Breath acetone is a reliable indicator of ketosis in adults consuming ketogenic meals1-3

Kathy Musa-Veloso, Sergei S Likhodii, and Stephen C Cunnane

ABSTRACT
Background: Ketogenic diets are used therapeutically to treat intractable seizures. Clinically, it appears that the maintenance of ketosis is crucial to the efficacy of the diet in ameliorating seizures. To understand how ketosis and seizure protection are related, a reliable, noninvasive measure of ketosis that can be performed frequently with minimal discomfort is needed.
Objective: The objective was to determine which index, breath acetone or urinary acetoacetate, is more strongly related to the plasma ketones acetoacetate and β-hydroxybutyrate.
Design: After fasting overnight for 12 h, 12 healthy adults consumed 4 ketogenic meals over 12 h. Blood, breath, and urine samples were collected hourly. Blood was analyzed for plasma acetoacetate and β-hydroxybutyrate, breath for acetone, and urine for acetoacetate.
Results: By the end of the 12-h dietary treatment, plasma acetoacetate, plasma β-hydroxybutyrate, and breath acetone had increased 3.5-fold, whereas urinary acetoacetate increased 13-fold when measured enzymatically and 25-fold when measured with urinary ketone dipsticks. Plasma acetoacetate was best predicted by breath acetone ($R^2 = 0.70, P < 0.0001$). Plasma β-hydroxybutyrate was equally predicted by breath acetone and urinary acetoacetate ($R^2 = 0.54, P = 0.0040$).
Conclusions: Breath acetone is as good a predictor of ketosis as is urinary acetoacetate. Breath acetone analysis is noninvasive and can be performed frequently with minimal discomfort to patients. As an indicator of ketosis in epilepsy patients consuming a ketogenic diet, breath acetone may be useful for understanding the mechanism of the diet, elucidating the importance of ketosis in seizure protection, and ultimately, enhancing the efficacy of the diet by improving patient monitoring. Am J Clin Nutr 2002;76:65-70.

KEY WORDS Ketogenic diet, breath acetone, ketosis, acetoacetate, β-hydroxybutyrate, epilepsy, adults

INTRODUCTION
Epilepsy is a chronic neurologic condition characterized by a predisposition to recurrent, usually spontaneous, seizures. With a prevalence of $\approx 1\%$, epilepsy is the most common chronic neurologic disorder after headache (1) and 20–30% of epilepsy cases are refractory (intractable) or the medications prescribed cause intolerable side effects (2). High-fat ketogenic diets (KDs) are important in the treatment of intractable epilepsy (3–5). In a recent systematic review of the efficacy of the KD, the KD was found to cause a complete elimination of seizures in 16% of children, a >90% reduction in seizures in 32% of children, and a >50% reduction in seizures in 56% of children (6). Although the use of KDs is generally limited to children with refractory seizures, several earlier studies (7–9) and 2 more recent studies (10, 11) document the successful use of the KD in adults with intractable seizures.

The mechanism of the KD is poorly understood. Clinical experience seems to support the hypothesis that a minimum level of ketosis is required to achieve seizure protection, but proof of this hypothesis awaits the opportunity to perform frequent, minimally invasive, reliable assessments of ketone concentrations. The current widely used assays of ketones in blood and urine have drawbacks. Frequent blood sampling is invasive, particularly in children. Urine dipstick analysis is less invasive but is also less reliable (12–16) and urine cannot easily be collected frequently throughout the day. A reliable, noninvasive measure of plasma acetoacetate, β-hydroxybutyrate, or both would therefore be useful in monitoring the efficacy of the KD and in establishing its mechanism of action.

Acetone is a normal breath constituent and is responsible for the sweet odor of the breath of ketogenic individuals. It is produced mainly from the spontaneous decarboxylation of acetoacetate and, to a lesser degree, by the enzymatic conversion of acetoacetate to acetone via the enzyme acetoacetate decarboxylase (EC 4.1.1.4) (17). Breath acetone rises during fasting or the consumption of a KD (18–21). Breath acetone is potentially useful as an indicator of ketosis, but its use has not yet been evaluated in patients with epilepsy consuming a KD. Thus, the main objective of this study was to determine whether breath acetone can be used as an indicator of ketosis in epilepsy patients consuming a KD.
used to predict plasma acetoacetate and β-hydroxybutyrate in healthy adults in acute ketosis. The secondary objective was to compare breath acetone and urinary acetoacetate as measures of mild systemic ketosis. The implication is that a more accurate and sensitive measure of ketosis could be useful in understanding the mechanism of the KD and determining whether seizure control and ketosis are positively related.

SUBJECTS AND METHODS

Subjects

Twelve adults, 6 men and 6 women, participated in this study. The subjects had a mean (±SEM) age of 27 ± 2 y and a BMI (in kg/m²) of 24.7 ± 1.3. None of the subjects were diabetic, pregnant, consuming weight-reducing diets, allergic to dairy products, or lactose intolerant. Each subject was fully informed of the experimental procedures before giving written consent and participating in the study. The study was approved by the Ethical Review Office of the University of Toronto.

Study design

Each participant fasted overnight for 12 h on the night before arriving at the laboratory at 0800. Fasting blood, breath, and urine samples were collected and then each subject was given a liquid ketogenic meal immediately after the collection of the fasting samples and every 3 h thereafter until a total of 4 ketogenic meals were consumed over the 12-h experimental period. Breath, blood, and urine samples were collected hourly, in as close proximity as possible. Subjects were given 125 mL water each hour to promote urination.

Ketogenic meals

Each of the ketogenic meals (g·kg body wt⁻¹·d⁻¹) was identical in composition and energy content (Table 1). The ketogenic meals, with a ketogenic ratio of 3.8:1 (fat:protein + carbohydrate), were composed of 35% whipping cream (Beatrice; Parateck, Canada, Toronto) and protein supplement powder (ProMod; Ross Laboratories, St. Laurent, Quebec). Resting energy requirements for each subject were calculated by using the Harris-Benedict equation (22). Because all of the subjects described themselves as being moderately active, a physical activity factor of 1.3 was used in the calculation of total energy requirements. Altogether, the 4 ketogenic meals furnished the participants with 40% of their total energy requirements because epileptic children consuming a KD are usually fed 75% of their total energy requirements (23).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Macronutrient composition of the ketogenic diet¹</th>
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<tr>
<td>Macronutrient</td>
<td>Contribution from whipping cream</td>
</tr>
<tr>
<td></td>
<td>% by dry wt</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>7.4</td>
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<tr>
<td>Fat</td>
<td>78.5</td>
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<tr>
<td>Protein</td>
<td>4.4</td>
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¹ The ratio of fat:(carbohydrate + protein) = 3.8:1.
² Sum of columns 1 and 2.

Breath sampling and analysis

Breath samples were collected with the use of breath collection bags (EasySampler; Quinton Instrument Company, Milwaukee). Each 500-mL polyethylene bag was equipped with a mouthpiece and a side port for a needle holder (Vacutainer; Becton Dickinson and Co, Orangeburg, NY). The subject exhaled normally through the mouthpiece into the polyethylene bag. Two small perforations in the bag allowed the air to be vented as the subject exhaled. Because approximately the first 150 mL of air in a normal expiration from an adult constitutes dead-space air (24), a breath sample was collected only after the 500 mL polyethylene bag was fully inflated to ensure that the breath sample was alveolar. Once the bag was inflated, a sample of the exhaled air was collected in a 12-mL evacuated glass tube by momentarily perforating its septum with the Vacutainer needle of the breath bag at the end of the expiration. A 1-mL breath sample was then drawn into a glass, gas-tight syringe (Hamilton Company, Reno, NV) and injected into a gas chromatograph for acetone analysis.

Breath acetone concentrations were determined immediately after collection with the use of a gas chromatograph equipped with a flame ionization detector (model 5890; Hewlett Packard Co, Palo Alto, CA). The 1.8-m glass column was packed with 80 (0.177 mm)/100 (0.149 mm) mesh Carbopack (Supelco, Bellefonte, PA). The 3-min chromatographic run was performed at 70°C with helium as the carrier gas at a flow rate of 20 mL/min. The injector temperature was 150°C and the detector temperature was 200°C. The acetone peaks were calibrated with the use of a 54.3-nmol/L aqueous solution of acetone, which was prepared by diluting 2 mL acetone in 500 mL distilled water and diluting 100 µL of this solution in 100 mL distilled water. A 1-µL sample was then injected into the gas chromatograph. The mean (±SEM) CV across triplicate calibrator measurements was 2 ± 1%.

Blood sampling and analysis

Blood was collected from the fingertips. A heating pad or hot water bottle was kept on the hand for 5 min before blood collection to stimulate blood flow. A lancet pen (Glucometer Elite; Bayer, Etobicoke, Toronto) was used to prick the finger; 300 µL blood was collected from the fingertip by applying pressure to the fingertip and collecting the blood in 75-µL heparin-containing capillary tubes. Blood samples were then dispensed into 2.5-mL heparin-containing microfuge tubes.

After the blood samples were centrifuged at 2500 × g for 9 min at 4°C, the plasma was immediately analyzed for β-hydroxybutyrate with an enzymatic assay kit (Sigma, St Louis) and for acetoacetate with a modified enzymatic assay described by Harano et al (25). In brief, 50 µL fresh plasma was added to
386 μL of 0.25 mol triethanolamine buffer/L, 200 μL of 5 g oxamic acid/L, and 100 μL of 3.0 mol NADH/L. A blank (consisting of 50 μL distilled water, 386 μL of 0.25 mol triethanolamine buffer/L, 200 μL of 5 g oxamic acid/L, and 100 μL of 3.0 mol NADH/L) was used as the reference. After the initial absorbance was measured, 20 μL -hydroxybutyrate dehydrogenase (EC 1.1.1.30; activity = 55.6 kU/L; Toyobo Company Ltd, Tokyo) was added and, after 15 min, the final absorbance was measured. Initial and final absorbances were measured at a wavelength of 340 nm. Changes in absorbance were calibrated against a standard curve, which was constructed with the use of lithium acetoacetate and distilled water.

Urine collection and analysis
Urine samples were collected in 50-mL sterilized specimen collection vials. Urine was analyzed immediately for acetoacetate via 2 methods: 1) the modified enzymatic assay of Harano et al (25) and 2) reagent strips for urinary acetoacetate analysis (Ketostix; Bayer, Etobicoke, Canada).

Statistical analysis
For all statistical analyses, SAS software (version 7; SAS Institute Inc, Cary, NC) was used, and significance was set at P < 0.05. To determine whether any of the measurements were significantly different from fasting values, a repeated-measures one-way analysis of variance was performed. A Tukey’s test was then conducted to determine where significant differences existed. A repeated-measures first-order autoregressive multiple linear regression model was used to determine whether any of the measured metabolites were significantly affected by age, BMI, or time. Time was defined as the number of hours after the last ketogenic meal: 0 (fasting), 1, 2, or 3 h. To determine whether urinary acetoacetate measured enzymatically and with the dipsticks were significantly different, a paired t test was conducted. To determine whether breath acetone and urinary acetoacetate were significant predictors of plasma acetoacetate and plasma β-hydroxybutyrate, a repeated-measures nonlinear regression analysis was conducted. The results are expressed as means ± SEMs. The regression equations are given in the figure legends.

RESULTS
Changes in the metabolites
Changes in breath acetone, plasma acetoacetate, plasma β-hydroxybutyrate, and urinary acetoacetate over the 12-h dietary study period are illustrated in Figure 1. By the end of the study, breath acetone increased 3.5-fold (from 33 ± 13 nmol/L at 0 h to 116 ± 19 nmol/L at 12 h). Compared with fasting, breath acetone was significantly elevated after the first ketogenic meal and remained significantly greater at all subsequent time points except at 2 h (P < 0.05).

Plasma acetoacetate and β-hydroxybutyrate increased 3.5-fold over the 12-h day (plasma acetoacetate: from 0.12 ± 0.03 mmol/L at 0 h to 0.42 ± 0.05 mmol/L at 10 h; plasma β-hydroxybutyrate: from 0.18 ± 0.04 mmol/L at 0 h to 0.68 ± 0.10 mmol/L at 10 h). Plasma
Acetoacetate and plasma β-hydroxybutyrate were significantly greater than their respective fasting concentrations 4 h into the study and remained so throughout the rest of the study (P < 0.05). Urinary acetoacetate measured enzymatically increased 13-fold over the 12-h day (from 0.11 ± 0.03 mmol/L at 0 h to 1.40 ± 0.40 mmol/L at 11 h), whereas urinary acetoacetate measured with the dipsticks increased 25-fold (from 0.13 ± 0.04 mmol/L at 0 h to 3.21 ± 0.93 mmol/L at 11 h). Urinary acetoacetate was significantly elevated at 4 h and remained so throughout the rest of the study (P < 0.05). Although there was a significant positive relation between urinary acetoacetate measured enzymatically and with the dipsticks (R² = 0.88, P < 0.0001; Figure 2), the dipsticks significantly overestimated the concentration of acetoacetate in the urine (P < 0.0001). The dipsticks more accurately predicted the concentration of acetoacetate (in mmol/L) in the urine when the following equation was used to correct the dipstick values: urinary acetoacetate = 0.40(dipstick value) + 0.15.

Age and BMI had no significant effects on any of the metabolites that were measured. The time elapsed after each meal had a significant negative effect on plasma acetoacetate (P = 0.0071) and plasma β-hydroxybutyrate (P < 0.0001). Thus, as more time elapsed after a ketogenic meal, the lower the plasma acetoacetate and plasma β-hydroxybutyrate concentrations became (Figure 1). There was no significant effect of time after each meal on breath acetone or urinary acetoacetate.

**Breath acetone and urinary acetoacetate as predictors of plasma ketones**

The relations between breath acetone and plasma acetoacetate and between urinary acetoacetate and plasma acetoacetate are shown in Figure 4. These relations were also nonlinear. Breath acetone (R² = 0.54, P = 0.0037) and urinary acetoacetate (R² = 0.54, P = 0.0045) were both significant predictors of plasma β-hydroxybutyrate.

**DISCUSSION**

None of the ketones measured were significantly affected by age or BMI. Schwartz et al (26) observed that, when placed on a KD, children aged ≥10 y had lower plasma acetoacetate and β-hydroxybutyrate concentrations than did children aged <10 y. In a study of infants and children aged ≤16 y, Nelson et al (27) also found that there was a significant but weak negative relation between age and breath acetone so that the older the subject, the lower the breath acetone concentration. In the present study, age had no significant negative effect on any of the ketones measured, but this may have been due to an insufficient sample size (n = 12) or to an age range (18–41 y) that did not include children or adolescents.

The time after the last ketogenic meal had a significant negative effect on plasma acetoacetate and plasma β-hydroxybutyrate, but not on breath acetone or urinary acetoacetate (Figure 1). Negative effects of time after consumption of the last ketogenic meal on total plasma ketones (acetoacetate and β-hydroxybutyrate) were also noted by Schwartz et al (26). The acute changes in plasma ketone concentrations in response to ketogenic meals may have clinical implications for patients with intractable seizures while consuming the KD. Some patients consuming a KD experience seizures early in the morning, many hours having elapsed since the last ketogenic meal was ingested and when plasma ketones are the lowest (26). More frequent meal feedings and

**Figure 2.** Relation between urinary acetoacetate (AcAc) measured enzymatically and with dipsticks. The relation was best described by a linear equation: \( y = A x + B \), where \( A = 0.40 \) and \( B = 0.15 \) (R² = 0.88, P < 0.0001; n = 156).

**Figure 3.** Relation between plasma acetoacetate (AcAc) and breath acetone or urinary acetoacetate measured enzymatically. Each relation was best described by a nonlinear equation: \( y = A x^B + C \). Top: \( A = 0.0818, B = 0.40 \), and \( C = -0.1432 \) (R² = 0.70, P < 0.0001; n = 156). Bottom: \( A = 0.3, B = 0.6 \), and \( C = 0.07 \) (R² = 0.59, P = 0.0040; n = 156).
acetone nor in urinary acetoacetate. However, this test has been found to be analyzed immediately or treated before freezing (28).

Because it is unstable and plasma samples have to either be thought of as a ketone reserve; when plasma acetoacetate concentrations begin to decrease, more of it is produced from dehydrogenase (28). In a sense, plasma hydroxybutyrate has been referred to as a "dead-end metabolite" (H9252). Between meals, plasma acetoacetate but not hydroxybutyrate itself does not provide energy directly via the portal blood (12). In the lungs it equilibrates with the relation between ketosis and seizure control. We recently validated breath acetone as a measure of systemic ketosis in a rat model of the ketogenic diet (32). In that study, breath acetone was found to be as reliable as was urinary acetoacetate in predicting plasma acetoacetate and β-hydroxybutyrate concentrations. Tassopoulos et al (20) also reported a significant positive correlation between breath acetone and plasma ketones (Figures 3 and 4), a breath acetone concentration of 2500 nmol/L corresponds to a plasma acetoacetate concentration of 1.73 mmol/L and a plasma β-hydroxybutyrate concentration of 4.17 mmol/L, values that are similar to those previously reported for children consuming a KD (26, 29).

Acetone is produced in the liver and is carried to the lungs directly via the portal blood (12). In the lungs it equilibrates readily with alveolar air (12). The analysis of breath acetone is noninvasive. In addition, although clinicians and caregivers are limited as to the frequency of urinary acetoacetate measurements they can make, breath acetone can be analyzed as frequently as necessary. This is an important feature of breath acetone analysis because many ketone measurements be necessary to assess the relation between ketosis and seizure control. We recently validated breath acetone as a measure of systemic ketosis in a rat model of the ketogenic diet (32). In that study, breath acetone was found to be as reliable as was urinary acetoacetate in predicting plasma acetoacetate and β-hydroxybutyrate concentrations. Tassopoulos et al (20) also reported a significant positive correlation between breath acetone and blood β-hydroxybutyrate in obese patients during 10–36 d of fasting.

The KD remains an important nonsurgical therapeutic alternative for persons with intractable seizures (3–5). The reliable and noninvasive nature of breath acetone analysis makes this method potentially

A dynamic equilibrium exists between plasma β-hydroxybutyrate and plasma acetoacetate. Plasma acetoacetate and β-hydroxybutyrate both increase acutely after the consumption of a ketogenic meal. Between meals, plasma acetoacetate but not β-hydroxybutyrate is directly metabolized for energy and, at other times, may also be used for fatty acid synthesis. Plasma β-hydroxybutyrate has been referred to as a "dead-end metabolite" in that its only known role is interconversion with acetoacetate (28). Thus, β-hydroxybutyrate itself does not provide energy unless it is first converted to acetoacetate via β-hydroxybutyrate dehydrogenase (28). In a sense, plasma β-hydroxybutyrate can be thought of as a ketone reserve; when plasma acetoacetate concentrations begin to decrease, more of it is produced from β-hydroxybutyrate. The equilibrium between plasma acetoacetate and plasma β-hydroxybutyrate was apparent neither in breath acetone nor in urinary acetoacetate.

Although the mechanism of the KD in ameliorating seizures is poorly understood, the ketosis induced by this diet is presumed to be important (16, 29, 30). Blood or plasma ketones may not be the most convenient indicators of ketosis, especially in the home setting. Blood sampling is invasive, particularly when frequent ketone monitoring is desired. Also, acetoacetate is difficult to measure because it is unstable and plasma samples have to either be analyzed immediately or treated before freezing (28).

Presently, patient monitoring of ketosis requires assessment of urinary ketone concentrations measured with a urinary nitroprusside dipstick ketone test. However, this test has been found to inaccurately reflect actual blood ketone concentrations (12–16). This is most likely because factors such as state of hydration and acid-base balance have complex effects on renal hemodynamics, urine volume, and excretion of ketone bodies (12). In the present study, urinary acetoacetate measured enzymatically and breath acetone were both significant predictors of plasma acetoacetate and β-hydroxybutyrate. All of the relations were best described by nonlinear equations. Owen et al (31) also found a significant nonlinear relation between blood and urinary acetoacetate. Although there was a significant difference between urinary acetoacetate measured enzymatically and with the dipsticks, there was a significant linear relation between these 2 sets of measures, indicating that a correction factor could be applied to urinary acetoacetate values determined with the dipsticks.

Our inability to conclude that urinary acetoacetate is a poor measure of ketosis may have been due to the tightly regulated conditions the participants were subjected to. The room temperature was kept constant at ≈24°C and the subjects were asked to remain seated throughout the study. Walking was permitted only when the subjects used the bathroom to provide a urine sample. Furthermore, fluid intake was restricted to 125 mL water, which the subjects were asked to drink immediately every hour on the hour. Because all these factors can affect urine volume, and hence, the concentration of urinary acetoacetate, we essentially minimized the variability in the urinary acetoacetate concentrations by controlling for these factors. In children with epilepsy and consuming a KD, fluctuations in room temperature, activity levels, and fluid intake volumes may very well lead to fluctuations in urinary acetoacetate concentrations.

A study is currently underway to assess breath acetone concentrations in children with intractable epilepsy and consuming a KD. Thus far, we have found that children with refractory seizures and consuming the classic KD have an average fasting breath acetone concentration of 2500 nmol/L (K Musa-Veloso, E Rarama, F Comeau, R Curtis, SC Cunnane, unpublished observations, 2001). On the basis of predictive equations describing the relation between breath acetone and plasma ketones (Figures 3 and 4), a breath acetone concentration of 2500 nmol/L corresponds to a plasma acetoacetate concentration of 1.73 mmol/L and a plasma β-hydroxybutyrate concentration of 4.17 mmol/L, values that are similar to those previously reported for children consuming a KD (26, 29).

Snacking may aid in keeping plasma ketone concentrations more stable and avoiding the acute rises and falls in plasma ketones that result from the consumption of ketogenic meals.

FIGURE 4. Relation between plasma β-hydroxybutyrate (β-HBA) and breath acetone or urinary acetoacetate (AcAc) measured enzymatically. Each relation was best described by a nonlinear equation: $y = Ax^B + C$.

Top: $A = 0.11$, $B = 0.47$, and $C = -0.18$ ($R^2 = 0.54$, $P = 0.0037$; $n = 156$).

Bottom: $A = 0.45$, $B = 0.5$, and $C = 0.1$ ($R^2 = 0.54$, $P = 0.0045$; $n = 156$).

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The KD remains an important nonsurgical therapeutic alternative for persons with intractable seizures (3–5). The reliable and noninvasive nature of breath acetone analysis makes this method potentially
useful for monitoring ketosis in patients with intractable epilepsy, especially children. As stated previously, a study is currently underway to assess breath acetone concentrations in children with refractory seizures who are consuming a KD. Once the range of breath acetone that exists during chronic consumption of a KD is determined, a portable, hand-held breath acetone analyzer will be developed and used to assess the relation between breath acetone and seizure control in children with intractable epilepsy who are consuming a KD.

We thank Mary Ann Ryan for technical assistance and Ray Ferris for statistical assistance.

REFERENCES