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Persistent diarrhoea: factors affecting absorption and clinical prognosis during management with a rice-based diet

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Twenty-six persistent diarrhoea patients aged 4 to 18 months were treated with a diet prepared with rice powder, soya oil, glucose, egg white and water. Absorption of macronutrients was estimated in a 72 h balance study and clinical response was examined during one week of dietary treatment. Nutrient absorption was compared with that of 25 healthy age-matched controls treated with the same diet. Twenty-one patients (81%) recovered from diarrhoea within seven days. Absorption of nutrients was significantly reduced among the persistent diarrhoea patients. More malnourished patients had a significantly reduced absorption of nutrients except carbohydrate and an increased severity and longer duration of diarrhoea. Total gut transit time had significant association with nutrient absorption in the persistent diarrhoea patients. The period of recovery negatively correlated with coefficient of absorption and positively with initial stool weight. Failure to recover was associated with severity of diarrhoea and systemic infection. The study indicates that nutrient absorption is significantly reduced in patients with persistent diarrhoea and nutritional status, and that initial purging rate and intestinal hurry are significantly related to the prognosis and nutrient absorption. □ *Absorption, coefficient, malnutrition, recovery, transit time*

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A significant risk of malnutrition and mortality are associated in persistent diarrhoea (an episode of acute diarrhoea which continues for more than two weeks). Management of this syndrome remains difficult and pathophysiology is little understood. Compared with acute diarrhoea, rehydration has a limited role and dietary manipulation remains the cornerstone of successful management of persistent diarrhoea (1). It has been reported that malnourished patients with acute diarrhoea suffer from increased severity (2) and duration (3) and may have a 14 times higher risk of mortality after discharge from the diarrhoea treatment centre (4). Recent studies have also documented that the incidence of persistent diarrhoea is higher in malnourished children (5, 6). However, there is little information about the effect of persistent diarrhoea on nutrient absorption and factors determining nutrient absorption and prognosis of persistent diarrhoea. To understand the above issues, we undertook a study with a 72 h balance period and a seven day dietary therapy in persistent diarrhoea patients and healthy controls using a rice-based lactose-free diet in the clinical research centre of the International Centre for Diarrhoeal Disease Research, Bangladesh..

Patients and methods

Twenty-six male patients aged 4–18 months who had liquid or watery stools with a frequency of three or more per day for at least 14 days were selected. Exclusion criteria included exclusive breast-feeding, presence of acute diarrhoeal pathogens such as *V. cholerae*, *Salmonella* or *Shigella* spp., systemic infections and kwashiorkor. Controls were selected from age-matched healthy children with no history of diarrhoea within the previous two months and no obvious malnutrition. Subjects taken as controls were selected from the children who attended the ICDDR,B outpatient department for the treatment of acute diarrhoea at least two months previously. They were contacted by the health workers and after carefully checking their history of not having had a diarrhoea within two months and having no signs of protein energy malnutrition (> 75% weight-for-age) were selected as controls. These children had no systemic disease except minor skin infections such as scabies. They were given the same diet ad libitum as was given to the patients with persistent diarrhoea. Breast-feeding was encouraged in both groups. Acceptability of the diet was similar in both the patients and the controls.

The study was approved by the ICDDR,B Ethics Review Committee. Informed consent was obtained from the parents of the children. Initial clinical management of patients included rehydration by intravenous fluid, eight hourly measurements of food and fluid intake, stool, urine and vomitus. Enteropathogens identified from stools included *V. cholera*, *Shigella* spp., *Salmonella* spp., enterotoxigenic *Escherichia coli*, *Campylobacter jejuni*, and Rotavirus. Anthropometric data on body weight, supine length and mid-upper arm circumference (MUAC) were taken by a trained nutritionist. Measurements were taken to the nearest 1 g for body weight, 1 mm for length and 2 mm for MUAC. Breast milk intake was estimated by the test weighing method. Mothers were told to inform the 24 h attendants about the desire of breast-feeding and subjects were weighed both before and after breast-feeding. The difference in body weight gave the amount of breast milk. Amount of urine or stool passed during the breast-feeding was added to the body weight taken after the breast-feeding. The patients were given an inexpensive local diet (cost USD 0.30 per litre) prepared with rice powder (30 g/l), egg white (50 g/l), soya oil (20 g/l), glucose (25 g/l), potassium chloride (1 g/l), sodium chloride (1 g/l), magnesium chloride (0.5 g/l), calcium chloride (1 g/l) and water (935 ml), which gave a cooked volume of 1 litre, energy 400 kcal/l, 8% protein and osmolality 280 per kg. Patients whose stool consistency improved from liquid to soft within seven days of dietary therapy were considered to have recovered from diarrhoea. To determine nutrient absorption, a 72 h balance study was carried out after a 24 h pre-balance period with the above study diet. Details of the method of balance study have been described previously (8). Briefly, 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 of the charcoal marker and its first appearance in the stool was taken as the total gut transit time (TGTT). A second marker was given 72 h after the first one. Aliquots of 72 h stools were analysed for total fat by Van de Kamer's method (9), nitrogen by the Microkjeldahl method (10) and total energy by adiabetic bomb calorimeter (Gallenkamp). Carbohydrate absorption was calculated by subtracting energy for fat and nitrogen from the total energy.

The coefficient of nutrient absorption was calculated as ((intake-loss)/intake) × 100. Stool weights and nutrient intake were expressed in g/kg body weight/day and total energy intake by Kcal/kg body weight/day.

Anthropometric assessment and nutritional classification

Weight-for-age, weight-for-length and length-for-age were expressed as percentages of the median values of the NCHS standard (11). MUAC was measured with an insertion tape with an accuracy of 2 mm (Teaching Aid at Low Cost, UK). Patients were classified into two nutritional groups below and above the anthropometric cut-off points as follows. The cut-off point for weight-for-age was 65%, below which a sharp rise in death rates has been reported by nutritional studies in this region (4, 12). The cut-off point for weight-for-length was taken at 80% to identify the wasted children (13). The cut-off point for MUAC was taken at 11 cm, below which the risk of death rises sharply (14).

Clinical management of patients

The patients were rehydrated with intravenous 'Dhaka Solution' (15) (Na 133 mmol/l, K^+ 13 mmol/l, Cl-98 mmol/l, HCO^{3-} 48 mmol/l). After initial observation for 8 h, the study diet was given ad lib for a 24 h pre-balance period followed by a 72 h balance period (8) and then continued for seven days. Patients having diarrhoea after seven days were defined as failures and were given a comminuted chicken diet (1) (ground chicken meat with glucose, soya oil, salts and water) or drugs according to the practice in ICDDR,B.

Statistical procedure

For non-normally distributed data, comparison between groups was done using the Mann-Whitney U test. Data were log-transformed when distribution was skewed and parametric tests were used. Multiple linear regression was performed in statistical models taking recovery period and coefficient of absorption as dependent variables. Statistical significance was assumed at 5% probability level.

Results

Twenty-one out of 26 patients recovered within seven days of starting the study diet with a median recovery period of four days. Patients who failed to recover had stool weight static or increased. Enteropathogens such as enterotoxigenic *E. coli*, *Rotavirus*, and *Campylobacter jejuni* were isolated from four patients. Among the failure cases, one developed bronchopneumonia, one both bronchopneumonia and septicaemia and one urinary tract infection with *E. coli* (2×10^6).

Median weight of stool of the diarrhoeal patients was 98 g/kg/day and frequency was 14/day on admission. At the end of five days on the study diet, those reduced significantly to 65 g/kg/day and 7/day respectively.

Table 1 compares the characteristics between the patients and controls. Age was similar in both groups but nutritional status was significantly better in the controls as selected.

During the 72 h balance period, median energy intake from the study diet was comparable between the patients and controls (0.29 MJ vs 0.26 MJ/kg/day, $p = 0.6$) but intake from breast milk was higher among the patients (0.18 vs 0.04 MJ/kg/day, $p < 0.001$). Loss of

Table 1. General characteristics of patients with persistent diarrhoea and control children on admission. Median (range).

Characteristics	Patients ($n=26$)	Controls' ($n=25$)
1. Age (mo)	8.5 (5–17)	10 (5–8)‡
2. Weight (kg)	6.0 (4.3–8.4)	8.0 (6.7–11.7)*
3. Length (cm)	66.6 (56.0–75.0)	70.5 (60.5–79.5)**
4. Weight-for-age†	67 (47–90)	85 (68–109)*
5. Weight-for-length†	81 (64–108)	99 (81–117)*
6. MUAC (cm)	11.5 (9.0–13.7)	13.3 (11.5–14.9)*

Mann Whitney U test. ‡ Not significant. * Significant ($p=0.001$). ** Significant ($p=0.002$). † % of 50th centile of NCHS.

Table 2. Comparison of the coefficients of absorption between the persistent diarrhoea subjects and their controls. Median (range).

Macronutrients	Cases ($n=26$)	Controls ($n=25$)	Statistical* significance (p value)
1. Total energy	68.2 (27.6–92.0)	89.8 (76.3–98.8)	0.001
2. Nitrogen	52.8 (−122–82.1)	70.3 (9.6–94.7)	0.001
3. Fat	60.3 (21.0–96.5)	94.5 (71.2–99.1)	0.001
4. Carbohydrate	81.2 (23.1–96.7)	92.6 (84.7–98.0)	0.001

* Mann–Whitney U test.

nutrients in stool was almost four times higher in the patients compared to the control (6.9 vs 1.8 MJ/kg/day, $p<0.001$). Seven of 26 persistent diarrhoea patients were in negative nitrogen balance.

Coefficients of absorption of nutrients have been compared between the patients and control children in Table 2. Coefficients of absorption of fat, protein and carbohydrate reduced to 36%, 25% and 12% respectively compared to the controls. Overall absorption reduced to 68% in patients as opposed to 90% in the controls. Carbohydrate absorption was least affected. In two of the controls, median coefficients of absorption of nitrogen were very low: 10% and 37% respectively.

Effect of nutritional status on stool weight, period of recovery and coefficients of absorption of energy and nutrients in persistent diarrhoea have been shown in Table 3. Patients having lower weight-for-age (<65% of median NCHS standard), lower weight-for-height (<80% of median NCHS) and lower MUAC (<11.0 cm) had significantly higher stool weight, longer recovery period and lower coefficients of absorption of total energy and fat. Coefficient of absorption of nitrogen, however, was not significantly reduced in the wasted children but was reduced in the undernourished children. Coefficient of absorption of carbohydrate was not reduced in any of the malnourished group.

The effect of stool weight, mid-upper arm circumference (MUAC) and total gut transit time (TGTT) on the coefficient of absorption of total energy was assessed using multiple linear regression analysis (Table 4). Stool weight in the first 24 h showed a significantly negative

Table 4. Coefficients of multiple regression taking absorption as dependent variable.

Multiple variable	Coefficient	SE	Statistical significance (p value)
TGTT	0.024	0.011	0.03
MUAC (cm)	4.941	2.151	0.03
Stool wt* (g/kg/day)	−0.115	0.039	0.008
(Constant)	10.501	29.892	0.72

* Stool weight in the first 24 h.
R = 0.84, R square = 0.71, $p<0.001$.

Table 5. Coefficients of multiple regression taking period of recovery as dependent variable.

Multiple variable	Coefficients	SE	Statistical significance (p value)
Log absorption	−1.204	0.475	0.01
Log stool weight	0.053	0.236	0.82
Log MUAC	−0.829	1.095	0.45
Log energy intake	0.858	0.427	0.05
(Constant)	2.945	3.652	0.19

R = 0.76, R square = 0.58, significance 0.0008.

Table 3. Outcome of dietary therapy according to nutritional status of the patients (% median NCHS standard). Median (range).

Outcome variables	≤65% ($n=11$)	>65% ($n=15$)	≤80% ($n=14$)	>80% ($n=12$)	≤11 cm ($n=10$)	>11 cm ($n=16$)
	Weight for age		Weight for length		MUAC	
Stool weight (g/kg)	479 (56–859)	195* (50–727)	345 (120–859)	186* (50–57)	476 (56–859)	202* (50–547)
Period of recovery (days)	6 (2–39)	3† (2–11)	6 (3–39)	3† (2–9)	7 (2–39)	4* (2–9)
Coefficient of absorption (%)						
Total energy	54 (28–77)	74† (30–92)	53 (28–90)	74* (53–92)	50 (28–77)	73† (53–92)
Fat	48 (21–97)	71† (38–95)	51 (21–97)	65* (44–95)	44 (21–65)	71† (44–97)
Nitrogen	48 (−10–63)	63† (−122–82)	53 (−10–70)	55 (−122–82)	31 (−10–63)	60† (−122–82)
Carbohydrate	73 (32–97)	85 (23–97)	77 (23–97)	85 (49–94)	64 (23–97)	85 (55–97)

*$p<0.05$; †$p<0.005$. (Mann–Whitney U test).

Table 6. Comparison of general features and dietary response between the improved and failure cases. Median (range).

	Success ($n=21$)	Failures ($n=5$)	Statistical significance (p value)
Duration of diarrhoea before admission (days)	17 (14-60)	25 (15-45)	NS
Age (months)	9 (5.0-1.7)	8 (7-11)	NS
Wt-for-age (% median NCHS)	67 (49-91)	63 (47-71)	NS
Wt-for-length (% median NCHS)	81.7 (66.4-90.7)	79 (64.7-83.1)	NS
MUAC (cm)	11.7 (9-13.7)	10.5 (9.4-10.9)	NS
Stool weight 1st 24 h ml kg^{-1} day^{-1}	91.8 (30-203.3)	236 (87.2-213.6)	0.01
72 h total stool weight	208.8 (50-605.8)	727 (285-859)	0.006
Coefficient of absorption total energy (%)	73 (28-92)	36 (29-63)	0.006
Fat (%)	61 (21-97)	38 (26-60)	0.02
Nitrogen (%)	59 (−122-82)	13 (−104-38)	0.006
Carbohydrate (%)	85 (35-97)	49 (23-94)	NS
Nitrogen balance (8N)	0.12 (−0.4-0.32)	−0.03 (−0.5-0.09)	0.003
Recovery (days)	4 (2-7)	15 (9-39)*	0.001

Mann-Whitney U test.
*Failure group with other management.

relationship ($p<0.05$) and MUAC and TGTT a significantly positive relationship ($p<0.03$) with coefficient of absorption.

Effects of nutrient absorption on period of recovery were assessed using multiple linear regression analysis including MUAC and dietary intake as continuous independent variables, because nutritional status and dietary intake have a marked effect on the recovery process (Table 5). Absorption of nutrients was negatively associated and energy intake positively associated with the duration of recovery ($p<0.01$ and $p<0.05$ respectively).

Table 6 compares the characteristics of the patients between those who improved ($n=21$) within seven days and those who failed ($n=5$) to improve. Intake of total energy or breast milk was comparable between the groups. However, median stool weights during the first 24 h of the balance period were significantly higher ($p<0.01$) in the failure group. Stool output during the balance period was also significantly higher (727 g/kg vs 209 g/kg, $p<0.006$) in the failure group. Coefficients of absorption of total energy, fat and nitrogen were significantly lower ($p<0.006$, $p<0.02$ and $p<0.006$ respectively) in the patients who failed to improve. Although carbohydrate absorption was lower by 42% in the failure group it was not statistically significant. As a result, significantly higher nutrient loss was observed in the failure group. Median duration for recovery among the improved patients was four days compared to 15 days in the failure group ($p<0.001$), who were subsequently managed with other drugs or diets.

Discussion

Persistent diarrhoea patients in this study are relatively severely afflicted cases who attended the diarrhoea treatment centre compared to those who remained in the community. Twenty-one of 26 (81%) persistent diarrhoea patients were successfully managed with an inexpensive local diet in a remarkably short period of time (median four days). The patients were more malnourished than the healthy controls. Hence the effects of persistent diarrhoea on the absorption of nutrients might partly have reflected the effect of malnutrition. However, the difference in absorption between the malnourished children and the well nourished children in the absence of diarrhoea is not known. This low cost culturally acceptable diet is easy to prepare and does not require logistic support like electricity or refrigeration, which are unavailable in most homes of the least developed countries. Digestibility is expected to be optimal as the ingredients contained rich starch, soya oil, egg albumin and glucose. Despite this, the absorption of fat, protein and carbohydrate was severely reduced among the patients.

The changes in small intestinal mucosal morphology and of absorption of water, electrolytes and nutrients are not known in persistent diarrhoea. Further complexity arises from the role of nutritional status, as prolonged diarrhoea can cause significant malnutrition to the patients while malnourished subjects contract more frequent diarrhoea and have a more severe and protracted course of diarrhoea. It is reported that malnourished children are deficient in digestive enzymes (16) and persistent diarrhoea is likely to cause more malabsorption and osmotic diarrhoea. Reduction of total digestive and absorptive surface area in malnourished patients plausibly explains the increased diarrhoea due to impaired fluid and nutrient absorption. Malnutrition in persistent diarrhoea patients may be an effect of diarrhoea but it is unlikely to be explained by only two weeks' diarrhoea. Pre-existing malnutrition might further deteriorate during the persistent diarrhoeal episode.

The effect of nutritional status on severity of diar-

rhoea has been reflected by three times higher stool weight among the more malnourished patients. This is consistent with a previous finding in cholera patients (2). Nutrient malabsorption, mucosal injury and severity of diarrhoea may affect the duration of recovery. In malnourished patients, recovery took twice as long as in the better nourished patients. There was no significant difference in carbohydrate absorption according to nutritional status. A modest amount of starch and glucose in the diet was probably well handled by the small intestine. Salivary amylase, pancreatic amylase and brush border maltase were less affected in malnutrition (16, 17). Reduced absorption of fat and protein in the more malnourished patients could be related to the insufficient exocrine pancreatic functions (17).

Duration of recovery could be a dependent of nutritional status or a function of absorption. Although the latter two were interrelated, multiple regression analysis showed that recovery had significant relationships with coefficients of absorption. Moreover, absorption of energy was affected positively by MUAC and TGTT and negatively by stool weight. Transit time is associated with malabsorption of nutrients and stool weight in our study. A previous study in children with acute diarrhoea, however, failed to document this (18). Increased transit time is dependent on intestinal peristaltic movements and fluid load in the intestine, which may occur due to osmotic diarrhoea from unabsorbed nutrients. Therefore, patients with low MUAC or high purging rate may be expected to have reduced absorption and delayed recovery from persistent diarrhoea.

A coexistence of high stool weight and nutrient malabsorption was noted among the patients who failed to improve. It is plausible that patients who presented with severe diarrhoea had more malabsorption during the treatment period. It was noted that there was no difference in the nutritional status between those who recovered and those who failed to recover. The patients in the failure group, however, presented with about a week longer duration of diarrhoea; they had 40% higher dietary intake and higher initial stool weight indicating more severe diarrhoea. They might have more severe mucosal injury, which was not investigated in this study.

The results suggest that 81% of the persistent diarrhoea patients improved within a week with a simple rice-based diet, despite a significant reduction in nutrient absorption. Malnutrition was responsible for severity of diarrhoea, delayed recovery and reduced absorption. As carbohydrate absorption is less affected in persistent diarrhoea, dietary management should include cereals which are locally available. Dietary management of severe persistent diarrhoea patients may be developed using information generated from this study.

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