

Monocarboxylate Transporter 1 Deficiency and Ketone Utilization

TO THE EDITOR: Van Hasselt et al. (Nov. 13 issue)¹ state that fasting, by increasing ketogenesis, is the usual precipitating condition for ketoacidosis in monocarboxylate transporter 1 (MCT1) deficiency through an increase in ketone-body levels when utilization is impaired. Fasting, or actually carbohydrate restriction,² works principally through reduced insulin levels and elevated free fatty acid levels, which foster ketogenesis.³ When insulin levels are sufficiently low to permit ketone-body production, increased glucagon levels further stimulate ketogenesis.³ However, the authors also list the catabolic stress of infection as another common precipitant, suggesting that infection increases ketogenesis. It is more likely that the accompanying anorexia and low carbohydrate intake are the primary factors with regard to infection, because insulin levels are stimulated by infection and ketogenesis is impaired.⁴ This is an important distinction, because ketogenesis can be easily prevented by the intake of small amounts of simple sugar during the prodrome and progression of infectious illness. Furthermore, the greater susceptibility to ketoacidosis in MCT1 deficiency with younger age may be related to the greater susceptibility to ketogenesis with fasting, which correlates inversely with age.⁵

Bruce R. Bistrian, M.D., Ph.D.

Beth Israel Deaconess Medical Center
Boston, MA
bbistria@bidmc.harvard.edu

No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1415111

TO THE EDITOR: Van Hasselt and colleagues report a ketoacidosis phenotype in carriers of null mutations in *SLC16A1*, encoding MCT1. They do not establish that loss of MCT1 directly impairs the ability of peripheral tissues to take up β -hydroxybutyrate or acetoacetate. It is conceivable that loss of MCT1 expression indirectly leads to ketoacidosis by altering the production of ketones — for example, by altering the delivery of branched-chain amino acid catabolites (ketoacids), which are major ketogenic substrates particularly in infants and children, to the liver.^{1,2} Have the authors assessed β -hydroxybutyrate or acetoacetate uptake and catabolism in fibroblasts cultured from the study patients? At present, we would conclude from the hyperketonemic phenotype of the patients described only that MCT1 is not the major hepatic exporter of ketone bodies in humans. On the basis of my laboratory's zebrafish genetic studies of a null mutant of the orthologous gene *slc16a6a*, I suspect that human *SLC16A6* (encoding MCT7) is the major hepatic ketone-body exporter.³ I await identification and characterization of humans with *SLC16A6* mutations.

Amnon Schlegel, M.D., Ph.D.

University of Utah School of Medicine
Salt Lake City, UT
amnons@u2m2.utah.edu

No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1415111

THE AUTHORS REPLY: Bistrian suggests that the deep ketoacidosis precipitated by infections in patients with an MCT1 deficiency is the consequence of a low carbohydrate intake per se, rather than catabolic stress. This would imply that small amounts of simple sugar would suffice to prevent or reverse ketoacidosis. The clinical histories of our patients do not support this notion.

As shown in Figure S2B and S2C in the Supplementary Appendix of the article (available at NEJM.org), there was no clear relation between glucose levels and the depth of ketoacidosis. Glucose levels actually were within the normal range (>4 mmol per liter) during most documented events. Ketoacidotic events were generally associated with reduced, but not absent, caloric intake, and events could be stopped only by supplying ample amounts of carbohydrates, in excess of the basal energy requirement. Our observations are in line with those in several other inborn errors of intermediary metabolism: metabolic derangements occur if — and are maintained as long as — the energy requirements are not met.¹ The energy requirement is known to be elevated during infections and to decrease with age,¹ providing an explanation for both risk factors.

We believe that our data are consistent with the concept that the metabolic derangement (i.e., ketoacidosis) is maintained as long as the body senses a low cellular energy status in peripheral tissues, regardless of the plasma glucose values. Under these low-insulin conditions, glucagon levels probably reflect a low cellular energy status. In patients with low insulin levels owing to diabetes mellitus, glucagon excretion correlates with the depth of ketoacidosis,² and ketoacidosis can be prevented by blocking the excretion of glucagon.³

Schlegel suggests that the profound ketoacidosis observed in our patients may be an indirect effect of disturbances in the production,

rather than utilization, of ketones. Following that line of reasoning, the loss-of-function mutations found in our patients would be expected to result in decreased import of substrates and, thus, decreased ketone formation. This would, in turn, lead to hypoketosis on fasting, not hyperketosis — a situation similar to the biochemical findings in ketogenesis defects and, perhaps, in a defect of ketone export. Even if the mutations would somehow lead to increased import, given the endocrine control of ketogenesis, that would have mild-to-moderate effects on ketones, at best.

Peter M. van Hasselt, M.D., Ph.D.

University Medical Center
Utrecht, the Netherlands

Sacha Ferdinandusse, Ph.D.

Academic Medical Center
Amsterdam, the Netherlands

Gijs van Haaften, Ph.D.

University Medical Center
Utrecht, the Netherlands
g.vanhaaften@umcutrecht.nl

Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1415111

Management of Withdrawal Delirium (Delirium Tremens)

TO THE EDITOR: The review by Schuckit (Nov. 27 issue)¹ of the management of delirium tremens offers the reader a concise lesson in pharmacologic treatment of this medical problem. I would caution those who refer to the lorazepam regimens in Table 3 of the article that the doses outlined may provide an amount of propylene glycol in excess of 25 mg per kilogram per day, the amount considered safe by the World Health Organization.² Lorazepam injection contains only small amounts of propylene glycol, yet when given at high doses continuously or for prolonged periods, the patient exposure may be substantial.

Metabolic acidosis may develop owing to propylene glycol accumulation, particularly in patients with preexisting renal or hepatic insufficiency. Several investigators have determined that high doses of lorazepam (i.e., >0.1 mg per kilogram per hour), particularly when given as continuous infusions for treatment of alcohol withdrawal for periods of 24 to 48 hours, are associated with propylene glycol levels of more than 25 mg per deciliter.³⁻⁵ Those of us who treat alcohol withdrawal should remain alert to the possibility of this toxicity when administering high-dose lorazepam.