolysis (3), and 2) residual endogenous insulin reserve at diagnosis has been reported to be adequate to prevent lipolysis ("insignificant ketonuria") but inadequate to inhibit hepatic glucose production and stimulate peripheral glucose uptake ("extreme hyperglycemia") (4).

As concerns the question whether the level of beta-hydroxybutyrate is always a reliable marker of the danger threatening the patient, we have not found evidences supporting this hypothesis. However it has been reported that ketoacid levels, first of all acetoacetate, may alter osmoticity in diabetic ketoacidosis and precipitate cerebral oedema (5). In our experience, the availability of beta-hydroxybutyrate dosage since admission can be a useful parameter as well as the traditional sensitive markers of metabolic decompensation like serum bicarbonate and anion gap, in order to program the initial therapeutic plan for Diabetic Ketoacidosis (DKA) management, insulin therapy at first. We have found that beta-hydroxybutyrate levels at diabetes diagnosis is correlated with HbA1c values, latency before diagnosis of diabetes and insulin dose infused during the first hours of treatment. Based on these observations, high levels of beta-hydroxybutyrate at diagnosis can be able to throw light on a long-standing insulin deficiency state and a possible insulin resistance due to a prolonged metabolic derangement (6).

The opportunity to prolong insulin and glucose infusion after the blood glucose has been controlled is due to the observation that acidosis and ketosis resolve more slowly than hyperglycaemia. In this process, glucagon may be of particular importance, as plasma levels correlate with ketone body and NEFA concentrations (7).

Despite DKA generally disappears spontaneously within a few hours of treatment, Edge et al. have recently reported that cerebral oedema continues to occur in 6.8 per 1000 episodes of DKA in children under the age of 16, first of all in those with newly

diagnosed diabetes. It remains a major complication of DKA with a mortality rate of 25%, and 35% of survivors suffers severe neurological sequelae (8). In this perspective, all preventive strategies are welcome (9).

The use of bicarbonate in the treatment of DKA is now generally discouraged because of the risks related to its administration such as hypokalaemia, paradoxical worsening of cerebrospinal fluid acidosis, rebound alkalosis and impaired oxyhaemoglobin dissociation. The comment of Assal et al. in this field did not exclude these potential complications (10). More recently, Glaser et al. reported that children with diabetic ketoacidosis treated with bicarbonate are at increased risk of death due to cerebral oedema (11).

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