Gastric Emptying of Liquids in Children

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ABSTRACT

Objectives: The present study was performed to determine normal values for gastric half-emptying time ($t_{1/2}$GE) of liquids in healthy children.

Methods: Gastric emptying (GE) of a standardized test milk-drink measured with ^{99m}technetium scintigraphy and the ^{13}C-acetate breath test (^{13}C-ABT) was compared in 19 children ages between 4 and 15 years with upper gastrointestinal symptoms. The ^{13}C-ABT was subsequently used to determine normal values for GE of the same liquid test meal in 133 healthy children ages between 1 and 17 years.

Results: In the group of children with upper gastrointestinal symptoms, the results showed a significant correlation ($r = 0.604$, $P = 0.0006$) between $t_{1/2}$GE measured with both techniques. In the group of healthy children, the results of $t_{1/2}$GE showed that there was no influence of age, sex, weight, height, and body mass index on GE.

Conclusions: Normal values for GE of a standardized test milk-drink in healthy children were determined with the ^{13}C-ABT. This technique is considered reliable and is well accepted by the patients.

Key Words: ^{13}C-acetate breath test, children, gastric emptying, liquids, nondispersive infrared spectrometry, normal values, scintigraphy

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What Is Known

- Gastric emptying is an important physiologic process that can be delayed in various pediatric diseases.
- ^{99m}Technetium scintigraphy is the criterion standard for measuring gastric emptying, but is associated with radiation.
- ^{13}C-acetate breath test for measuring gastric emptying of liquids was developed with the nonradioactive isotope ^{13}C.

What Is New

- ^{13}C-acetate breath test was validated in comparison with ^{99m}technetium scintigraphy in children with upper gastrointestinal symptoms.
- Normal values for gastric emptying of liquids measured with ^{13}C-acetate breath test were established in healthy children.
- ^{13}C-acetate breath test using the present standardized methodology and test meal can be used to study gastric emptying of children in health and disease.

Gastric emptying (GE) is an important step in the assimilation of nutrients. GE can be delayed in various diseases. Delayed GE may cause symptoms including abdominal pain, anorexia, early satiety, failure to thrive, nausea, postprandial fullness, regurgitation, and vomiting. GE is a complex process that is regulated by several factors such as hormone secretions, neural regulation, and motor activity of the stomach. A variety of other factors related to the meal (caloric density, composition, osmolarity, temperature, and volume) and the subject (age, sex, physical activity, position, drug intake, and diseases) can also influence GE (1,2).

The criterion standard for measuring GE is ^{99m}technetium scintigraphy (^{99m}TS) (3). This technique, however, has the inherent risk of radiation exposure for patients and personnel, and requires an expensive detection and data analysis system. Alternative nonradioactive methods using the stable isotope ^{13}C, a naturally occurring nonradioactive isotope, have been developed for this reason. The ^{13}C-octanoic acid breath test (^{13}C-OBT) was developed by Ghoos et al (4) to measure the GE of solids. It can also be used to measure the GE of liquids (5). The ^{13}C-acetate breath test (^{13}C-ABT) was developed by Braden et al (6) to measure the GE of liquids. Acetate is hydrophilic, poorly absorbed in the stomach, and rapidly metabolized after absorption in the duodenum. The ^{13}C-ABT is based on the principle that ^{13}C-labeled acetate remains well mixed in the liquid phase of a meal during its passage through the gastric environment. It is released and absorbed in the duodenum, metabolized and oxidized in the liver, and eliminated by the lungs as $^{13}CO_2$ through expired air. GE is the rate-limiting step for the appearance of $^{13}CO_2$ in the breath. Analysis of breath samples for ^{13}C-enrichment can be performed using nondispersive infrared spectrometry (NDIRS) or isotope ratio mass spectrometry (IRMS). NDIRS uses photo-acoustic detectors to measure variation in the absorbance of the light between isotopes without measuring mass weight, whereas IRMS uses a magnet chamber to measure mass weight based on different light absorbance between isotopes. IRMS was first developed, and is the most frequently used technique. NDIRS is cheaper and easier to perform. There is a good agreement between these techniques in the isotope ratio determination (1,7). All of the measurements in the present study have been done by NDIRS. We have shown in an earlier study

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that the ^{13}C-ABT is an easy and noninvasive procedure with a large intraindividual variation for measuring GE of liquids in healthy children, but comparable to the variation reported by other techniques (8). In the present study, the ^{13}C-ABT was compared with ^{99m}TS as reference method to measure GE of liquids in children with upper gastrointestinal symptoms. Because a good correlation was obtained between both techniques, we also determined normal values for GE of liquids in healthy children measured with the ^{13}C-ABT.

METHODS

Subjects

GE of liquids was performed in 19 children ages between 4 and 15 years with dyspeptic and/or gastro-esophageal reflux symptoms to compare the ^{13}C-ABT with ^{99m}TS. The group consisted of 16 girls and 3 boys with a mean age of 11 ± 3 years (range 4–15 years), mean weight of 37 ± 10 kg (range 17–56 kg) and mean height of 143 ± 21 cm (range 103–176 cm). GE for liquids was also performed in 133 healthy children ages between 1 and 17 years to establish normal values for GE of liquids measured with the ^{13}C-ABT. The group consisted of 69 girls and 64 boys with a mean age of 9 ± 4 years (range 1–17 years), mean weight of 35 ± 18 kg (range 10–89 kg) and mean height of 137 ± 27 cm (range 80–189 cm). The healthy volunteers were recruited through an intranet demand within the hospital personnel. The local ethics committee approved the protocol. Written informed consent was obtained from the parents, and if possible from the children themselves.

Test Meal

After an overnight fast, the children ingested within 5 to 10 minutes a standardized liquid test meal consisting of 200 mL milk with strawberry taste and caloric content of 112 kcal (composition: 2 g proteins/100 g, 11.9 g carbohydrates/100 g, and 0.04 g fats/100 g) (INZA Drink, Schoten, Belgium). The test meal was doubly labeled with ^{13}C-acetate related to body weight (50 mg for weight between 10 and 30 kg and 100 mg for weight more than 30 kg) (Eurisotop, Saint-Aubain, France) and 18.5 MBq ^{99m}technetium (Hepatate; Amersham, UK) for the study related to the children with the upper gastrointestinal symptoms. In the study related to the healthy children, the same test meal labeled with ^{13}C-acetate related to body weight but without ^{99m}technetium has been administered. During the test no drinking or eating, and only limited physical activities were allowed.

^{13}C-Acetate Breath Test

Breath samples were collected before, every 5 minutes for the first 40 minutes and every 10 minutes for the following 140 minutes after ingestion of the test meal. Breath samples were collected in aluminum bags using the Infra Red Isotope (IRIS)-breath sample double bag with a content of 100 mL, connected with the mouthpiece for IRIS breath sample bag with internal rebreath stop valve (Wagner Analysen Technik, Bremen, Germany). Basal CO_2 production was assumed to be 300 mmol/m^2 of body surface area (BSA) per hour. BSA was calculated by the weight-height formula of Haycock et al (9). Breath samples were analyzed for $^{13}CO_2$-enrichment using NDIRS with the IRIS-lab-infrared-^{13}C-isotope-analyzer (Wagner Analysen Technik). The measured $^{13}CO_2/^{12}CO_2$ ratio in the breath samples was compared with the international Pee Dee Belemnite limestone of North Carolina, the international reference for $^{13}CO_2/^{12}CO_2$ ratios, and expressed as δ-values and δ over baseline-values. The δ-values and δ over baseline-values given by NDIRS were converted into the percentage ^{13}C-recovery per hour and to the cumulative ^{13}C-recovery after 3 hours. Nonlinear regression analysis of the curve that best fits the cumulative $^{13}CO_2$ excretion curve and the $^{13}CO_2$ excretion by time curve was performed according to the methods described by Ghoos et al (4) using the IRIS software "GE2.DEM" for Microsoft Windows (Wagner Analysen Technik). It allowed the calculation of the gastric half-emptying time ($t_{1/2}$-ABT), which is the time on which half of the dose of $^{13}CO_2$ is excreted of the cumulative $^{13}CO_2$ when time is infinite. A higher value corresponds to a slower GE.

^{99m}TS

Scintigraphic image acquisition began immediately after the feeding and at 15 minutes interval for the following 180 minutes with a dual-headed gamma camera (ECAM; Siemens Inc, Hoffman Estates, IL). Radioactivity remaining in the stomach at each scanning period was expressed as percentage of the initial activity, and the scintigraphic gastric half-emptying time ($t_{1/2}$-SCINTI) was calculated, which is the time at which 50% of the radiolabeled material has left the stomach.

Statistical Analysis

Results are presented as means, standard deviations, and ranges. A linear regression analysis was performed to calculate correlation between $t_{1/2}$-ABT and $t_{1/2}$-SCINTI. $P < 0.05$ was considered statistically significant. Statistical parameters were calculated using the statistical program SPSS version 21 for Windows (IBM SPSS Statistics, Armonk, NY).

Age-related reference ranges of $t_{1/2}$-ABT were estimated with the LMS method (10). This method uses a power transformation to normalize the distribution of $t_{1/2}$-ABT conditional on age, and summarizes the complete distribution in 3 smooth curves: L for the normalizing box-cox power, M for the median, and S for the coefficient of variation. Models were selected using the deviance criterion, and validated by analyzing the distribution of residuals. $t_{1/2}$-ABT was found to be lognormal distributed at each age, in which case $L = 0$, and percentiles can be calculated as M exp(SZ), in which Z is the percentile expressed in standard deviation units. The z score of an observation is calculated as $\ln(t_{1/2}\text{-ABT/M})/S$. Data from boys and girls were combined as there was no evidence for differences according to sex. Measurements of $t_{1/2}$-ABT were converted to z scores to assess the effect of sex, weight, height, and body mass index, either individually with a t test or simple linear regression, or combined, and corrected for age, using multiple linear regression analysis.

RESULTS

The group of 19 children with upper gastrointestinal symptoms showed a mean $t_{1/2}$-ABT of 81.7 ± 13.8 minutes (range 58–106 minutes) and a mean $t_{1/2}$-SCINTI of 62.2 ± 20.9 minutes (range 26.8–99.0 minutes). $t_{1/2}$-ABT correlated significantly with $t_{1/2}$-SCINTI: $t_{1/2}\text{-ABT} = 56.816 + 0.4 \times t_{1/2}\text{-SCINTI}$ ($r = 0.604$, $P = 0.0006$).

The group of 133 healthy children showed a mean $t_{1/2}$-ABT of 81.7 ± 13.6 minutes (range 49–142 minutes). Simple and multiple linear regression showed no significant effects of age, sex, weight, height, and body mass index on normalized $t_{1/2}$-ABT, but the variance was larger in younger children (Fig. 1 and Table 1).

There was no difference between the mean $t_{1/2}$-ABT from the group with upper gastrointestinal symptoms in which the ^{13}C-ABT was performed at rest, and the mean $t_{1/2}$-ABT from the group of

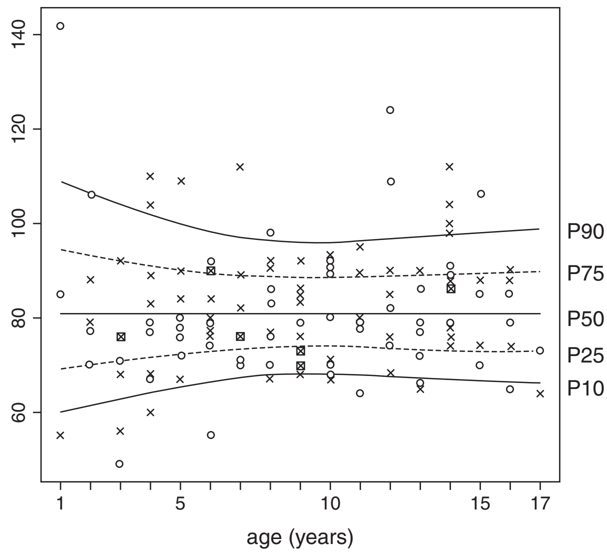

FIGURE 1. ^{13}C-acetate breath test gastric half-emptying time ($t_{1/2}$-ABT) according to age with smoothed age related reference range. $t_{1/2}$-ABT = ^{13}C-acetate breath test gastric half-emptying time in minutes; age in years; dots = boys, crosses = girls.

healthy children in which limited physical activities were allowed during the ^{13}C-ABT.

We propose to define delayed GE as $t_{1/2}$-ABT > P90 and rapid GE as $t_{1/2}$-ABT < P10. There were 3 patients with a delayed GE and 3 patients with a rapid GE in the patients with upper gastrointestinal symptoms.

DISCUSSION

In the present study we measured GE of a test milk-drink with the ^{13}C-ABT according to a standardized study protocol. This allowed us to validate the ^{13}C-ABT compared with ^{99m}TS in

TABLE 1. Percentiles of $t_{1/2}$-ABT according to age

				Percentiles				
Age	L	M	S	10	25	50	75	90
1	0	80.8	0.23145	60.1	69.1	80.8	94.5	108.8
2	0	80.8	0.21351	61.5	70.0	80.8	93.4	106.3
3	0	80.8	0.19614	62.9	70.8	80.8	92.3	103.9
4	0	80.8	0.17969	64.2	71.6	80.8	91.3	101.8
5	0	80.8	0.16485	65.5	72.4	80.8	90.3	99.8
6	0	80.8	0.15242	66.5	73.0	80.8	89.6	98.2
7	0	80.8	0.14286	67.4	73.4	80.8	89.0	97.0
8	0	80.8	0.13642	67.9	73.8	80.8	88.6	96.2
9	0	80.8	0.13335	68.2	73.9	80.8	88.4	95.9
10	0	80.8	0.13344	68.2	73.9	80.8	88.4	95.9
11	0	80.8	0.13578	67.9	73.8	80.8	88.6	96.2
12	0	80.8	0.13906	67.6	73.6	80.8	88.8	96.7
13	0	80.8	0.14204	67.3	73.4	80.8	89.0	97.1
14	0	80.8	0.14459	67.0	73.2	80.8	89.2	97.5
15	0	80.8	0.14676	66.7	73.1	80.8	89.4	97.9
16	0	80.8	0.14879	66.5	72.9	80.8	89.6	98.3
17	0	80.8	0.15090	66.2	72.8	80.8	89.8	98.7

$t_{1/2}$-ABT = ^{13}C-acetate breath test gastric half-emptying time in minutes; age in years; L = box-cox power; M = median; S = coefficient of variation.

children with upper gastrointestinal symptoms, and to establish normal values for GE of liquids in healthy children measured with the ^{13}C-ABT. This is the biggest study concerning normal values for GE of liquids in children to the best of our knowledge.

There were more girls in the group of children with upper gastrointestinal symptoms. This is in accordance with a female predominance of dyspepsia and other functional gastrointestinal disorders in children and adults (11–14).

The test milk drink had strawberry taste and was consumed without any problem by all children. This test milk-drink can of course not be used in children with a cow's milk allergy or intolerance.

Because GE is influenced by a variety of factors, we standardized energy content, temperature, and volume of the test milk-drink, moment of the day the test was performed, physical activity of the children during the test and the ^{13}C-ABT procedure. All of the children performed the entire test without any problem.

GE is not measured in the same way by ^{13}C-ABT and ^{99m}TS. ^{13}C-ABT determines GE in an indirect way by measuring the quantity of $^{13}CO_2$ in the exhaled air. This allows the calculation of $t_{1/2}$-ABT, which is the time when the first half of the ^{13}C-acetate has been metabolized. ^{99m}TS determines GE in a direct way by measuring the progressive disappearance of the radioactive tracer from the stomach. This allows the calculation of $t_{1/2}$-SCINTI, which is the time at which 50% of the radiolabeled material has left the stomach. This explains why the values of $t_{1/2}$-ABT and $t_{1/2}$-SCINTI are different. Braden et al showed in the initial validation study of the ^{13}C-ABT using IRMS compared with ^{99m}TS for the measurement of GE of liquids in dyspeptic adults that $t_{1/2}$-ABT differed from $t_{1/2}$-SCINTI by 49 minutes corresponding to the time necessary for the postgastric processing of ^{13}C-acetate (6). We found in our study a difference of 19.5 minutes between $t_{1/2}$-ABT and $t_{1/2}$-SCINTI. Other studies that have compared the ^{13}C-ABT using IRMS or NDIRS and ^{99m}TS for the measurement of GE of liquids in children and adults, have shown a difference between $t_{1/2}$-ABT and $t_{1/2}$-SCINTI varying between 13 and 56 minutes (15–19).

We validated the ^{13}C-ABT using NDIRS in comparison with ^{99m}TS for the measurement of GE of a standardized test milk-drink in children with upper gastrointestinal symptoms and showed a significant correlation of 0.604 between the gastric half-emptying times ($t_{1/2}$GE) obtained with both techniques. Braden et al showed in the initial validation study comparing the ^{13}C-ABT using IRMS with ^{99m}TS for the measurement of GE of liquids in dyspeptic adults a significant correlation of 0.95 between $t_{1/2}$GE obtained with both techniques (6). One study in dyspeptic children and 2 studies in healthy adults have also compared the ^{13}C-ABT using NDIRS with ^{99m}TS for the measurement of GE of liquids. The adult studies did not perform a correlation between $t_{1/2}$GE, but they showed that there was a difference between the results obtained with both techniques corresponding to the postgastric processing of ^{13}C-acetate as discussed before (18,19). The pediatric study showed no significant correlation between $t_{1/2}$GE measured with both techniques, (17) but the ^{13}C-ABT using IRMS has, however, been validated in comparison with ^{99m}TS in children for the measurement of GE of liquids (Table 2). Other studies that have compared the GE breath tests with ^{99m}TS for the measurement of GE of liquids in adults have shown a significant correlation between $t_{1/2}$GE obtained with both techniques (supplementary Table S1, *http://links.lww.com/MPG/A538*; *http://links.lww.com/MPG/A611*).

We established normal values for GE of a standardized test milk-drink in healthy children measured with the ^{13}C-ABT using NDIRS. We found a mean $t_{1/2}$-ABT of 81.7 minutes with a range between 49 and 142 minutes. We have already shown in a previous study that there was an important interindividual and intraindividual variability for $t_{1/2}$-ABT reflecting true day-to-day variations in GE,

TABLE 2. Gastric emptying of liquids and semisolids in children measured with the ^{13}C-acetate breath test compared with ^{99m}technetium scintigraphy

Study	Patients, n, age, symptoms	Meal type, kcal	Technique	Correlation $t_{1/2}$GE
Present study	19 1–17 y Upper GI symptoms	Milk 112 kcal	^{13}C-ABT NDIRS	0.604 ($P = 0.0006$)
Jones et al (17)	25 5–17 y Dyspeptic symptoms	Milk ? kcal	^{13}C-ABT NDIRS	0.164 ($P = 0.44$)
Gatti et al (15)	30 4.4 ± 3.5 y GOR symptoms and DGE	Milk 105–160 kcal	^{13}C-ABT IRMS	0.97 ($P = ?$)
Barbosa et al (16)	11 2–6 mo GOR symptoms	Milk ? kcal	^{13}C-ABT IRMS	0.75 ($P = 0.01$)
Braden et al (20)	26 4–16 y dyspeptic or respiratory symptoms	Semisolid meal 250 kcal	^{13}C-ABT IRMS	0.76 ($P < 0.00001$)

? = not provided in the original article; ^{13}C-ABT = ^{13}C-acetate breath test; DGE = delayed GE; GI = gastrointestinal; GOR = gastroesophageal reflux; IRMS = isotope ratio mass spectrometry; NDIRS = nondispersive infrared spectrometry; $t_{1/2}$GE = gastric half-emptying time.

instead of variations with the measurement technique (interindividual range between 65 and 112 minutes, intraindividual range between 4 and 33 minutes, coefficient of variation intraindividual 8.3%) (8). We did not show an effect of age or sex on GE of liquids in healthy children in the present study. Barbosa et al and Gatti et al did not look at the influence of age and sex on GE of liquids in children probably because the studied populations were too small (15,16). Knatten et al (21) showed no influence of age on GE of a test milk-drink measured with ^{99m}TS in 24 healthy children ages 2 to 10 years. Maes et al (5) showed that a test milk-drink was emptied at a slower rate in 15 healthy children ages 4 to 15 years compared with 27 healthy adults measured with the ^{13}C-OBT using IRMS. Hellmig et al (22) showed no effect of age and sex on GE of apple juice measured with the ^{13}C-ABT using NDIRS in 90 healthy adults. Several other studies have established normal values for GE of liquids in healthy children measured with the ^{13}C-ABT and ^{13}C-OBT using IRMS, but the studied populations are smaller than in our study (Table 3). One should be cautious when comparing the results of these different studies because there are differences in the used test meals (caloric content and composition) and used ^{13}C-labeled substrate (^{13}C-acetate or ^{13}C-octanoic acid). Further differences can also be of technical nature (way of collecting samples, time interval between samples, total duration of sampling, IRMS, or NDIRS for breath sample analysis). Finally, results can be presented either as real calculated breath test data not corrected for scintigraphy or as breath test data corrected for scintigraphy according to Ghoos et al (4) corresponding to scintigraphic equivalent values. Our results are generally in good agreement with those of other studies (Table 3). Normal values for GE of liquids in healthy children have also been established using techniques other than breath tests. We choose to present only studies in which $t_{1/2}$GE was calculated. Our results are generally higher because these other techniques measure GE in a direct way (Table 4). Normal values for GE of liquids in healthy adults measured with GE breath tests have

TABLE 3. Normal values for gastric emptying of liquids in healthy children measured with the ^{13}C-acetate breath test or ^{13}C-octanoic acid breath test

Study	Patients, n, age	Meal type, kcal	Technique	$t_{1/2}$GE
Present study	133 1–17 y	Milk 112 kcal	^{13}C-ABT NDIRS	Mean 81.9 min*
Meal: 200 mL INZA milk drink				
Gatti et al (15)	30 4.4 ± 3.5 y	Milk 105-160 kcal	^{13}C-ABT IRMS	Mean 74 min*
Meal: <2 y: milk amounts normalized per body weight; >2 y: 200 mL milk				
Barbosa et al (16)	14 2–6 mo	Milk ? Kcal	^{13}C-ABT IRMS	Mean 68.5 min*
Meal: 59.15 mL milk + amount of formula according to age requirement				
Maes et al (5)	15 4–15 y	Milk 134 kcal	^{13}C-OBT IRMS	Median 86 min**
Meal: 210 mL full cream milk				

^{13}C-ABT = ^{13}C-acetate breath test; ^{13}C-OBT = ^{13}C-octanoic acid breath test; IRMS = isotope ratio mass spectrometry; NDIRS = nondispersive infrared spectrometry; $t_{1/2}$GE = gastric half-emptying time.
* Real calculated breath test data not corrected for scintigraphy.
** Corrected breath test data for scintigraphy according to Ghoos et al (3) (scintigraphic equivalent values).

TABLE 4. Normal values for gastric emptying of liquids in healthy children measured with other techniques

Study	Patients (n, age)	Meal (type, kcal)	Technique	$t_{1/2}$GE
Hoekstra et al (23)	4	25 g 20 % fructose—? kcal	^{13}C-GBT	Mean 45.5 min
	12–16 y	27.5 g 20% glucose—? kcal	IRMS	Mean 64.3 min
		25 g 20% fructose + 27.5 g 20% glucose—? kcal		Mean 85.3 min
Ravelli et al (24)	6	20 mL/kg milk—? kcal	APT	Mean 61.5 min
	3 mo–17 y	20 mL/kg 5% glucose—? kcal		Mean 10.7 min
Smith et al (25)	45	400 mL/m^2 orange squash	EI	Mean 13.5 min
	7 mo–17 y	? kcal		
Euler and Byrne (26)	20	20 mL/kg water, max 700 mL	MDT	Mean 15 min
	2–24 mo	0 kcal		
Schmitz et al (27)	16	7 mL/kg diluted raspberry syrup 32.2 kcal/100 mL	MRI	Median 23.6 min
	6–12 y			
Schmitz et al (28)	14	3 mL/kg diluted raspberry syrup	MRI	Median 20 min
	8–12 y	7 mL/kg diluted raspberry syrup		Median 27 min
		32.2 kcal/100 mL		
Schmitz et al (29)	18	7 mL/kg diluted raspberry syrup 4 h after breakfast	MRI	Mean 30.8 min
	6–12 y	7 mL/kg diluted raspberry syrup 6 h after breakfast		
		32.2 kcal/100 mL		Mean 28.3 min
Knatten et al (21)	24	<4 y: minimum 100 ml full cream cow's milk	^{99m}TS	Mean 46 min
	2–10 y	>4 y 200 mL full cream cow's milk		
		66 kcal/200 mL		
Fahmy et al (30)	20	20 mL/kg tap water	Ultrasound	Mean 27.1 min
	8.25 ± 2.24 y	0 kcal		

^{13}C- GBT = ^{13}C- glycine breath test; ^{99m}TS = ^{99m}technetium scintigraphy; APT = applied potential tomography; EI = electric impedance; IRMS = isotope ratio mass spectrometry; MDT = marker dilution technique; MRI = magnetic resonance imaging; $t_{1/2}$GE = gastric half-emptying time.

also been established (supplementary Table S2, *http://links.lww.com/MPG/A539*; *http://links.lww.com/MPG/A611*).

We conclude that we have validated the ^{13}C-ABT using NDIRS in comparison with ^{99m}TS for the measurement of GE of a standardized test milk-drink in children with upper gastrointestinal symptoms. We have also established normal values for GE of a standardized test milk-drink in healthy children measured with the ^{13}C-ABT using NDIRS. It is, however, important to mention that the reported reference values are only valid for the ^{13}C-ABT using the described methodology and test meal. The ^{13}C-ABT is a safe, simple, and noninvasive test that does not involve radiation exposure so that GE studies can be performed in children without biological hazard.

REFERENCES

1. Bruno G, Lopetuso LR, Ianiro G, et al. ^{13}C-octanoic acid breath test to study gastric emptying time. *Eur Rev Med Pharmacol Sci* 2013;17:59–64.
2. Mishima Y, Amanao Y, Takahashi Y, et al. Gastric emptying of liquid and solid meals at various temperatures: effect of meal temperature for gastric emptying. *J Gastroenterol* 2009;44:412–8.
3. Abell TL, Camilleri M, Donohoe K, et al. Consensus recommendations for gastric emptying scintigraphy: a joint report of the Society of Nuclear Medicine and the American Neurogastroenterology and Motility Society. *Am J Gastroenterol* 2008;103:753–63.
4. Ghoos YF, Maes BD, Geypens BJ, et al. Measurement of gastric emptying rate of solids by means of carbon-labelled octanoic acid breath test. *Gastroenterology* 1993;104:1640–7.
5. Maes BD, Ghoos YF, Geypens BJ, et al. Relation between gastric emptying rate and energy intake in children compared with adults. *Gut* 1995;36:183–8.
6. Braden B, Adams S, Duan LP, et al. The (13C)-acetate breath test accurately reflects gastric emptying of liquids in both liquid and semisolid test meals. *Gastroenterology* 1995;108:1048–55.
7. Pizzoferrato M, Del Zompo F, Mangiola F, et al. Specific 13C functional pathways as diagnostic targets in gastroenterology breath tests: tricks for a correct interpretation. *Eur Rev Med Pharmacol Sci* 2013;17:45–50.
8. Hauser B, De Schepper J, Caveliers V, et al. Variability of the 13C-acetate breath test for gastric emptying of liquids in children. *J Pediatr Gastroenterol Nutr* 2006;42:392–7.
9. Haycock G, Schwartz G, Wisotsky D. Geometric method for measuring body surface area: a height-weight formula validated in infants, children and adults. *J Pediatr* 1978;93:62–6.
10. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. *Stat Med* 1992;11:1305–19.
11. Devanarayana NM, Mettananda S, Liyanarachchi C, et al. Abdominal pain-predominant functional gastrointestinal diseases in children and adolescents: prevalence, symptomatology, and association with emotional stress. *J Pediatr Gastroenterol Nutr* 2011;53:659–65.
12. Rejchrt S, Koupil I, Kopácová M, et al. Prevalence and sociodemographic determinants of uninvestigated dyspepsia in the Czech Republic. *Eur J Gastroenterol Hepatol* 2008;20:898–905.
13. Basandra S, Bajaj D. Epidemiology of dyspepsia and irritable bowel syndrome (IBS) in medical students of northern India. *J Clin Diagn Res* 2014;8:JC13–6.
14. Oshima T, Miwa H. Epidemiology of functional gastrointestinal disorders in Japan and in the world. *J Neurogastroenterol Motil* 2015;21:320–9.
15. Gatti C, di Abriola FF, Dall'Oglio L, et al. Is the 13C-acetate breath test a valid procedure to analyse gastric emptying in children? *J Paediatr Surg* 2000;35:62–5.
16. Barbosa L, Vera H, Moran S, et al. Reproducibility and reliability of the 13C-acetate breath test to measure gastric emptying of liquid meal in infants. *Nutrition* 2005;21:289–94.
17. Jones BL, Pearce RE, Abdel-Rahman SM, et al. Characterization of delayed gastric emptying in children by the (13)C-acetate breath test. *J Breath Res* 2009;3:047004.
18. Sanaka M, Urita Y, Sugimoto M, et al. Comparison between gastric scintigraphy and the (13C)-acetate breath test with Wagner-Nelson analysis in humans. *Clin Exp Pharmacol Physiol* 2006;33:1239–43.
19. Glerup H, Bluhme H, Villadsen GE, et al. Gastric emptying: a comparison of three methods. *Scand J Gastroenterol* 2007;42:1182–6.
20. Braden B, Peterknecht A, Piepho T, et al. Measuring gastric emptying of semisolids in children using the 13C-acetate breath: a validation study. *Dig Liver Dis* 2004;36:260–4.

21. Knatten CK, Avitsland TL, Medhus AW, et al. Gastric emptying in children with gastroesophageal reflux and in healthy children. *J Pediatr Surg* 2013;48:1856–61.
22. Hellmig S, Von Schöning F, Gadow C, et al. Gastric emptying time of fluids and solids in healthy subjects determined by 13C breath tests: influence of age, sex and body mass index. *J Gastroenterol Hepatol* 2006;21:1832–8.
23. Hoekstra JH, van den Aker JH, Kneepkens CM, et al. Evaluation of 13CO2 breath tests for the detection of fructose malabsorption. *J Lab Clin Med* 1996;127:303–9.
24. Ravelli AM, Ledermann SE, Bisset WM, et al. Foregut motor function in chronic renal failure. *Arch Dis Child* 1992;67:1343–7.
25. Smith HL, Hollins GW, Booth IW. Epigastric impedance recording for measuring gastric emptying in children: how useful is it? *J Pediatr Gastroenterol Nutr* 1993;17:201–6.
26. Euler A, Byrne W. The gastric emptying rate of water in normal human children. *Pediatr Res* 1980;14:498.
27. Schmitz A, Kellenberger CJ, Liamlahi R, et al. Gastric emptying after overnight fasting and clear fluid intake: a prospective investigation using serial magnetic resonance imaging in healthy children. *Br J Anaesth* 2011;107:425–9.
28. Schmitz A, Kellenberger CJ, Lochbuehler N, et al. Effect of different quantities of a sugared clear fluid on gastric emptying and residual volume in children: a crossover study using magnetic resonance imaging. *Br J Anaesth* 2012;108:644–7.
29. Schmitz A, Kellenberger CJ, Liamlahi R, et al. Residual gastric contents volume does not differ following 4 or 6 h fasting after a light breakfast—a magnetic resonance imaging investigation in healthy non-anaesthetised school-age children. *Acta Anaesthesiol Scand* 2012;56:589–94.
30. Fahmy ME, Osman MA, Mahmoud RA, et al. Measuring of gastric emptying in Egyptian pediatric patients with portal hypertension by using real-time ultrasound. *Saudi J Gastroenterol* 2012;18:40–3.