Komalben Parmar*, Maua Mosha, David A. Weinstein and Rebecca Riba-Wolman

Fasting ketone levels vary by age: implications for differentiating physiologic from pathologic ketotic hypoglycemia

https://doi.org/10.1515/jpem-2022-0589
Received November 18, 2022; accepted April 20, 2023;
published online May 11, 2023

Abstract

Objectives: Ketone production is a physiological phenomenon that occurs during beta-oxidation of free fatty acids. Distinguishing physiologic ketosis from pathologic over-production/underutilization of ketones is critical as part of the diagnostic evaluation of disorders of carbohydrate metabolism, but there is limited literature on normal ketone production with fasting. Our aim is to measure fasting serum beta-hydroxybutyrate (BHB) concentrations in healthy children after an overnight fast.

Methods: Children ≤18 years of age were prospectively recruited from elective procedures through our surgery centers. Exclusion criteria included a history of diabetes, hypopituitarism, adrenal, metabolic or inflammatory disorders, dietary restrictions, trauma, or use of medications that might affect blood glucose. Serum glucose, cortisol, and BHB were assessed after an overnight fast.

Results: Data from 94 participants (mean 8.3 ± 5.7 years, 54 % male, 46 % female, were analyzed. Children ≤3 years of age (19) have significantly higher mean (0.40 ± 0.06 mmol/L) and median (0.4, IQR 0.2–0.6 mmol/L) BHB concentrations compared to children >3 years of age (75) with mean (0.21 ± 0.02 mmol/L) and median BHB (0.1, IQR 0.1–0.2 mmol/L) ($p<0.0001$). Fasting BHB levels of >1.0 mmol/L was rare (2 %, N=2) and 74 % (N=70) of participants had BHB levels <0.3 mmol/L.

Conclusions: BHB concentrations are significantly higher in young children (≤3 years of age) compared to older children. Fasting BHB levels >1.0 mmol/L are rare within our population and therefore may identify a value above which there may a greater concern for pathologic ketotic hypoglycemia. It is imperative to establish the normative range in children to differentiate physiological from pathological ketotic hypoglycemia.

Keywords: beta-hydroxybutyrate; fasting ketosis; ketotic hypoglycemia; pathologic ketotic hypoglycemia; pediatrics, idiopathic ketotic hypoglycemia; physiological ketotic hypoglycemia.

Introduction

Ketone productionis a physiological phenomenon which results from beta-oxidation of free fatty acids. Ketones are a critical alternative energy source for the brain, skeletal muscle, cardiac muscle during fasting and periods of hypoglycemia [1]. Ketone bodies consist of acetone, acetoacetate and beta-hydroxybutyrate (BHB). In prolonged fasting states, BHB may comprise up to 78 % of total ketones [2]. The presence and degree of elevation or suppression of ketone levels are necessary to guide the diagnostic evaluation of hypoglycemia [3, 4]. Ketone formation is part of normal physiologic glucose homeostasis. In the context of illness, young children can develop both hypoglycemia and elevated ketone levels. This has traditionally been considered a part of the spectrum of normal response and identified as “idiopathic ketotic hypoglycemia”. This is a diagnosis of exclusion, and therefore, testing must be done to eliminate metabolic/endocrine diseases as the cause of pathologic ketosis. Yet, misdiagnosis of many metabolic disorders, including ketotic glycogen storage diseases, as a physiologic/idiopathic ketotic hypoglycemia can and does occur. Diseases of pathologic ketotic hypoglycemia can have euglycemic ketosis representing progressive metabolic stress prior to the development of hypoglycemia (ref). An improved understanding of normal ketogenesis may help distinguish normal physiologic ketosis from excessive ketone formation due to pathology [5–8]. Defining more

***Corresponding author: Komalben Parmar**, MD, Department of Pediatric Endocrinology, Connecticut Children Medical Center, Hartford, CT, 06109, USA; and Department of Pediatrics, University of Connecticut School of Medicine, 505 Farmington Avenue, Farmington, CT, 06032, USA, Phone: 860-837-6700, E-mail: drkomal.parmar87@gmail.com

Maua Mosha, Department of Research, Connecticut Children Medical Center, Hartford, CT, USA

David A. Weinstein, Department of Pediatrics, University of Connecticut School of Medicine, Farmington, CT, USA

Rebecca Riba-Wolman, Department of Pediatric Endocrinology, Connecticut Children Medical Center, Hartford, CT, USA; and Department of Pediatrics, University of Connecticut School of Medicine, Farmington, CT, USA

effective testing strategies and tools to identify the children presenting with an initial episode ketotic hypoglycemia that have underlying metabolic disorders has significant implications for safety, treatment and cost.

The essential first step to this process is to accurately describe fasting ketone levels in healthy children.The majority of studies regarding ketone assays, "normative" values or factors affecting those values have been done in animals [9, 10], adults [11] and patients with diabetes [12].

Previous studies in children [13–17] have described the distribution of serum ketones in healthy children as they relate to age, blood glucose and duration of fast. These studies are the current basis for the use of quantitative serum ketone measurements in the diagnostic evaluation of pediatric hypoglycemia. Yet, these studies are limited by small numbers of patients, particularly with minimal to no inclusion of young children who represent the most frequent population of those presenting with ketotic hypoglycemia [13–16]. Further limitations to utilize these studies are that they do not reflect current methods of BHB measurement including latest serum measurement of BHB, ability to separate BHB accurately from other ketone bodies and use of currently available point of care testing (POCT) [18, 19]. Utilizing data on fasting ketosis in populations undergoing evaluation for suspected hypoglycemic disorders cannot be used to represent healthy children [17, 20]. In addition, the values are generated via prolonged controlled observed fasts, which are costly and have safety risks.They do not represent values from potential home testing under real life daily fasting conditions.

It is imperative to understand the ketone levels, and factors influencing them, in healthy children to be able to differentiate physiologic vs. pathologic ketosis. This understanding will then provide the basis for identifying children with ketotic hypoglycemia disorders. We aim to describe the distribution of BHB across a pediatric population and the correlation with age, glucose, cortisol, BMI and fasting duration.

Materials and methods

Patient selection

The Institutional Review Board (IRB) of Connecticut Children's Medical Center approved this study. 100 participants were recruited from those scheduled to undergo elective surgeries at Connecticut Children's main campus and ambulatory surgical centers from July 1, 2020 until November 31, 2020 in cooperation with the surgical departments of Otolaryngology, Orthopedics, Urology and General Surgery. Children of ≤18 years of age undergoing elective surgeries per standard operating protocol (tonsillectomy and/or adenoidectomy, circumcision (new or revision), meatotomy, hernia repair, hydrocele repair, varicocele repair, orchiopexy, hypospadias repair, non-acute orthopedic surgeries) who required peripheral intravenous (IV) line placement were eligible. Ability and willingness to provide written informed consent from a legal guardian was necessary for study participation. Assent of a participant was sought when appropriate based on age and cognitive status. Children with serious medical and/or surgical conditions with co-morbidities, diabetes, metabolic or mitochondrial disorders, adrenal gland disorders, suspected or diagnosed hypopituitarism, emergency surgeries, dietary restrictions or those on specialized diets (e.g. ketogenic diet), a history of enteral or parenteral steroid use in the previous 30 days, and those who drank any carbohydrate containing liquid on the day of surgery were excluded from participation.

Study protocol

Our team obtained IRB approval to contact the legal guardian(s) of potential eligible participants prior to surgery and provided a brief description of the study to determine willingness to participate. Interested participants and their legal guardian(s) met the investigator in the pre-operative area where informed written consent was obtained. At the time of IV placement (before intravenous fluid administration), 3–4 mL of whole blood was collected. POCT BHB was performed immediately (0.5 mL of unclotted whole blood at room temperature). The blood was collected in gold top serum separator tube. To allow for clot formation the samples was upright for 30 min at room temperature prior to centrifugation for 15 min at 3,000 RPM (equivalent to 1,008 RCF). Once centrifuged, serum was transported at room temperature within 12 h and processed within 24 hrs of the blood collection at University of Connecticut Health Center, Department of Laboratory and Pathology Medicine. In addition to the sample of whole blood, participant demographic information was collected, including age, procedure performed, current medical diagnosis, date and time of last food/drink ingested, medication history, anthropometrics (height (cm), weight (kg), BMI (kg/m^2)), and BMI standardized for age (*z*-score)) and date and time of blood collection.

POCT BHB measurements were performed using a Precision Xtra Meter (Abbott Pharmaceuticals), which displays BHB concentrations to a tenth of a unit in mmol/L, with a reported assay range of 0 to more than 8 mmol/L. It uses an enzymatic measurement with hydroxybutyrate dehydrogenase (HBDH). Precision XTRA meter was calibrated with abbot medisense glucose & ketone control solutions per manufacturer instructions. Serum BHB was measured by an Abbott Architect Chemistry System using the same method of enzymatic measurement with Beta-hydroxybutyrate dehydrogenase at CLIA certified lab. Serum glucose was measured by spectrophotometry and serum Cortisol was measure by Chemiflex immunoassay (Abbott Architect ChemistrySystem) at CLIA certified lab. Coefficient of Variation (COV) for laboratory method for serum BHB is 0.99 and Precision Xtra ketone meter is 0.96 [21]. Serum glucose was measured by spectrophotometry. Serum Cortisol was measure by Chemifleximmunoassay (Abbott Architect ChemistrySystem).

Statistical analysis

Baseline characteristics and primary outcomes were analyses using mean (±SD) and or median (IQR). Spearman rank correlation was used for correlation analysis. A p-value of less than 0.05 was considered

statistically significant. For non-normal distributed continuous data, for ordinal data, or for data with relevant outliers, a Spearman rank correlation is used as a measure of a monotonic association. Serum BHB in different age groups (≤3 vs. >3 years) were analyzed using Mann-Whitney U Test. Age groups were defined based on previous study [14].

Results

Of the 100 participants recruited for our study six were excluded from analysis (4 did not meet the inclusion/exclusion criteria and for 2 all samples were not collected). Samples of 94 participants were analyzed. See Table 1 for baseline characteristics of the participants. The age of the participants ranged from 6 months to 18.7 years with median (IQR) of 5.9 (3.6–13.6) years. 50 % (47/94) of patients received medication (n=26 acetaminophen, n=8 supplements, n=3 epilepsy medication, n=3 allergy medication, n=2 psychiatric medications, n=2 antacids, n=1 for antibiotic, stimulant, and anti-inflammatory non-steroid medication like ibuprofen). Serum BHB ranged from 0 to 1.2 mmol/L. Serum glucose ranged from 70 to 121 mg/dL. The rest of primary outcomes are listed in Table 2.

Table 1: Baseline characteristics of participants.

	n=94, (%)	Mean ± SD
Age, Years		8.3 ± 5.7
BMI, Kg/m^2		19.3 ± 5.2
Standardized BMI (Z score)		0.50 ± 1.1
Duration of fast, hours		12.5 ± 2.4
Sex		
Male	51 (54.3)	
Female	43 (45.7)	
Type of procedure		
Otolaryngology	43 (46)	
Orthopedic	20 (21)	
Urology	16 (17)	
General surgery	15 (16)	
Race		
White	60 (64)	
African American	13 (13)	
Asian	4 (4)	
Native Hawaiian or PI	1 (1)	
Others	10 (10)	
Refused	5 (5)	
Unknown	1 (1)	
Ethnicity		
Non-hispanic	74 (79)	
Hispanic	16 (17)	
Refused	3 (3)	
Unknown	1 (1)	

Table 2: Measured primary outcome.

Variable (unit)	Mean ± SD	Median (IQR)
Serum BHB, mmol/L	0.25 ± 0.23	0.15 (0.10–0.40)
POCT BHB, mmol/L	0.18 ± 0.20	0.10 (0.10–0.20)
Serum glucose, mg/dL	90 ± 9.5	89 (83–95)
Serum cortisol, mg/dL	9.4 ± 4.6	9.0 (6.4–11.6)

We have found statistically significant but weak negative correlations between serum BHB and age (r_s=−0.345, p 0.001) (Figure 1). We found that BHB values vary by age in our pediatric group. Strikingly, young children ≤3 years of age (19/94) have significantly higher mean (0.40 ± 0.06 mmol/L) and median (0.4, IQR 0.2–0.6 mmol/L) compared to older children >3 years of age (75/94) with mean (0.21 ± 0.02 mmol/L) and median BHB (0.1, IQR 0.1–0.2 mmol/L) (Mann-Whitney U Test, p value <0.0001) (Figure 2). We found only 2 % (n=2) of participants had fasting ketone values more than 1.0 mmol/L and 74 % (n=70) had fasting ketone values <0.3 mmol/L. Those two participants' baseline characteristic includes age 4.8 and 6.5 years with BMI percentile 23.5 %tiles (BMI Z score: −0.72) and 50 %tile (BMI Z score: 0.01), fasting duration 13.2 hrs and 14.1 hrs. There was no defined carbohydrate metabolic disorder in those 2 participants.

We have found statistically significant but weak negative correlations between serum BHB and serum glucose (r_s=−0.258, p 0.0012) (Figure 3) and serum BHB and standardized BMI (r_s=−0.372, p<0.001). Correlation between serum BHB and fasting duration was found to be statistically significant weak positive (r_s=0.247, p 0.0016) (Figure 4). With partial correlation to control for standardized BMI, age, glucose and fasting duration, p values or correlation coefficient did not change further. Due to known effect of cortisol levels on blood sugar levels, correlation between serum cortisol and serum BHB was analyzed and no significant correlation was found. Serum BHB and POCT BHB were measured in every sample and demonstrated similar findings. We have previously demonstrated the concordance between serum BHB and home POCT meters [19].

Discussion

We demonstrated an inverse correlation of BHB levels with age in a fasting pediatric population (Figure 1). There is a significant difference in fasting BHB values in the less than 3-year-old age group compared to those between the ages of 3 and 18 years (Figure 2). Pediatric patients, particularly in

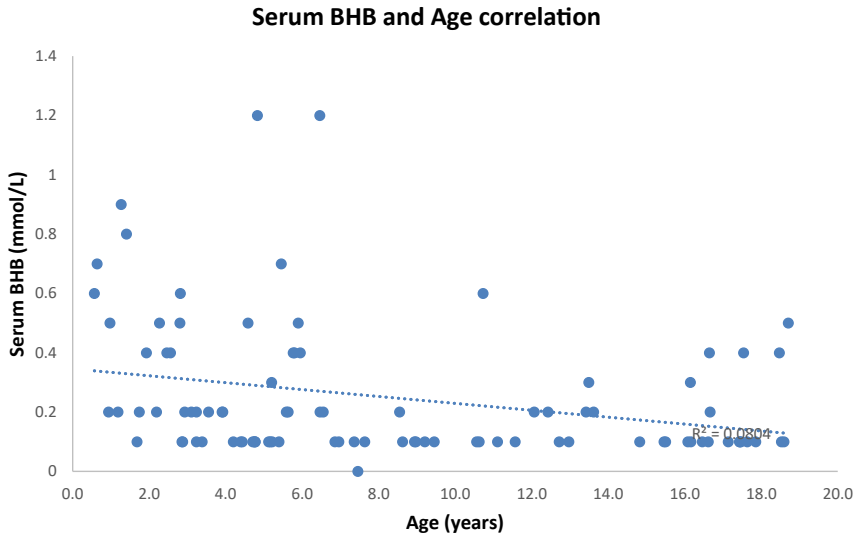

Figure 1: Correlation coefficient (*r*) of −0.345 (low negative correlation) p value <0.01 level (2-tailed) using Spearman's rank.

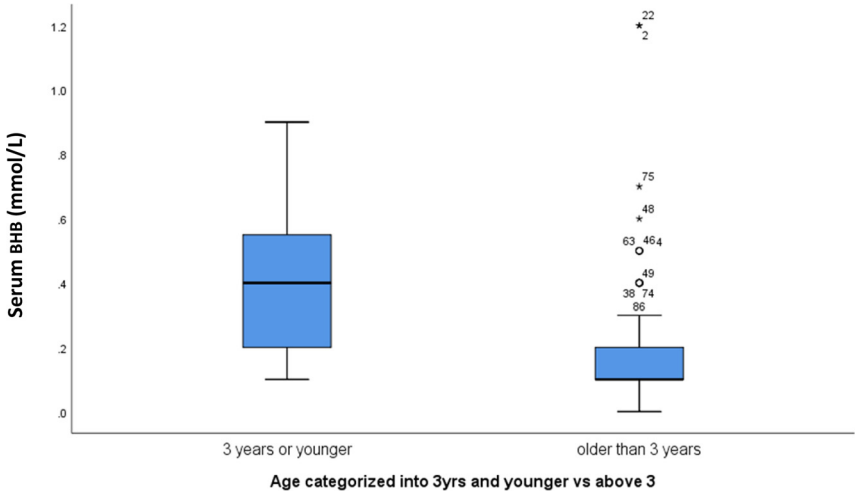

Figure 2: Serum BHB values for ≤3 years and >3 years of age p value <0.0001 using Mann-Whitney U test.

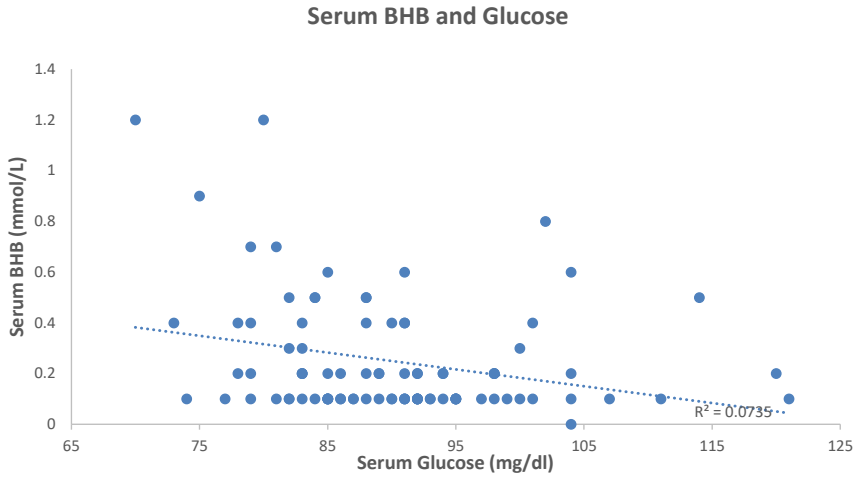

Figure 3: Correlation coefficient (*r*) of −0.258 (low negative correction) p value <0.05 using (2-tailed) using Spearman's rank.

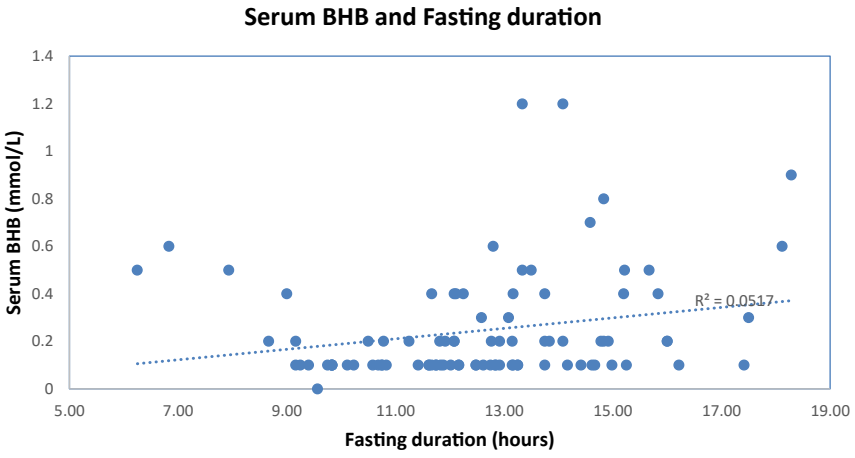

Figure 4: Correlation coefficient (*r*) of 0.247 (low positive correlation) p value <0.05 (2-tailed) using Spearman's rank.

younger age groups, can present with ketosis (associated with hypoglycemia or euglycemia) in the context of poor oral intake or illness. When associated with hypoglycemia, this is referred to as ketotic hypoglycemia. With this initial presentation it can be unclear if this is a normal physiologic response to a pathologic process (illness or under-nutrition) vs. the first presentation of an underlying metabolic or endocrine disorder. In our study, most children with overnight fast rarely (2 %, n=2) had ketone values more than 1.0 mmol/L and 74 % (n=70) of children had ketone values <0.3 mmol/L. We propose, that this represents a high likelihood of having a pathological cause with a value higher than 1.0 after an overnight fast. A future larger scale study can define age appropriate ranges to differentiate physiologic vs. pathologic ketotic hypoglycemia.

There is a wide spectrum of severity, associated metabolic features and age of medical presentation of a disorder of hypoglycemia. The most severe forms generally will present early in life [22]. The spectrum can encompass disorders that can be undiagnosed for years despite serious, potentially lifelong, effects including seizures, developmental delays and behavioral problems [23]. "Milder" hypoglycemic disorders have been diagnosed after repeated presentation with "presumed physiologic" ketotic hypoglycemia following years of management of resultant disorders [24] While ketosis in these conditions often protects the children from neuroglycopenic symptoms like seizures and neurologic injury, the chronic ketosis can be associated with poor growth, recurrent vomiting, hospitalizations, and osteoporosis. The ketotic forms of glycogen storage disease (GSD 0, III, VI, and IX), in particular, will present with ketosis and hypoglycemia after an overnight fast, and the information generated form this study may form the foundation for distinguishing physiologic from pathologic ketosis.

Previous studies [13–16] have done fasting studies to look at metabolic parameters of healthy children. This has established the necessity of BHB levels in the evaluation of hypoglycemic disorders. Our findings of mean serum BHB and inverse relationship by age are in line with these studies. These studies are limited by small sample sizes, paucity of inclusion of the highest frequency of patients presenting with ketotic hypoglycemia (infants and toddlers) and limitation in interpretability with modern laboratory and POCT based assays. The basis of evaluation for disorders of hypoglycemia is analysis of a critical sample (laboratory testing done at thetime of hypoglycemia), which often requires a fasting study to obtain. Although fasting studies have significant sensitivity [25], they are costly (hospital admission, close monitoring, and frequent laboratory testing) and have potential medical risk of seizures and metabolic stress. The expansion of genetic testing has added a potential, but costly, alternative to a fasting study based on wider access to broad panels for hypoglycemic disorders [26] and potential avoidance of diagnostic fasting studies. The ability to stratify and focus the need for these costly or medically intensive evaluations outpatient or home based screening would have a significant impact to the field in reducing cost and improving safety. For patients who ultimately need admission for a fasting study, BOHB values earlier in the process (i.e. before hypoglycemia) that could differentiate pathologic disease vs. physiologic process would improve the safety of the test.

Our study has the potential limitation that it may not fully represent the healthy general population, given that subjects were selected from a cohort of elective surgeries. To minimize the selection bias, we avoided elective surgeries that could have a higher proportion of patients with underlying inflammation or illness. Furthermore, we avoided children on medications that have known effects

on glucose metabolism (for example: steroids, insulin). An additional limitation is that the fasting duration is by patient report, and we do not have reliable content of the pre-fasting meal, exercise on the previous day. Although not a "controlled prolonged fast" the results are representative of home overnight fasting and therefore may represent a safer screening to evaluate for euglycemic ketosis prior to the development of hypoglycemia.

Currently the ability to differentiate the physiological from pathological causes in children with ketotic hypoglycemia is lacking. Through our study finding, we are able to demonstrate that fasting ketones >1.0 mmol/L is uncommon in this pediatric population. This suggests that values >1.0 mmol/L (in routine overnight fast of 6–16 hrs) may indicate a higher likelihood of pathological ketosis. Further study to assess the ketone levels in children with pathologic ketosis/ketotic hypoglycemia will support defining range limits.The ability to quickly and easily identify children with ketotic hypoglycemia disorders that may be "mild" based on lack of easily identifiable signs of an underlying metabolic/hormonal disorder, will have significant implications for a child's health, development and behavior. Our study is the first step in defining the need for age based normative values for BHB to help differentiate physiological from pathological causes of ketotic hypoglycemia.

Acknowledgments: We thank Ketotic Hypoglycemia International (KHI) organization for financial support for Open Access publication of this article. We express our gratitude to our colleagues in department of surgery, department of anesthesia, and the operating room clinical staff who provided support for this study. We also thank Dr. Monika Williams, a pediatric resident at Connecticut Children's Medical Center, for her assistance with study recruitment. We express our gratitude to Dr. Christine Trapp for her assistance with reviewing and editing this manuscript.

Research funding: This research was supported by Connecticut Children's Medical Center. This work is a part of a fellow's scholarly work product in a three-year fellowship program. The author(s) confirm(s) independence from the sponsors; the content of the article has not been influenced by the sponsors.

Author contributions: Komalben Parmar, David A. Weinstein, and Rebecca Riba-Wolman have significantly contributed to all aspects of this study, including conception and design of the study, interpretation of data, and manuscript preparation. Komalben Parmar consented participants, collected demographic data, as well as being responsible for collecting and preparing the laboratory samples. Maua Mosha has contributed extensively to data analysis and statistical interpretation of the results section. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

Informed consent: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). This research was approved by the Institutional Board Review of our institution. Informed consent of the legal guardian and/or participant was obtained prior to participation in the study.

Ethical approval: This research was approved by the Institutional Board Review of our institution.

Employment or leadership: Komalben Parmar, Maua Mosha, David A Weinstein and Rebecca Riba-Wolman: None declared.

Honorarium: Komalben Parmar, Maua Mosha, David A Weinstein and Rebecca Riba-Wolman: None declared.

Data availability: Data can be available on a reasonable request from authors.

References

1. Millar R, Harding A. Review article: accelerated starvation of childhood: have I judged ketones? EMA – Emerg Med Australas 2019; 31:314–20.
2. Vanelli M, Mastrorilli C, Fainardi V, Iovane B, Scarabello C, Veronese P, et al. Clinical utility of beta-hydroxybutyrate measurement in the management of physiological ketosis at home in children under 5. Acta Biomed 2019;90:215–20.
3. Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics 2011;127:575–9.
4. Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, et al. Recommendations from the pediatric endocrine society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. J Pediatr 2015;167:238–45.
5. Hoogeveen IJ, van der Ende RM, van Spronsen FJ, de Boer F, Heiner-Fokkema MR, Derks TGJ. Normoglycemic ketonemia as biochemical presentation in ketotic glycogen storage disease. JIMD Rep 2016;28: 41–7.
6. van Hasselt PM, Ferdinandusse S, Monroe GR, Ruiter JPN, Turkenburg M, Geerlings MJ, et al. Monocarboxylate transporter 1 deficiency and ketone utilization. N Engl J Med 2014;371:1900–7.
7. Pershad J, Monroe K, Atchison J. Childhood hypoglycemia in an urban emergency department: epidemiology and a diagnostic approach to the problem. Pediatr Emerg Care 1998;14:268–71.
8. Haymond MW, Karl IE, Clarke WL, Pagliara AS, Santiago JV. Differences in circulating gluconeogenic substrates during short-term fasting in men, women, and children. Metabolism 1982;31:33–42.
9. Ratanapob N, VanLeeuwen J, McKenna S, Wichtel M, Rodriguez-Lecompte JC, Menzies P, et al. Evaluation of the Precision Xtra meter for monitoring blood β-hydroxybutyrate concentrations in late-gestation ewes. J Vet Diagn Invest 2019;31:17–22.

10. Sailer KJ, Pralle RS, Oliveira RC, Erb SJ, Oetzel GR, White HM. Technical note: validation of the BHBCheck blood β-hydroxybutyrate meter as a diagnostic tool for hyperketonemia in dairy cows. J Dairy Sci 2018;101: 1524–9.
11. Foster KJ, Alberti KG, Hinks L, Lloyd B, Postle A, Smythe P, et al. Blood intermediary metabolite and insulin concentrations after an overnight fast: reference ranges for adults, and interrelations. Clin Chem 1978;24: 1568–72.
12. Kurup PM, Rameshkumar R, Soundravally R, Satheesh P. Capillary versus serum b-hydroxybutyrate in pediatric diabetic ketoacidosis. Indian Pediatr 2019;56:126–9.
13. Lamers KJ, Doesburg WH, Gabreëls FJ, Romsom AC, Renier WO, Wevers RA, et al. Reference values of blood components related to fuel metabolism in children after an overnight fast. Clin Chim Acta 1985;145: 17–26.
14. Saudubray JM, Marsac C, Limal JM, Dumurgier E, Charpentier C, Ogier H, et al. Variation in plasma ketone bodies during a 24-hour fast in normal and in hypoglycemic children: relationship to age. J Pediatr 1981;98:904–8.
15. Wolfsdorf JI, Sadeghi-Nejad A, Senior B. Fat-derived fuels during a 24-hour fast in children. Eur J Pediatr 1982;138:141–4.
16. Chaussain JL, Georges P, Olive G, Job JC. Glycemic response to 24-hour fast in normal children and children with ketotic hypoglycemia: II. Hormonal and metabolic changes. J Pediatr 1974;85:776–81.
17. Bonnefont JP, Specola NB, Vassault A, Lombes A, Ogier H, de Klerk JB, et al. The fasting test in paediatrics: application to the diagnosis of pathological hypo- and hyperketotic states. Eur J Pediatr 1990;150: 80–5.
18. Williamson DH, Mellanby J, Krebs HA. Enzymic determination of D(−)-beta-hydroxybutyric acid and acetoacetic acid in blood. Biochem J 1962;82:90–6.
19. Parmar K, Mosha M, Weinstein DA, Riba-Wolman R. Method comparison of beta-hydroxybutyrate point-of-care testing to serum in healthy children. JIMD Reports 2021;62:85–90.
20. van Veen MR, van Hasselt PM, de Sain-van der Velden MGM, Verhoeven N, Hofstede FC, de Koning TJ, et al. Metabolic profiles in children during fasting. Pediatrics 2011;127:e1021–7.
21. Bach KD, Heuwieser W, McArt JAA. Technical note: comparison of 4 electronic handheld meters for diagnosing hyperketonemia in dairy cows. J Dairy Sci 2016;99:9136–42.
22. Weinstein DA, Steuerwald U, De Souza CFM, Derks TGJ. Inborn errors of metabolism with hypoglycemia: glycogen storage diseases and inherited disorders of gluconeogenesis. Pediatr Clin 2018;65:247–65.
23. Drachmann D, Hoffmann E, Carrigg A, Davis-Yates B, Weaver V, Thornton P, et al. Towards enhanced understanding of idiopathic ketotic hypoglycemia: a literature review and introduction of the patient organization, Ketotic Hypoglycemia International. Orphanet J Rare Dis 2021;16:173.
24. Brown LM, Corrado MM, van der Ende RM, Derks TGJ, Chen MA, Siegel S, et al. Evaluation of glycogen storage disease as a cause of ketotic hypoglycemia in children. J Inherit Metab Dis 2015;38:489–93.
25. Morris AA, Thekekara A, Wilks Z, Clayton PT, Leonard JV, Aynsley-Green A. Evaluation of fasts for investigating hypoglycaemia or suspected metabolic disease. Arch Dis Child 1996;75:115–9.
26. Ponzi E, Maiorana A, Lepri FR, Mucciolo M, Semeraro M, Taurisano R, et al. Persistent hypoglycemia in children: targeted gene panel improves the diagnosis of hypoglycemia due to inborn errors of metabolism. J Pediatr 2018;202:272–8.e4.

Supplementary Material: This article contains supplementary material (https://doi.org/10.1515/jpem-2022-0589).