Original Article

Pancreatic exocrine insufficiency in malnourished children and those with persistent diarrhoea

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Background and Objectives: Persistent diarrhoea, a serious health problem, is closely related to malnutrition. Children with severe malnutrition have a 9-fold risk of death, and children with severe stunting have a 4-fold risk of death. Prolonged mucosal injury from diarrhoea causes reduced secretin and cholecystokinin secretion, which decreases stimulation to the pancreas, and is indicated by faecal elastase-1 levels. This further aggravates persistent diarrhoea and malnutrition because of the low levels of digestive enzyme production. This study evaluated the exocrine function of the pancreas in children with persistent diarrhoea and malnutrition. **Methods and Study Design:** This study used a cross-sectional design to compare exocrine pancreatic function among children with persistent diarrhoea, children with malnutrition, and apparently healthy children as reference Children aged 6–60 months were selected from the inpatient and outpatient units of various general hospitals in Jakarta. Faecal elastase-1 levels were used to determine exocrine pancreatic function. **Results:** The median values of faecal elastase-1 in children with persistent diarrhoea, children with malnutrition, and reference children were 743 (1–1503) mcg/g, 861 (17–2909) mcg/g, and 1210 (26–3000) mcg/g, respectively. A significant difference was observed in the faecal elastase-1 levels between reference children and those with persistent diarrhoea ($p<0.001$). However, no differences in the faecal elastase-1 levels were noted between malnourished and reference children ($p>0.05$). Children with both persistent diarrhoea and malnutrition showed mean FE-1 392.3±206.9 and median 419 (125-593). **Conclusions:** Exocrine pancreatic insufficiency is found in children with persistent diarrhoea. Children with combined persistent diarrhoea and malnutrition have the lowest FE-1, to which persistent diarrhea has the most significant contribution.

Key Words: persistent diarrhoea, undernutrition, exocrine pancreatic insufficiency, faecal elastase-1, children

INTRODUCTION

Diarrhoea is the second leading cause of death in children under five years of age, responsible for one in every nine of these deaths.[1,2] The WHO considers diarrhoea one of the most prominent causes of malnutrition in children under five years of age.[3] Notably, diarrhoea lasting for ≥14 days is termed persistent diarrhoea, and is a serious health problem that causes 36%–45% of all diarrhoea deaths.[4-6] In Indonesia, the prevalence of persistent diarrhoea is 0.1%, with the highest incidence observed in children aged 6–11 months.[7]

Malnutrition is very common in children with persistent diarrhoea. The Indonesian Basic Health Research (Riskesdas, 2013) reported that compared with the prevalence in 2010, the prevalence of acute and chronic malnutrition in Indonesian children has been increasing despite aggressive preventive measures, from 17.9% to 19.6% for acute malnutrition and from 35.6% to 37.2% for chronic malnutrition.[8] Children with severe malnutrition have a 9-fold risk of death, and children with severe stunting have

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a 4-fold risk of death.[9,10] Malnutrition is also associated with lower socio-economic conditions.[11]

The pancreas plays a significant role in the digestive system. Acinar cells, which make up the exocrine pancreas gland, synthesise and secrete most of the essential digestive enzymes for nutrient digestion.[12,13] Thus, a disruption in pancreatic functioning can have serious consequences for the body, because if the nutrients are not absorbed properly, then persistent diarrhoea, malnutrition, and growth and development problems can ensue. The disruption may not be symptomatic and may go unnoticed.[14]

The role of the pancreas, especially in terms of the absorptive function and nutritional status, has not been properly examined in children in Indonesia. The maldigestion of nutrients can manifest as persistent diarrhoea, malnutrition, or growth and development problems. Algerina (2000) studied 36 children with prolonged diarrhoea (diarrhoea persisting for 7–14 days) and reported that the levels of carbohydrate, protein, and fat malabsorption were 25%, 94.4%, and 100% respectively.[15] Prolonged mucosal injury in persistent diarrhoea is thought to cause reduced secretin and cholecystokinin secretion, which reduces the stimulation to the pancreas and results in reduced pancreatic enzyme production.[16]

Indonesia is a developing country, with an increasing number of malnutrition cases.[8] Therefore, accurate data regarding exocrine pancreatic functioning in children with persistent diarrhoea and malnutrition are required. Consequently, this study evaluated the exocrine pancreatic functioning in children with persistent diarrhoea and malnutrition.

MATERIALS AND METHODS

This cross-sectional study compared the exocrine pancreatic functioning among children with persistent diarrhoea, children with malnutrition, and apparently healthy children as reference children (RC). It is part of a larger study, where FE-1 in RC will be reported separately in detail but is used in this report as reference values. This study recruited participants from the inpatient and outpatient units of Harapan Kita Women and Children Hospital, Dr. Cipto Mangunkusumo Hospital, Budhi Asih Hospital, Persahabatan Hospital, and Fatmawati Hospital from January 2015 to July 2016. Children aged 6–60 months were selected and further categorised into persistent diarrhoea, malnutrition, and reference groups. Children diagnosed with exocrine pancreatic dysfunction at birth, those with confirmed inflammatory bowel disease or other types of chronic diarrhoea, and those who had consumed antacids, antidiarrheal or antiparasitic medications, antibiotics, or laxatives within 2 days before sample collection were excluded. Consecutive sampling was performed for the persistent diarrhoea and malnutrition groups, and RC were selected through stratified random sampling.

After obtaining informed consent from the parents or guardians of the children who fulfilled the inclusion criteria, the primary data questionnaire was completed through an interview, followed by the measurement of body weight, height, head circumference, and arm circumference. We educated the childrens' parents/guardians regarding the procedures for collecting, storing, and transporting faecal samples, and provided the necessary tools. When the samples arrived at the laboratory, macroscopic, microscopic, and chemical faecal analyses, as well as acid steatocrit examination and faecal elastase-1 (FE-1) examination through the ELISA method, were conducted; we also determined the serum prealbumin levels in children with persistent diarrhoea.

Data were analysed using SPSS for Windows version 11.5 (SPSS Inc. 2004, Chicago, USA). Univariate and bivariate analyses were performed to evaluate the relationships between variables, in accordance with the specific aims of this study. Ethical clearance was obtained from the Ethics Committee of the Faculty of Medicine Universitas Indonesia-Dr Cipto Mangunkusumo Hospital.

RESULTS

A total of 182 children aged 6–60 months participated in this study; among them, 31 children had persistent diarrhoea, 31 children were malnourished (moderate or severe malnutrition), and 120 were RC. Table 1 shows the demographic data and characteristics of the children. Notably, the highest percentage of exclusive breastfeeding was observed in the RC group (67 children), and a significant statistical difference was observed in the proportion

Table 1. General characteristics of reference children, children with persistent diarrhoea, and children with malnutrition

	Reference (n=120)	Persistent diarrhoea (n=31)	Malnutrition (n=31)
Number of subjects	120	31	31
Age (months)	33.5 (6-59)†	19 (8-51)†	16 (6-59)†
Gender, n (%)			
Boys	48 (40)	20	15
Girls	72 (60)	11	16
Exclusive breastfeeding, n (%)	75 (62.5)	9*	13**
Socioeconomic (regional minimum salary), n (%)			
>Minimum regional salary	45 (37.5)	19	9
<Minimum regional salary	75 (65.2)	12	22
Birth weight (gram)	3111 (475)‡	2906 (531)‡	2724 (515)‡***

†Mean (SD).
‡Median (min–max).
*Significantly differs from the normal group (p<0.001); **Significantly differs from the healthy group (p=0.038); ***Significantly differs from the healthy group (p=0.01).

Table 2. Clinical characteristics of reference children, children with persistent diarrhoea, and children with malnutrition

	Reference(n=120)	Persistent diarrhoea (n=31)	Malnutrition (n=31)
Anthropometric			
Weight (kg)	12 (6.9-21)‡	10 (2.55)†	7 (3.3-17)‡
Height (cm)	89 (63-116)‡	80.4 (8.28)†	75 (56-117)‡
Head circumference (cm)	48 (38-52)‡	45.4 (3.02)†	45 (37-50)‡
Arm circumference (cm)	15 (12-21)‡	15 (1.99)†	12.9 (2.2)†
Nutritional status, n (%)			
Normal	120 (100)	23	0
Moderate-severe malnutrition	0 (0)	8	31
Clinical symptoms			
Frequency of bowel movements (times)	1 (1-3)‡	5 (3-15)‡	1 (1-5)‡
Loose stools consistency, n (%)	7 (5.8)	30	3
Abnormal faeces colour, n (%)	5 (4.2)	7	0
Mucous, n (%)	4 (3.3)	26	1
Acidic/foul smell, n (%)	6 (5)	25	4
Abdominal pain, n (%)	5 (4.2)	12	1
Bloating, n (%)	0 (0)	2	0

†Mean (SD).
‡Median (min–max).

Table 3. Laboratory examination results of reference children, children with persistent diarrhoea, and children with malnutrition

	Reference (n=120)	Persistent diarrhoea (n=31)	Malnutrition (n=31)
Fecal analysis, n (%)			
pH <6.0	11 (9.2)	7	5
Sugar +/++/+++	27 (22.5)	14	11
Leukocytes/HPF >5	4 (3.3)	9	3
Erythrocytes/HPF >3	2 (1.7)	5	0
Amylum +	25 (20.8)	7	9
Muscle fibres +	31 (25.8)	11	8
Fat +/++/+++	8 (6.7)	11	3
Steatocrit	0 (0-38.5)†	0 (0-87)†	3.6 (0-33.3)†
Fecal elastase-1	1210 (26-3000)†	743 (1-1503)†	861 (17-2909)†

†Median (min–max)

of exclusive breastfeeding between children with persistent diarrhoea and RC (p<0.001) and between malnourished and RC (p=0.038). The socioeconomic status of children with malnutrition was lower than that in the other groups. The difference in the proportion of low birth weight between the malnutrition and reference groups was statistically significant (p=0.010)

The anthropometric status in the malnutrition group was lower than that in the other groups; this was determined from the median body weight, median height, and mean arm circumference of the children. Additionally, the frequency of bowel movement, percentage of loose stools, abnormal (green) faeces colour, the presence of mucous, the presence of foul-smelling or acidic smelling stools, and the presence of abdominal pain and bloating were higher in the persistent diarrhoea group than in the other groups (Table 2).

The laboratory characteristics of the children in the persistent diarrhoea, malnutrition, and reference groups are presented in Table 3. The highest abnormal values for the faecal analysis and the steatocrit and FE-1 tests were observed in the persistent diarrhoea group. Statistically, a significant difference was observed in the fat variables between the persistent diarrhoea and malnutrition groups (p=0.015) and the persistent diarrhoea and RC (p<0.001).

The highest steatocrit level was observed in the persistent diarrhoea group (87%). The differences in the steatocrit levels among the three groups were statistically nonsignificant (p=0.113). Moreover, the lowest median value of FE-1 was observed in the persistent diarrhoea group (743 mcg/g).

The distribution of FE-1 levels in the persistent diarrhoea, malnutrition, and reference groups is depicted in Figure 1. The Kruskal–Wallis test showed a significant difference in the FE-1 levels between the persistent diarrhoea and reference groups (p<0.001). However, no significant difference was observed the between persistent diarrhoea and malnutrition groups (p=0.186), nor the malnutrition and reference groups (p=0.202). Children with both persistent diarrhoea and malnutrition have the lowest FE-1 and the most narrow FE-1 range with mean FE-1 392.3±206.9 and median 419 (125-593). There was significant difference between reference children and persistent diarrhea and malnutrition tested using independent T-test (p<0.001) with the mean difference of 911.623 (95% CI: 674.612 to 1148.633)

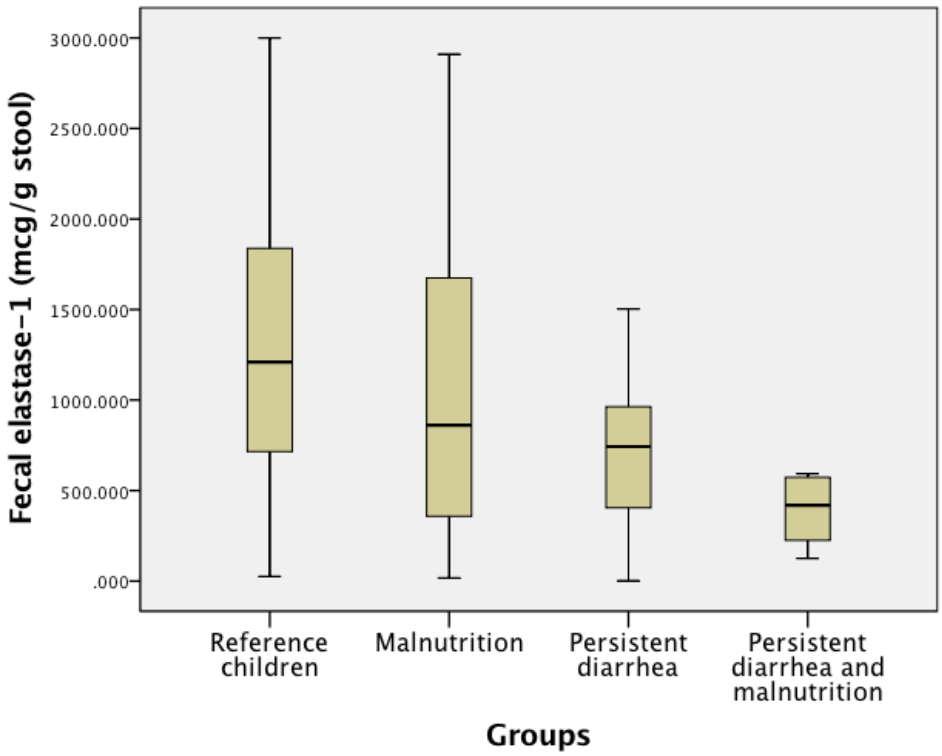

Figure 1. Distribution of fecal elastase-1 in the subject groups.

DISCUSSION

This study was conducted on children younger than 5 years old, who are a susceptible population for persistent diarrhoea. For the control group, we selected apparently healthy children and children with (moderate or severe) malnutrition, because children with persistent diarrhoea are generally at risk of malnutrition; thus, a comparison was required to examine the profile of exocrine pancreatic dysfunction in malnourished children.

We observed significantly lower FE-1 levels in children with persistent diarrhoea than in reference children, which confirms that children with persistent diarrhoea suffer from exocrine pancreatic insufficiency and addresses our study aims. The exocrine pancreatic insufficiency in children with persistent diarrhoea is thought to be caused by injury to the intestinal villi, which in turn triggers a reduction in the feedback response of secretin and cholecystokinin from the intestine to the pancreas; this results in low pancreatic functioning.

Even in children with malnutrition, we observed decreased FE-1 levels compared with the levels in RC. However, this difference was not statistically significant, which may be a result of the small sample size. Additional studies with a larger sample size are warranted to more accurately determine the presence of exocrine pancreatic insufficiency in children with malnutrition. Firmansyah et al demonstrated that in preconditioned malnourished mice, malnutrition causes hypoplasia and hypotrophy of the pancreas, while in the intestine it only causes hypotrophy.[17]

Not all persistent diarrhea children were accompanied by malnutrition. This variation was because the duration of persistent diarrhea were different for each children, and some of the children have even experienced recurrent persistent diarrhea. Also there are many factors contributing to the occurrence of persistent diarrhea such as malnutrition, irrational antibiotics use during acute diarrhea episode, quality of drinking water, and not breastfeeding exclusively in children under 6 months of age.[18] Exclusive breastfeeding was found highest in RC compared to other groups, and proportion of low birth weight is highest in malnutrition group. Previous study showed that exclusive breastfeeding in low birth weight infants for the first 6 months were more protected to diarrhea.[19] Some of the children with persistent diarrhea who also has malnutrition appeared to show lower FE-1 compared to children with persistent diarrhea (mean difference 283.8 mcg/g) and to children with malnutrition only (mean difference 655.6 mcg/g). This fact proves that persistent diarrhea and malnutrition as a separate entiety is a factor interfering with pancreatic exocrine function, and as a combination causing even a more severe dysfunction. In malnourished children the range of FE-1 is still relatively wide, probably because the levels of malnutrition varies from mild to severe, and thus in some malnutrition subjects the protein level was still adequate as an ingredient for enzyme while it was not adequate in some others, causing wide variability of FE-1. Children with persistent diarrhea show more narrow variability due to lower protein reserve as ingredient, and this is more clearly visible in persistent diarrhea children with malnutrition. The capacity to produce FE-1 enzyme in this group is lowest, showed by a very narrow range. This fact is supported by a recent study by Bartels et al.[20] who shows that 92% of malnourished children in Malawi has pancreatic exocrine insufficiency. Malnourished children with edema have a greater possibility to have lower FE-1 compared to the ones without edema (98% vs. 82.8%, p=0.026).

This study provides new information regarding exo-

crine pancreatic insufficiency in children with persistent diarrhoea and malnutrition. A limitation of this study is the sampling bias that occurs because of the differences in populations from which the persistent diarrhoea and reference children were sampled. The faeces samples were collected once, without conditioning.

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AUTHOR DISCLOSURES

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