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13C-Sucrose Breath Test: Novel Use of a Noninvasive Biomarker of Environmental Gut Health

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^{13}C-Sucrose Breath Test: Novel Use of a Noninvasive Biomarker of Environmental Gut Health

WHAT'S KNOWN ON THIS SUBJECT: Australian Aboriginal children have a high incidence of acute diarrheal disease and an underlying environmental enteropathy.

WHAT THIS STUDY ADDS: In this study we used the application of a breath test to detect small intestinal integrity and health in Australian Aboriginal children living in remote communities of northern Australia.

abstract

OBJECTIVE: Environmental enteropathy syndrome may compromise growth and predispose to infectious diseases in children in the developing world, including Australian Aboriginal children from remote communities of the Northern Territory. In this study, we described the use of a biomarker ^{13}C-sucrose breath test (SBT) to measure enterocyte sucrase activity as a marker of small intestinal villus integrity and function.

METHODS: This was a hospital-based prospective case-control study of Aboriginal and non-Aboriginal children with and without acute diarrheal disease. Using the SBT, we compared 36 Aboriginal case subjects admitted to a hospital (18 diarrheal and 18 nondiarrheal disease), with 7 healthy non-Aboriginal control subjects. Intestinal permeability using the lactulose/rhamnose (L/R) ratio on a timed 90-minute blood test was performed simultaneously with the SBT. The SBT results are expressed as a cumulative percentage of the dose recovered at 90 minutes.

RESULTS: Aboriginal children with acute diarrheal disease have a significantly decreased absorptive capacity, as determined by the SBT, with a mean of 1.9% compared with either Aboriginal children without diarrhea (4.1%) or non-Aboriginal (6.1%) control subjects. The mean L/R ratio in the diarrhea group was 31.8 compared with 11.4 in Aboriginal children without diarrhea. There was a significant inverse correlation between the SBT and the L/R ratio.

CONCLUSIONS: The SBT was able to discriminate among Aboriginal children with diarrhea, asymptomatic Aboriginal children with an underlying environmental enteropathy, and healthy non-Aboriginal controls. This test provides a noninvasive, easy-to-use, integrated marker of the absorptive capacity and integrity of the small intestine and could be a valuable tool in evaluating the efficacy of interventions aimed at improving gut health. *Pediatrics* 2009;124:620–626

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KEY WORDS

environmental enteropathy, tropical enteropathy, tropic sprue, gut function, sucrose breath test, Australian Aborigines, intestinal permeability

ABBREVIATIONS

SBT—^{13}C-sucrose breath test
L/R—lactulose/rhamnose
RDH—Royal Darwin Hospital
WCH—Women's and Children's Hospital
MCV—mean corpuscular volume
cPDR90—cumulative percentage of dose recovered at 90 minutes
CI—confidence interval

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The use of selected stable isotopes of ^{13}C-labeled substrates can provide a direct assessment of the digestive and absorptive capacity of the small intestine.[1] After hydrolysis and absorption of the labeled substrate, internal sampling of the $^{13}CO_2$ expired in breath provides a quantitative measure of small intestinal function and damage. Brush-border enzyme activity in the cells of small intestinal villi is a measure of villus integrity and maturity and a marker of functional efficiency. Although reduced lactase activity is associated with small intestinal mucosal damage, lactase activity in healthy individuals is genetically determined and affected by race and age.[2] Downregulation of the lactase gene is detectable from the second year of life, although the onset and degree are variable. In contrast, sucrase activity is regulated independently of lactase, and inherited deficiencies are relatively rare.[3] Sucrase levels are reduced with mucosal injury but are relatively stable by race and throughout life.[2,4] The ^{13}C-sucrose breath test (SBT) is a noninvasive measure of small intestinal villus health based on the level of sucrase activity in the brush border of enterocytes.[5]

Environmental enteropathy is common in young children living in environments with increased bacterial contamination and recurrent diarrheal infections.[6] This condition is characterized by changes in small intestinal histology, malabsorption of nutrients, and abnormal permeability of the intestinal mucosa and has been identified as a major cause of growth faltering and childhood morbidity in the developing world.[7,8] Histologically, there are villous atrophy, moderate-to-severe crypt-cell hyperplasia, and marked infiltration with intraepithelial lymphocytes.[9] The use of intestinal permeability testing as an index of environmental enteropathy has been well documented in studies in the developing world.[7,8,10–13] Asymptomatic small intestinal mucosal damage from environmental enteropathy has been shown previously to be common among northern Australian Aboriginal children living in remote communities.[14–16] We proposed that the severity of environmental enteropathy among Aboriginal children may be assessed using the SBT. Thus, the primary aim of this study was to determine whether the SBT is a reliable measure of small bowel mucosal damage. The secondary aim was to compare the SBT with the more invasive intestinal permeability using a timed lactulose/rhamnose (L/R) ratio in blood. Although L/R ratios can be measured in urine, we have found great difficulty with 6-hour urine sample collections in young Aboriginal children.[17]

METHODS

Participants

This study was conducted at the Royal Darwin Hospital (RDH) in the Northern Territory for all of the Aboriginal participants and the Children, Youth, and Women's Health Service at the Women's and Children's Hospital (WCH) campus in South Australia for non-Aboriginal enrollments. RDH is a tertiary referral center serving a catchment population of Aboriginal children living in remote communities across the Top End of the Northern Territory. The WCH is a large tertiary pediatric center for the state of South Australia.

All of the Aboriginal children admitted to the pediatric infectious diseases ward were eligible to enroll provided that they were between 4 months and 5 years of age. Subjects were assigned to the diarrhea group if they had acute gastroenteritis with ≥3 loose stools over a 24-hour period. Aboriginal control subjects were selected from patients admitted to the RDH without any acute or chronic gastrointestinal symptoms. Recruitment of these children was from a hospitalized sample representative of acute Aboriginal pediatric admissions and consistent with baseline characteristics of previous hospital-based studies.[14,17,18] The exclusion criteria were (1) inability to fast for ≥4 hours before receiving the sugar probe, (2) inability to tolerate either oral or nasogastric fluids, (3) need for supplemental oxygen, or (4) diabetes mellitus. Children with diarrhea were fully rehydrated before breath testing was performed on the second day of admission. All of the non-Aboriginal participants were between 4 months and 5 years of age and were recruited for this trial from healthy subjects in the community. Breath testing was performed in an outpatient setting.

The study was approved by the institutional human research ethics committee in Darwin and the WCH Research Ethics Committee in Adelaide. Written informed consent was obtained from all of the parents or guardians. An Aboriginal health worker was available to obtain consent for all of the Aboriginal children participating in this trial.

Study Protocol

After a fast of ≥4 hours, baseline expiratory breath samples were collected from the nose or mouth using a nasal prong attached to a syringe, as described previously.[19] Subjects received a sugar probe solution containing 2 g/kg of body weight of sucrose up to a maximum of 20 g (SBT kits with selected ^{13}C-enriched sucrose were provided by Nidor Pty Ltd [Armadale, Victoria, Australia]), 5 g of lactulose (Dupholac, Solvay Pharmaceutical, New South Wales, Australia), and 1 g of rhamnose (Merck Pty Ltd, Kilsyth, Victoria, Australia), with the volume adjusted to give an osmolality of ~400 mOsm/L. Fasting breath samples were taken and thereafter collected every 15 minutes for a total of 90 minutes. A handheld bedside O_2 analyzer was used to monitor the quality of all of the expiratory samples. Suitable samples were defined as having an O_2 level of <19.5%.

For all of the hospitalized subjects requiring venipuncture, a 1-mL sample of venous blood was collected simultaneously with the 90-minute breath test to assess small intestinal permeability. Blood samples were analyzed in batches. Measurement of the lactulose and L-rhamnose are reported as an L/R ratio (×100), as described previously.[17] The percentage of dehydration was assessed by both clinical assessment and from the change in total body weight after 24 hours of rehydration. For all of the case subjects with diarrhea, stool output was monitored and a severity score assigned using a previously validated method.[17] Serum potassium, hemoglobin, mean corpuscular volume (MCV), C-reactive protein, and venous blood gas results on admission were recorded for all of the hospitalized patients.

Breath samples were transferred to evacuated 10-mL glass tubes for storage and handling. The ratio of $^{13}C/^{12}C$ in breath CO_2 samples was analyzed using an isotope ratio mass spectrometer (ABCA 20/20 [Europa Scientific, Crewe, United Kingdom]) according to the manufacturer's instructions. The ^{13}C-enrichment of the sucrose substrate was provided by the manufacturer according to the batch of substrate. The isotope ratio mass spectrometer was calibrated using an internal standard of calcium carbonate (Pee Dee Belemnite Limestone, Atlantic Coastal Plain, SC).

The SBT results were expressed as a cumulative percentage dose recovery of sucrose at 90 minutes (cPDR90 [%]). The 90-minute period was selected to best represent villus integrity and the absorption capacity only in the small intestine. Samples collected after this point may include the additive effects of digestion and fermentation of ^{13}C-sucrose by colonic bacteria.

TABLE 1 Baseline Characteristics of Aboriginal Children With and Without Acute Diarrhea

Characteristic	Aboriginal Children With Diarrhea ($N = 18$)	Aboriginal Controls ($N = 18$)	*P*
Age, mean (95% CI), mo[a]	11.3 (8.14 to 15.9)	17.8 (12.8 to 24.8)	.051
Gender, male/female	9:9	8:10	.74
Breastfed, *n* (%)	11 (60)	10 (55)	.73
Length of admission, mean (95% CI), d[a]	8.3 (6.3 to 10.8)	8.9 (5.9 to 13.4)	.74
Birth weight, mean (95% CI), kg	2.6 (2.2 to 3.0)	2.8 (2.6 to 3.1)	.27
Weight/age, mean (95% CI), *z* score	−1.6 (−2.2 to −0.9)	−0.4 (−4.8 to 4.0)	.58
Weight/height, mean (95% CI), *z* score	−1.2 (−1.7 to −0.6)	−1.5 (−1.9 to −1.0)	.31
Height/age, mean (95% CI), *z* score	−1.2 (−1.8 to −0.6)	−1.9 (−2.5 to −1.3)	.10
Lower respiratory infection, *n* (%)	3 (16)	9 (50)	.034
Dehydration, clinical, mean (95% CI), %	5.6 (4.1 to 7.1)	0.2 (0.0 to 0.8)	<.0001
Weight change, mean (95% CI), %[b]	5.5 (3.8 to 7.1)	1.0 (0.3 to 1.6)	<.0001
Antibiotic treatment, *n* (%)[c]	15 (83)	17 (94)	.28
Venous pH, mean (95% CI)	7.31 (7.26 to 7.36)	7.37 (7.34 to 7.40)	.085
Bicarbonate, mean (95% CI), mmol/L	16.6 (14.3 to 19.0)	26.3 (24.7 to 28.1)	<.0001
Potassium, mean (95% CI), mmol/L	2.9 (2.5 to 3.2)	3.7 (3.5 to 3.9)	.0001
Hemoglobin, mean (95% CI), g/L	118.0 (111.0 to 125.0)	115.0 (111.0 to 119.0)	.44
MCV, mean (95% CI), fL	72.8 (69.6 to 76.0)	71.5 (69.4 to 73.6)	.48
C-reactive protein, mean (95% CI), mg/L	9.7 (5.9 to 15.8)	11.7 (9.3 to 14.9)	.69
Diarrhea pathogen isolated, *n*/*N* (%)[d]	9/18 (50)	1/15 (6.6)	.007

[a] Data are expressed as geometric means.
[b] Data show the total body weight change after 24 hours of rehydration.
[c] Antibiotics include amoxicillin, third-generation cephalospins, and gentamicin.
[d] Pathogens in the group with diarrhea included rotavirus (3), *Shigella* sp (1), salmonella sp (1), and *Cryprosporidium* sp (4).

Statistical Analysis

Data were analyzed by using Stata 7 (Stata Corp, College Station, TX). Normally distributed data are expressed as arithmetic means with 95% confidence intervals (CIs). Asymmetric data were logarithmically transformed for statistical analysis and are expressed as geometric means with 95% CIs (Tables 1 and 2; age, L/R ratio, and length of stay). Continuous variables with homogeneity of variance were compared by using *t* test or analysis of variance and categorical variables using χ^2. The correlation between the cPDR90 and the L/R ratio was examined using Pearson's correlation coefficient. Anthropometric indexes were calculated with Epi Info (Centers for Disease Control and Prevention, Atlanta, GA, and World Health Organization, Geneva, Switzerland) by using the Centers for Disease Control and Prevention 2000 reference standards. Statistical significance was considered if the *P* value was <.05.

RESULTS

The baseline characteristics of the 36 Aboriginal children (18 with diarrhea

TABLE 2 Risk Factors for Aboriginal Children Affecting the SBT (Expressed as cPDR90 [%]), Using Unadjusted Logistic Regressions

Risk Factors	No. Present/Absent	cPDR90 (%) Risk Factor (95% CI)		*P*
		Present	Absent	
High L/R ratio (>16)[a]	20/12	1.9 (1.0 to 2.9)	5.2 (4.1 to 6.2)	.0001
Diarrhea	18/18	1.9 (0.9 to 3.0)	4.1 (3.0 to 5.2)	.004
Iron deficiency (MCV < 70 fL)	15/21	1.8 (0.8 to 2.9)	3.9 (2.8 to 5.0)	.008
Anemia (<110 g/L)	6/30	2.2 (0.3 to 4.1)	3.2 (2.3 to 4.1)	.36
Breastfed	21/15	2.7 (1.8 to 3.7)	3.5 (1.9 to 5.0)	.37
Malnutrition (wasted)	10/26	2.9 (1.9 to 3.9)	3.1 (2.0 to 4.2)	.84
Infection (C-reactive protein > 8 mg/L)	26/10	3.0 (1.9 to 4.0)	3.2 (1.9 to 4.6)	.77
Age (<12 mo)	10/26	3.2 (2.3 to 4.1)	3.3 (2.2 to 4.3)	.32

[a] $N = 32$; missing data include failed venipuncture ($n = 2$) and parental refusal ($n = 2$).

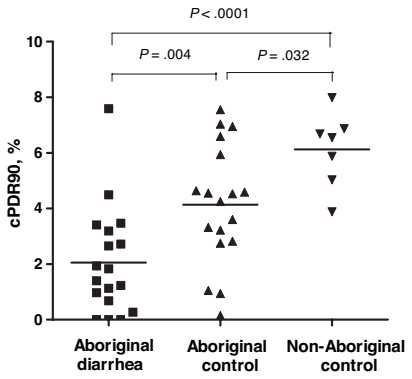

FIGURE 1
SBT results expressed as cPDR90 in Aboriginal children with diarrhea (1.9% [95% CI: 0.9%–3.0%]; $n = 18$), the Aboriginal control group (4.1% [95% CI: 3.0%–5.2%; $n = 18$), and the non-Aboriginal control group (6.1% [95% CI: 4.8%–7.3%] $n = 7$).

and 18 without diarrhea) are shown in Table 1. Using World Health Organization clinical criteria, the severity of dehydration in case subjects with diarrhea was mild in 4, moderate in 12, and severe in 4, with hypokalemia in 11 and metabolic acidosis in 5. Half of the Aboriginal group without diarrhea had lower respiratory tract infections, reflecting the high proportion of admissions for this condition in our setting. Seven asymptomatic non-Aboriginal control participants were enrolled (data not shown). There was no significant difference in age ($P = .051$), gender ($P = .23$), or weight/age z score ($P = .70$) among the 3 groups. Baseline weight/height and height/age, however, were significantly higher in the non-Aboriginal children compared with Aboriginal participants ($P < .0005$).

Sucrose Breath Test

The mean cPDR90 was significantly lower for the diarrhea group (1.9% [95% CI: 0.9%–3.0%]) compared with both Aboriginal (4.1% [95% CI: 3.0%–5.2%]) or non-Aboriginal (6.1% [95% CI: 4.8%–7.3]; $P < .0001$) control case subjects (Fig 1). Furthermore, among the 2 control groups, the mean cPDR90 was significantly lower in Aboriginal compared with non-Aboriginal children ($P = .032$).

Intestinal Permeability (L/R Ratio)

The mean L/R ratio in the diarrhea group was 31.8 (95% CI: 24.9–40.7) compared with 11.4 (95% CI: 8.5–15.5) in Aboriginal children without diarrhea ($P < .0001$). Using single unadjusted linear regression analysis, reduced villous function as determined by the cPDR90 was most closely associated with high permeability ratios, reflecting small intestinal mucosal damage, which explained 45% of the variance in the cPDR90 (Table 2). This compares with 28% of the variance in cPDR90 explained by diarrhea and 26% by iron deficiency.

Combined SBT and Intestinal Permeability Testing

We demonstrated a statistically significant inverse correlation between the SBT and L/R ratio among Aboriginal children ($r = 0.67$ [95% CI: 0.82–0.42]; $P < .0001$; Fig 2). There was no association between the SBT and markers of diarrhea severity examined, including degree of dehydration ($P = .24$), diarrhea score ($P = .78$), serum bicarbonate level ($P = .92$), hypokalemia ($P = .78$), and acidosis ($P = .4$).

DISCUSSION

Environmental enteropathy is endemic in children of the developing world and in Aboriginal children living in remote regions of tropical northern Australia.[14] This condition may not only predispose children to severe manifestations of diarrheal disease but also important long-term nutritional consequences by contributing to malnutrition and growth faltering from malabsorption of macronutrients and micronutrients.[7,8,20] Intestinal permeability using the L/R ratio has been commonly used to assess loss of small intestinal barrier function. However, this test does not differentiate

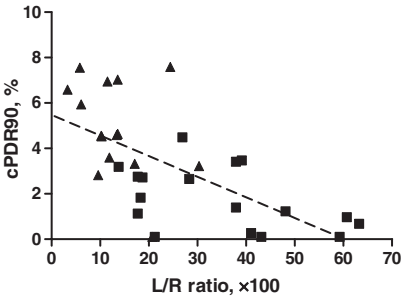

FIGURE 2
Inverse linear regression (dotted line) of SBT expressed as cPDR90 and L/R ratio ($r = 0.67$ [95% CI: 0.42–0.82; $P < .0001$). ▲ indicates control subjects; ■, subjects with diarrhea.

changes in the absorptive capacity of the small intestinal mucosa that can result from either slowed maturation or damage to the primary absorptive unit, the small intestinal villus. Traditionally, urinary excretion of nonmetabolized markers, such as D-xylose and 3-*O*-methyl-D-glucose, has been used to measure absorption, but obvious limitations with this method have restricted their widespread use.[12,19]

In the present study, we used the SBT to determine small intestinal absorptive capacity as a measure of small bowel mucosal damage. The mean cPDR90 value was highest in asymptomatic non-Aboriginal children, reflecting normal sucrase activity of the small intestine. As expected, the lowest mean cPDR90 was seen in children presenting with acute diarrheal disease. Most importantly, we have also shown that Aboriginal children admitted to the hospital even without gastrointestinal symptoms have subclinical malabsorption of sucrose and abnormal permeability consistent with an underlying environmental enteropathy.[17,18,20] Therefore, poor absorptive capacity among Aboriginal children reflects the degree of underlying damage to the small intestinal mucosa.

Although the exact histologic features of the underlying small bowel abnormalities were not determined in our subjects, there have been limited

studies previously characterizing gut morphology in Australian Aboriginal children.[21,22] In addition, the mucosal lesion of environmental enteropathy syndrome has been studied extensively in developing countries by both dissecting and light microscopy, showing crypt hyperplasia, villous stunting, hypercellularity of the lamina propria, decreased mucosal surface area, and increased intestinal permeability.[17,23–25] Despite some uncertainty about the exact cause of environmental enteropathy, it is clear that the biopsy changes are environmental rather than genetic or racial.[26–28] The changes increase progressively over childhood, with adults showing similar changes. The increased likelihood of isolation of enteric pathogens from asymptomatic people in areas where there is a high prevalence of environmental enteropathy suggests that failure to clear enteropathogens is a likely contributor to mucosal damage.[29,30]

The extent to which environmental enteropathy contributes to malnutrition and growth faltering in Australian Aboriginal children is unknown. From a population perspective it would be important to provide a standard of absorptive capacity on which to monitor the impact of any community preventative measures or therapeutic interventions aimed at improving nutritional, gastrointestinal, and environmental health. For individuals, a safe, easy-to-use, and noninvasive biomarker of small intestinal health that signals impaired absorptive function would provide a very useful index.

In this study, we found that an association between iron deficiency (defined as MCV $<$ 70 fL) and SBT results from both unadjusted and multiple linear regression in Aboriginal subjects. This is consistent with studies showing that severe iron deficiency in both humans and animals is linked with impaired small intestinal sucrase activity, reduced sucrose absorption, and abnormal permeability.[31–33]

Although other investigators have shown reduced sucrase-isomaltase expression and activity in severely malnourished infants with small intestinal villous atrophy, we observed no significant change in the SBT with malnutrition among the Aboriginal children enrolled, probably because the degree of acute malnutrition was not severe.[34] The significant correlation between the SBT and L/R ratio performed in Aboriginal children admitted to the hospital clearly shows that these biomarkers agree when the severity of the small intestinal damage or functional impairment is high from either acute diarrheal disease and/or underlying environmental enteropathy (Fig 2). Although these tests evaluate different physiologic processes, the use of the SBT has additional advantages that would appeal to health workers operating outside of the hospital setting. Ease of administration of a single and safe oral sugar probe, noninvasive collection of expired breath samples over a short period, and the ability to store and send breath samples in the original collection tubes make the SBT an attractive option in the community.

There are some limitations with this study. First, although we have attempted to control for differences in transit time between subjects with and without diarrhea, we were not able to accurately predict the effects of any solvent drag resulting from the use of the oral sugar probe solution. This could be an important factor in young Aboriginal children, particularly those with existing diarrhea.[35] Second, the small number of participants enrolled may have prevented us from identifying other significant factors that may influence the SBT result.

CONCLUSIONS

We have demonstrated that this gut biomarker can assess the integrity and absorptive capacity of the small intestine. Importantly, the SBT can be used to reliably measure the degree of small intestinal mucosal damage among asymptomatic children with an underlying environmental enteropathy. The easy application of this noninvasive test, its portability and applicability to remote regions, and the stability of the collected breath samples make it an extremely useful biomarker for assessing gut health in the field. No similar easy-to-use alternative test currently exists. The SBT should be of great use in settings where there is a high burden of enteric infections and environmental contamination and could prove useful in evaluating the effectiveness of community interventions aimed at improving gut health.

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