Reviewer’s report

Title: Low carbohydrate diet-associated ketoacidosis: a second case report

Version: 3 Date: 3 October 2007

Reviewer: Johan H Koeslag

I am familiar with the literature and believe that this case meets one of the 7 criteria for evaluation in the journal: Presentations, diagnoses and/or management of new and emerging diseases

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: No

Does the case report have diagnostic value?: Yes

Will the case report make a difference to clinical practice?: Yes

Comments to authors:

General


Two things should possibly be highlighted. The first is that despite the widespread use of weight reducing low carbohydrate diets for many years now, these two reports seem to be the first to highlight this complication. This either means that it is a rare complication, or that it has, so far, not been recognized as a possible complication of a very strict low carbohydrate diet. The hyperglycemic ketoacidosis could easily, in the past, have simply been passed off as a complication of type 2 diabetes mellitus or metabolic syndrome (the low carbohydrate diet being viewed as an irrelevancy). A third possibility is that people are applying the diet in an ever increasingly more fanatical way. And a final possibility, which I explain below, is that the syndrome is brought about by some, as yet unknown, trigger in persons on a very low carbohydrate diet.

This brings me to the second point. The most surprising aspect of this syndrome is that the patient developed a hyperglycemic ketoacidosis on a very low
carbohydrate diet. This is not emphasized enough in the article (it appears neither in the title, nor among the several references to the findings). This is a great mystery. Hyperglycemia would intuitively not easily be associated with a deficiency of carbohydrate in the diet. It is also very difficult to explain biochemically. A low insulin:glucagon ratio, the physiological response to a low carbohydrate diet, easily explains the ketosis, but it is difficult to imagine how it could stimulate the liver to overproduce glucose via gluconeogenesis to bring about hyperglycemia. The vast majority of persons on these low carbohydrate diets maintain euglycemia with these low insulin:glucagon ratios in the blood. What in this patient (and in the one described by Shah and Isley) causes the liver to overcompensate to produce vastly more glucose than can be used at that moment? Obviously something has gone wrong. The authors suggest "insulin resistance", but it is difficult to envisage insulin resistance when there is almost no insulin in the blood of patients on these diets. Furthermore what would have caused the sudden insulin resistance? A more pertinent question would be why did the hyperglycemia not trigger an insulin response (i.e. a reversal of the low insulin:glucagon ratio)?

The patient, in this case, had imbibed alcohol the evening before. But this would more likely have produced hypoglycemia, as ethanol metabolism in the liver inhibits gluconeogenesis. Shah and Isley's patient denied alcohol consumption on any of the occasions when she developed this syndrome. Nevertheless it is just possible that the alcohol consumption produced hypoglycemia in this patient, and that the epinephrine/cortisol/glucagon/growth hormone reaction to the hypoglycemia caused an overshoot, which is what the clinicians saw the next day. This hyperglycemia would be expected to be accompanied by ketosis or possibly even ketoacidosis, because it is caused by vigorous gluconeogenesis.

Shah and Isley's patient did not consume alcohol. However patients on low carbohydrate diets are more prone than persons on a normal diet to hypoglycemia, especially if they exercise or if they suddenly ingest an easily absorbable form of carbohydrate (Koeslag et al. J. Physiol. (Lond) 1982, 325:363 - 376, and Adams et al. J. Physiol. (Lond) 1982, 1987, 386:439-454). The ingestion of sugar in such persons seems to induce a reactive hypoglycemia. The reaction to the hypoglycemia might then be the same as that caused by alcohol consumption.

If the syndrome described by the present authors is not due to an overcompensation to a hypoglycemic attack, then clinicians who see such cases in the future should enquire about any other changes in habit/consumption that occurred in the hours before the presentation of symptoms. It is possible that a common denominator will be discovered, which patients need to be warned about if they go on to these low carbohydrate diets.

Revisions necessary for publication

1. I think that the term hyperglycemic should prefix "ketoacidosis" whenever it is
mentioned in this article.

2. The second paragraph of the discussion contains some inaccuracies, and awkward grammar. The first sentence should, for instance read: "Low-carbohydrate, fat-rich meals stimulate glucagon secretion, lower insulin secretion, and increase insulin resistance [4,5]." The second, and subsequent sentences give a wrong impression. When carbohydrate intake is restricted, liver glycogen is used up within 24 hours. After that the blood sugar concentration is maintained by gluconeogenesis alone. Muscle glycogen cannot be "mobilized" to maintain the blood sugar level. It is trapped in the muscle cells, which do not contain the enzyme glucose-6-phosphatase. This enzyme releases glucose from glucose-6-phosphate, the breakdown product of glycogenolysis. The body "derives energy" from glucose and fat metabolism, and not from gluconeogenesis (which consumes energy to produce glucose from non-carbohydrate precursors). The sentence about glycolysis generating citrate which limits beta-oxidation... reducing ketogenesis [4], while true, is irrelevant in this discussion. The ketosis is caused by the removal of oxaloacetate from the liver mitochondria for gluconeogenic purposes, leading to an inability to form citrate. Acetyl CoA from fatty acid beta-oxidation is then turned by the liver into ketone bodies.

3. The abstract makes mention of "elevated concentrations of lactate". This is not mentioned amongst the findings in the main body of the article, nor is it referred to again. If there was indeed a lactacidemia, then this would strengthen the argument that the symptoms were caused by an overreaction to an earlier bout of hypoglycemia. The epinephrine released triggered by the hypoglycemia would stimulate muscle glycogenolysis, with the production of lactate, which escapes into the blood.

What next?: Accept after minor revisions

Quality of written English: Needs some language corrections before being published