Journal of Pediatric Gastroenterology and Nutrition
13:409–414 © 1991 Raven Press, Ltd., New York

Persistent Diarrhea: Total Gut Transit Time and Its Relationship with Nutrient Absorption and Clinical Response

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Summary: The study was undertaken to better understand the role of total gut transit time (TGTT) on the absorption of nutrients in patients with persistent diarrhea. Twenty-six boys aged 3–18 months with persistent diarrhea and 25 age-matched healthy controls were studied. Their TGTT was measured with charcoal markers during their treatment with a diet made up with rice powder, soya oil, glucose, and egg white. Coefficients of absorption of nutrients were estimated in a 72-h balance study. The median TGTTs in patients and controls were 5 and 11.6 h, respectively. Among the patients, the TGTT correlated significantly with absorption of total energy ($p < 0.01$), absorption of fat ($p < 0.01$), stool frequency ($p < 0.01$), and stool weight during the 1st 24 h ($p < 0.01$). Coefficients of absorption of energy, fat, and carbohydrate were significantly different among the patients above or below the median transit time (5 h). None of these relationships was present among the healthy controls. The TGTT was negatively associated with the duration of clinical recovery. The results of this study suggested that intestinal transit time is an important factor for absorption of nutrients that may influence clinical recovery in patients with persistent diarrhea. **Key Words:** Transit time—Nutrient absorption—Malnutrition—Recovery.

The interrelationship of diarrhea and malnutrition has been a subject of interest for several decades (1). The most significant effect of diarrhea in children is the reduction of weight percentiles (2,3). Malabsorption of nutrients due to diarrhea has been considered to be one of the mechanisms of malnutrition and the magnitude of nutrient loss may be related to intestinal transit time during the diarrheal episodes. Reduction in contact time due to rapid passage of intestinal contents during diarrhea is likely to impair digestion and subsequent absorption of dietary ingredients. Intestinal transit time has been reported to vary significantly during diarrhea or constipation (4). It has been reported by Molla et al. (5) that absorption of nutrients is not associated with the total gut transit time (TGTT) in acute diarrhea or during convalescence. There may be high risk of development of malnutrition from a persistent diarrhea episode due to significant malabsorption of nutrients (6). Since there is no available information on the role of TGTT (period taken for ingested food to pass from mouth to anus and excreted in stool) on nutrient absorption in persistent diarrhea compared to healthy controls, we investigated this issue in a 72-h metabolic balance study.

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MATERIALS AND METHODS

Subjects

Twenty-six boys aged 4–18 months with a history of persistent diarrhea (diarrhea of acute onset and lasting for more than 2 weeks, and with a frequency of three or more watery stools per day) were selected for the study. Patients who were exclusively

breast fed or had kwashiorkor, systemic infection, fever, bloody mucoid diarrhea, *Vibrio cholerae, Shigella* spp. or *Salmonella* spp. as enteropathogens were not included. Control children were selected of similar age without history of diarrhea during the previous 2 months and without having obvious malnutrition (≤75% weight/age). The controls allowed us to compare the effects of persistent diarrhea in malnourished patients with that in a healthy state. Prior approval by the Human Rights Ethical Committee of the International Centre for Diarrhoeal Disease Research, Bangladesh, was obtained. Informed and written consent was obtained from the parents of each child before inclusion in the study. The following routine investigations were performed for each patient on admission: stool pathogens in patients were identified by standard microbiological techniques for *V. cholerae, Shigella* spp., *Salmonella* spp., *Escherichia coli* ST and LT, *Campylobacter;* enzyme-linked immunoabsorbent assay for rotavirus in stool; microscopic examination of stool for identification of ova and parasites including formol ether concentration method for identification of *Giardia lamblia* and modified Ziehl Neelsen stain for cryptosporidium; urine analysis; blood electrolyte determination; and total and differential count of white blood cells.

Clinical Management

Initial rehydration was done by intravenous Dhaka solution (Na^+ 133, K^+ 13, Cl^- 98, and HCO_3^- 48 mmol/L) for moderate and severe dehydration. Strict inputs and outputs were maintained by eight hourly measurements of stool, urine, vomitus, food, and fluid. Daily body weight was determined during a scheduled period (9–10 a.m.). On admission, supine length was taken on a length board with a precision of 1 mm and middle upper arm circumference (MUAC) was taken by an insertion tape (TALC) to a sensitivity of 2 mm. All anthropometric measurements were taken by a trained nutritionist. Since no national reference for assessment of nutritional status is available this was calculated as a percentage of the 50th percentile National Centre for Health Statistics (NCHS) standard (7). Recovery was defined as the change of stool consistency from liquid to soft (that did not take the shape of the container) by 7 days with the study diet.

Measurement of Transit Time and Procedure of Balance Study

The patients and controls received an ad libitum intake of diet designed for persistent diarrhea (6) containing rice powder, 30 g/L; glucose, 25 g/L; soya oil, 20 g/L; egg albumin, 50 g/L; potassium chloride, 1 g/L; sodium chloride, 1 g/L; magnesium chloride, 0.5 g/L; and calcium chloride, 1 g/L, with energy density of 1.67 mJ/L and osmolality of 280 mmol/kg. The diet was continued for 7 days and breast milk intake was encouraged. Strict inputs and outputs were maintained. The test weighing method was applied for accurate estimation of breast milk intake. The balance study was started after a 24-h prebalance period with the study diet and was conducted according to the method previously described (5). A 0.5-g charcoal marker dissolved in water was fed, after which the study diet was given ad libitum. The time interval between feeding the charcoal marker and its first appearance in the stool was taken as the TGTT. The time of appearance of the marker in the stool was taken as the zero hour. All stools were collected till the appearance of the second marker, which was fed 72 h after the first one. The TGTT for control children was estimated similarly.

Biochemical Estimations

Five-milliliter aliquots from 72-h homogenized stool, vomitus, and urine samples were collected and preserved at −70°C until biochemical assays were done within a week. Duplicate samples were used for estimation of nutrients. The total number of calories was estimated by adiabatic bomb calorimeter (Gallenkamp, Leicestershire, England), nitrogen by micro-Kjeldahl method (8), and fat by Vande Kamer's method (9). Estimation of dietary nutrients was also done in duplicate. The coefficient of absorption of nutrients was estimated by the following calculation:

$$\text{coefficient of absorption} = \left(\frac{\text{intake} - \text{loss in stool}}{\text{intake}}\right) \times 100$$

Statistical Methods

Data were entered into the microcomputer using software Statpac Gold (Walonick Associates,

Minneapolis, MN, U.S.A.) and checked and analyzed by the statistical package SPSS/PC+ (SPSS Inc., Chicago, IL, U.S.A.). After examining for distribution of data, appropriate statistical tests were selected. The patients were grouped according to their TGTT values lying above or below the median, and the significance of the difference between means of the two groups was determined. Relationships were tested by linear and multiple regression analysis. Statistical significance was tested at the 5% probability level.

RESULTS

The selected general characteristics of the patients and the control subjects on admission are shown in Table 1. Twenty-one (81%) of the 26 cases recovered within 7 days. Four patients had known stool pathogens. Enterotoxicogenic *E. coli* was isolated in two patients, *Campylobacter jejuni* in one patient, and rotavirus in the other one. No ova or parasite was detected in the stool of the patients. The median TGTT was 5 h (range, 2.5–18.5) in the patients and that of control subjects was 11.6 h (range, 5–32.5). This difference was significant ($p < 0.0001$). On admission, the median weights for age of the cases and controls were 67 and 85% of 50th percentile NCHS standard ($p < 0.03$).

The median total energy intakes of the patients and controls were 96 and 79 kcal/kg/day ($p < 0.05$). There was no significant difference in median intake of the rice-based diet (60 vs. 68 kcal/kg/day), but there was significant difference in median breast milk intake (40 vs. 9 kcal/kg/day, $p < 0.03$). The patients obviously had significantly higher stool weights than the healthy controls during the balance study (6).

TABLE 1. *Selected general characteristics of patients with persistent diarrhea and control children on admission*

Characteristics	Median (range)	
	No. of patients (n = 26)	Controls (n = 25)
Age (mo)	8.5 (5–17)	10 (5–18)[a]
Weight (kg)	6.0 (4.3–8.4)	8 (6.7–11.7)[b]
Length (cm)	66.6 (56.0–75.0)	70.5 (60.5–79.5)[c]
Weight-for-age[d]	67 (47–90)	87 (76–109)[b]
Weight-for-length[d]	89 (64–108)	99 (81–117)[b]
MUAC (cm)	11.5 (9.0–13.7)	13.3 (11.5–14.9)[b]

MUAC, middle upper arm circumference.
[a] Not significant, Mann-Whitney U test.
[b] $p < 0.001$, U test.
[c] $p < 0.002$, U test.
[d] Percent of 50th percentile, National Centre for Health Statistics.

Coefficient of Nutrient Absorption

The absorption of nutrients in persistent diarrhea patients and the control subjects has been described previously in detail (6). The median coefficients of absorption of nutrients in control subjects were significantly higher than those in the patients. The coefficients of absorption for total energy, fat, nitrogen, and carbohydrate of control subjects were 89.8, 94.5, 70.3, and 93%, respectively, and those of patients were 68.2%, 60.3, 52.8, and 81.2%, respectively.

TGTT and Nutrient Absorption

Nutrient absorption and nutritional indices did not show any relationship with TGTT in the controls. There was no difference in either nutritional status or nutrient intake and absorption between the groups of healthy controls classified by the median TGTT (5 h) of the patients (Table 2).

Although there was no difference in age and nutritional status between the groups of patients, significant differences were detected in absorption of total energy, fat, and carbohydrate. The groups also showed significant differences in period of recovery and stool weight during the balance period (Table 2).

Table 3 shows that TGTT significantly correlated with absorption of total energy, stool frequency, and stool weight on admission in patients. The MUAC significantly correlated with stool weight, absorption of total energy, and fat. Stool weight negatively correlated with absorption of total energy ($p < 0.01$) and fat ($p < 0.001$). In these patients, stool weights and stool frequencies were in good agreement ($r = 0.8$; $p < 0.001$), which was expected.

Table 4 shows the coefficient of multiple regression taking absorption of total energy as a dependent variable. The coefficient of absorption was highly significant with the model ($r^2 = 0.7$, $p < 0.0001$) and then individually with the TGTT, MUAC, and stool weight during the 1st 24-h period.

TABLE 2. *Comparison of nutritional indices, diarrheal severity, and nutrient absorption below and above the median TGTT of patients (5 h)*

Variables	TGTT (mean ± SD)			
	Control		Patients	
	<5 h (n = 9)	5 h (n = 16)	<5 h (n = 15)	>5 h (n = 11)
Age (mo)	12.5 ± 4.9	10.4 ± 3.7	8.9 ± 2.1	10.0 ± 3.9
Weight for age, % of 50th percentile of NCHS	96 ± 9	96 ± 9	67 ± 12	68 ± 8
MUAC (cm)	13.4 ± 0.6	13.2 ± 0.9	11.5 ± 1.2	11.7 ± 1.3
Stool weight during balance period (g/kg/72 h)	—	—	443.4 ± 236.2	173.5 ± 120.7[a]
Period of recovery (days)	—	—	9.5 ± 9.7	4.2 ± 1.9[b]
Total energy intake (kcal/kg/day)	77.7 ± 16.5	77.8 ± 17.7	110.0 ± 31.0	94.0 ± 22.2
Coefficient of absorption of total energy (%)	89.6 ± 5.4	89.3 ± 5.8	54.8 ± 18.1	78.1 ± 12.2[c]
Coefficient of absorption of fat (%)	91.0 ± 8.6	91.3 ± 7.8	53.7 ± 20.7	72.1 ± 17.1[d]
Coefficient of absorption of nitrogen (%)	72.0 ± 12.0	65.7 ± 19.8	42.5 ± 25.8	44.1 ± 56.5
Coefficient of absorption of carbohydrate (%)	92.6 ± 4.0	91.3 ± 4.3	64.1 ± 22.4	86.5 ± 13.2[d]

Groups were compared within controls and patients. TGTT, total gut transit time; NCHS, National Centre for Health Statistics; MUAC, middle upper arm circumference.
[a] $p < 0.001$.
[b] $p < 0.02$.
[c] $p < 0.004$.
[d] $p < 0.05$.

DISCUSSION

A limitation of our study was that only TGTT was used for comparison of absorption whereas differentiation could not be made among the gastric, the small intestinal, and the colonic transit time. The colonic transit time may have a significant contribution in the TGTT, and its role on absorption of nutrients in persistent diarrhea is almost unknown. We did not study the digestive functions that might have been reduced in persistent diarrhea patients reflected in our previous study (6). It was found that the patients with persistent diarrhea had significantly reduced nutrient absorption compared with healthy controls. Patients were more malnourished than the controls but the difference in absorption of nutrients and diarrheal severity within patient groups was reflected according to length of transit time. Nevertheless, our study has several unique features for better understanding of persistent diar-

TABLE 3. *Correlations among the MUAC, stool frequencies, stool weight on admission, nutrient absorption, recovery period, and TGTT in patients with persistent diarrhea*

	Frequency of stool	Weight of stool on admission	Absorption of total energy	Absorption of fat	Absorption of nitrogen	Recovery	TGTT
MUAC (cm)	−0.35	−0.48[a]	0.54[a]	0.63[a]	0.03	−0.36	−0.01
Stool frequency on admission	—	0.77[b]	−0.75[b]	−0.64[b]	−0.12	0.26	−0.49[a]
Stool weight on admission	—	—	−0.78[a]	−0.70[b]	−0.20	0.44	−0.49[a]
Absorption of total energy	—	—	—	0.89[b]	0.22	−0.53[a]	0.54[a]
Absorption of fat	—	—	—	—	0.13	−0.51[a]	0.38
Absorption of nitrogen	—	—	—	—	—	−0.33	0.15
Period of recovery	—	—	—	—	—	—	0.35

TGTT, total gut transit time; MUAC, middle upper arm circumference.
One-tailed significance.
[a] $p < 0.01$.
[b] $p < 0.001$.

TABLE 4. *Coefficient of multiple regression taking absorption as a dependent variable and TGTT as an independent variable*

Variable	Coefficient	Standard error	Statistical significance (p value)
TGTT	0.024	0.011	0.03
MUAC (cm)	4.941	2.151	0.03
Stool wt[a] (gm/kg) (constant)	−0.115 (10.50)	0.039 (29.90)	0.008 (0.72)

TGTT, total gut transit time, MUAC, middle upper arm circumference.
Multiple R = 0.83973; R squared = 0.71; F = 17.53. Dependent variable = absorption of total energy.
[a] Stool weight in the 1st 24 h.

rhea on nutrient absorption, its relation with TGTT, nutritional status of the patients, and characteristics on initial appearance.

It has been shown that transit time has an effect on nutrient absorption (10) that was explored in our patients. In acute diarrhea, patients' carbohydrate absorption ranges from 76 to 91% when the TGTT ranges from 3.6 to 7.3 h for different etiological groups (5). No relationship was found between the TGTT and nutrient absorption in acute diarrhea whereas in our patients there were striking differences in absorption, stool weight, and diarrheal duration according to total transit time. The median TGTT in our patients was less than half of that in the controls. Patients had a higher stool weight, higher malabsorption of nutrients, and lower nutritional status compared to the control children. The dietary intake from the rice-based diet was not different between patients and controls. This is in agreement with a previous observation that patients with anorexia due to diarrhea consumed a substantial amount of food when it was offered (5). The carbohydrate-based diet could cause osmotic diarrhea in these malnourished persistent diarrhea patients (11) that was not investigated. Significantly higher breast milk intake among the patients contributed to higher energy intake. The controls, being healthier, might be meeting most of their energy requirements from the diet since their coefficient of absorption was much higher. Increased breast milk intake in the face of possible mucosal injury (12), associated lactase deficiency (11), and reduced pancreatic enzyme levels (13) due to malnutrition might have contributed to increased malabsorption of nutrients in the patients. Breast milk contains a considerable amount of lactose (70 g/L); this might have caused lactose malabsorption in the lactase-deficient patients, contributing to excess osmotic load and increased stool weight.

The duration of recovery was significantly shorter in patients with longer TGTT and correlated negatively with nutrient absorption. There was a significant positive correlation between the TGTT and nutrient absorption. This indicates that a longer TGTT was associated with increased nutrient absorption and in turn might have enhanced recovery through nutritional benefits at the mucosa (14). On the other hand, nutrient absorption in chronic nonspecific diarrhea syndrome is not related to TGTT where mucosal injury is usually absent (15). In this study, digestive functions were not studied, yet the associated mucosal injury might increase malabsorption of nutrients, especially when TGTT was shorter.

In our patients, shorter TGTT, smaller MUAC, and higher stool weight were significantly related to reduced absorption of nutrients with a linear regression analysis. The effect of TGTT on nutrient absorption was evident even after controlling for other variables using a multiple regression model. The relationship has been clear, yet the effects of nutritional status and diarrheal severity remain an important determinant of nutrient absorption. Stool weight was negatively correlated with MUAC. Stool weight correlated negatively with nutrient absorption, which could be due to impaired digestion and/or absorption and a consequence of osmotic diarrhea. No direct relationship between the nutritional status and TGTT could be detected.

The absorption in healthy controls in relation to TGTT is in agreement with the previous reports (4,5) that healthy subjects can have a better absorption even with a short transit time. The plausible cause is the presence of adequate digestive activity in the healthy subjects. However, the underlying factors for the lower absorption of nitrogen were not understood clearly.

It is concluded from our study that the coefficient

of absorption of nutrients is significantly related to the TGTT in persistent diarrhea patients. Clinical implication would suggest formulation of diets with ingredients that are absorbed better and do not cause osmotic diarrhea. Dietary fat is known to increase transit time in chronic nonspecific diarrhea syndrome but it remains to be seen whether a further increase of fat in these children would be beneficial.

Further studies might be undertaken using a radiopaque nonabsorbable marker or radiolabeled stable isotopes for differentiation in gastric and small and large intestinal transit times and their relation with nutrient absorption in persistent diarrhea patients, which may lead to a better understanding of this disease. We suggest further studies be undertaken with appropriate diets and/or drugs to increase TGTT for better absorption of macronutrients, which may enhance clinical recovery from persistent diarrhea.

Acknowledgment: The authors are grateful for the financial support of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B). The ICDDR,B is supported by countries and international agencies that share its concern for the health problems of developing countries. Current donors include the aid agencies of the governments of Australia, Bangladesh, Belgium, Canada, Denmark, France, Japan, the Netherlands, Norway, Sweden, Switzerland, and the United Kingdom, and the United States; international organizations including the United Nations Capital Development Fund, the United Nations Development Programme, the United Nations Children's Fund, and the World Health Organization; and private foundations including the Ford Foundation and the Sasakawa Foundation. We thank Prof. R. Eeckels, ex-Director of ICDDR,B, for his encouragement in this work. We are grateful to Dr. D. Mahalanabis for reviewing this manuscript, Mr. M. A. Wahed and Ms. Ferdous Jahan for the biochemical work, and Mr. M. Ramzan Ali for secretarial work.

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