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The Relationship between Fecal Myeloperoxidase Concentration and Growth Velocity in 2-5 Year-Old Children in Rural Areas of Zanjan, Iran

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ABSTRACT

Background & Objective: Growth is an important marker of child health. It has been shown recently that a chronic inflammatory condition, known as Environmental Enteric Dysfunction might play a more significant role on growth velocity than clinical infections. The present study aims to investigate the fecal myeloperoxidase concentration (a marker of gut inflammation) and its relationship with growth velocity.

Materials & Methods: In this prospective cohort study, 74 children from rural population of Iran (2 to 5 years of age) were randomly included. The heights and weights of the children were measured at a quarterly interval. The stool samples were obtained from all children in order to measure myeloperoxidase (MPO) concentration. The growth velocity was assessed on the basis of height for age Z-score and weight for age Z-score changes. A questionnaire on socioeconomic status was also completed by children's parents.

Results: 82 children aged 2 to 5 years (37 females and 45 males) with mean age of 40.63 ± 12.7 months participated in this study. The mean fecal MPO level was 71.26 ng/ml (Min – Max: 2 – 232.33 ng/ml). There was no significant relationship between fecal myeloperoxidase level and changes in height and weight Z scores. Moreover, there was no significant relationship between socioeconomic status of households and fecal myeloperoxidase level.

Conclusion: The mean level of fecal MPO in the present study was lower than similar studies. This significant difference might be mainly due to the better social status of families and environmental conditions of villages in our study.

Keywords: Myeloperoxidase, Biomarkers, Environmental Enteric Dysfunction, Child growth

Introduction

According to the recent WHO estimates, 151 million children under 6 years of age are suffering from stunting (low height-for-age), and wasting (low weight-for-height) that threaten the lives of the children worldwide. Asia alone has 83 million stunted children and 35 million wasted children under 6 years of age (1). Stunting is one of the manifestations of chronic malnutrition which could hinder children's physical and cognitive potential and affect the children especially in low and middle-income countries (2). Malnutrition is also one of the major consequences of intestinal infections and diarrhea, which can diminish the economic potential of developing countries by causing physical and cognitive deficits in children (3). Significant efforts have been made to reduce the risk of diarrhea in children, which have been largely successful. Nevertheless, this significant reduction has not led to an expected and concomitant decline in malnutrition and growth failure prevalence. Thus, there is a big gap in our understanding about prevention and treatment of malnutrition. It is assumed that a subclinical bowel inflammation known as Environmental Enteric Dysfunction (EED) plays an important role in malnutrition and growth failure (4, 5). In addition, it seems that EED can cause developmental disorders in children through micronutrient malabsorption and chronic systemic inflammation (4, 6-9). EED is a subclinical acquired chronic inflammatory condition of the small intestine that widely affects children under 5 years of age in developing countries. This disorder can occur due to the chronic fecal-oral contact with enteropathogens. Moreover, EED is associated with poverty and unsanitary environmental conditions (5, 10-12). There is evidence that close contact with animals such as cows and chickens as well as having an earthen floor and geophagy are

important risk factors for EED because soil can be a potential source of enteric pathogens **(13)**. The histological hallmark of EED is villous blunting and endoscopy is the gold standard for diagnosis. However, due to the high cost and aggressiveness of endoscopy, researchers have been looking for a biomarker or a set of biomarkers to diagnose EED in children **(5, 6)**. Myeloperoxidase (MPO) is one of these biomarkers that has been used mostly with alpha-1 antitrypsin (AAT) and neopterin (NEO) as EED fecal biomarkers in numerous studies **(2, 4, 8, 10, 14)**. MPO, a lysosomal protein, is secreted from neutrophils and other phagocytes into the intestinal lumen due to inflammation, hence it is considered a marker of neutrophil activity and its elevated level is an indicator of intestinal inflammation which is the main characteristic of EED **(14, 15)**. According to the WHO reports, the prevalence of stunting and wasting in Iran, as a developing country, are 6.8% and 4%, respectively **(1)**. As no study has been conducted on subclinical bowel inflammation and its correlation with child growth yet, the current study aimed to investigate the association between fecal myeloperoxidase concentration as a marker of bowel inflammation and growth status of children in rural areas of Zanjan, Iran.

Materials and Methods

The present research is a prospective cohort study conducted in rural areas (Dizaj Abad, Paiin kooh and sayan) of Zanjan, northwest of Iran, between July and October 2018. The study protocol was evaluated and approved by the Ethics Committee of Zanjan University of Medical Sciences (IR.ZUMS.REC.1397.005). Written informed consent was obtained from participants' parents or guardians. A total of 82 Healthy children aged 2 to 5 years were randomly selected and enrolled in the study using the children's electronic health records that were available at primary healthcare centers. Children with underlying gastrointestinal diseases (i.e. inflammatory bowel diseases, celiac) as well as other chronic diseases and acute diarrhea symptoms during the last 7 days before the study were excluded. Diarrhea was defined as having loose stool three or more times a day **(14)**. Heights and weights of the subjects were measured by trained community health workers. The weights of subjects were measured using digital scales (SECA, 769) with an accuracy of 0.1 kg and their heights were measured using a wall- mounted height gauge with an accuracy of 1 mm. A stool sample was obtained from each child to measure MPO concentration without a stabilizer. Then, stool samples were carried to the laboratory by polystyrene boxes containing ice bags and kept at -80 ° C. Socioeconomic status of the families, including parental education, household monthly income, maternal age, and the household size was collected using a questionnaire at the beginning of the study. Fecal MPO concentration was assessed in the laboratory of Zanjan School of Pharmacy by skilled laboratory experts using MPO ELISA kit (Eagle Biosciences, Amherst, NH, USA) according to the manufacturer's instructions. The heights and weights of the children were measured again three months later. We did not make any interventions during this time. Children with severe illnesses leading to hospitalization, as well as those who did not return for height and weight re-measurement, were excluded from the study. Height for age Z score (HAZ), weight for age Z score (WAZ), and weight for height Z score (WHZ) were separately calculated for each gender using raw data of heights and weights according to the WHO standard curves and also using WHO software for calculating Z-scores **(16)**.

The minimum sample size was determined 70 samples for a linear regression model, in which the sample size is optimally equal to 10 samples for predictor and intervening variables (7 variables were available in this study).

The correlation between fecal MPO concentration and changes in HAZ (ΔHAZ), WAZ (ΔWAZ) and WHZ (ΔWHZ) was evaluated using correlation coefficient. Distribution of data was assessed using the Kolmogorov-Smirnov test. Independent samples T-test was used to compare the means of MPO concentration between the two groups, and one-way ANOVA was applied to compare the means of MPO in three or more groups. Data analysis was performed using SPSS V.24. A significance level of 0.05 was considered for all analyses.

Results

Of 82 participants, at the end of the 3-month follow-up, eight children were excluded (5 females and 3 males) due to the migration. Therefore, 74 children aged 2 to 5 years (32 females and 42 males) with mean age of 40.63 ± 12.7 months were included in the study. Stool samples of all subjects were collected and MPO concentrations were measured for all of them.

The mean MPO level was 71.26 ± 50.36 ng/ml (Min – Max: 2 – 232.33 ng/ml). We considered the cutoff point of 2000 ng/ml for myeloperoxidase (2, 14). Additionally, the mean age of mothers was 30.86 ± 5.8 years and the average household size was 4.08 (Table 1).

Table 1. Descriptive characteristics of the participants *

Variable	Participants (n=74)
Age, months	40.63 ± 12.7
Sex,	

Variable	Participants (n=74)
Male	42 (61)
Female	32 (39)
Maternal age, y	30.86 ± 5.8
Paternal education level	
Primary	36 (50)
Secondary	13 (17.6)
Post-secondary and above	25 (32.4)
Maternal education level	
Primary	15 (20.3)
Secondary	20 (27)
Post-secondary and above	39 (52.7)
Household size	
1–3 people	22 (29.7)
4 people	31 (41.9)
>5 people	21 (28.4)
Height	
Baseline	98.38 ± 9.21
End line	100.08 ± 8.18
Weight	
Baseline	14.68 ± 2.22
End line	15.17 ± 2.23
HAZ	
Baseline	0.06 ± 0.93
End line	0.01 ± 0.91
WAZ	
Baseline	-0.13 ± 0.77
End line	-0.29 (1.19)
WHZ	
Baseline	-0.28 ± 0.93
End line	-0.25 ± 0.89
ΔHAZ	-0.05 ± 0.07
ΔWAZ	-0.01 ± 0.06
ΔWHZ	0.01 ± 0.13

*** Values are n (%) and means ± SDs or median (IQR). HAZ, height-for-age Zscore; WAZ, weight-for-age Zscore; WHZ, weight-for-height Zscore; ΔWHZ, weight-for-height Zscores changes; ΔHAZ, height-for-age Zscores Changes; ΔWAZ, weight-for-age Zscores changes.**

Furthermore, the correlation results showed ΔHAZ and ΔWHZ were not statistically significant regarding the MPO concentration. However, a weak and negative relationship was observed between MPO and ΔWAZ, this relationship was not statistically significant. (Table 2).

Table 2. Relationship between fecal MPO concentration and anthropometric characteristics

variable	Coefficient (95% CI)	P-value
ΔHAZ	-0.04 (-0.29, 0.18) *	0.68
ΔWAZ	-0.16 (-0.37, 0.08) †	0.17
ΔWHZ	0.02 (-0.31, 0.23) *	0.811

CI, confidence interval; ΔWHZ, weight-for-height Zscores change; ΔHAZ, height-for-age Zscores change; ΔWAZ, weight-for-age Zscores change.
*** The correlation coefficient (95% CI) and P-values were obtained from Pearson's correlation.**
† The correlation coefficient (95% CI) and P-values were obtained from spearman's correlation.

The results showed that the mean MPO concentration was not significantly different in family size and parental education. In addition, there was no significant relationship between MPO concentration and maternal age (P=0.09). The mean MPO concentration was not significantly different in the gender of participants (Table 3). The average monthly income of the families was also included in the questionnaire. Notably, all of households according to World Bank statistics, were living below the absolute poverty line ($1.90 per person) **(17)**. Therefore, the relationship between household income level and MPO concentration has not been evaluated.

Table 3. Associations between MPO level and household socioeconomic status.

Variable	mean ± SD, ng/ml	P-value
Sex		
Male	69.92 ± 51.65	0.45
Female	78.85 ± 49.74	
Paternal education level		
Primary	65.63 ± 48.22	0.32
Secondary	73.79 ± 40.18	
Post-secondary and above	85.51 ± 58.07	
Maternal education level		
Primary	81.94 ± 49.54	0.75
Secondary	74.62 ± 46.57	
Post-secondary and above	70.22 ± 53.91	
Household members		
1–3 people	68.55 ± 46.81	0.07
4 people	89.13 ± 57.73	
>5 people	58.05 ± 37.008	

Discussion

To our knowledge, the current survey is the first study on evaluating the relationship between fecal MPO level and growth velocity in Iranian children. The aim of the present study was to appraise the relationship between fecal MPO level and 3-month growth status of children based on changes in weight and height Z-scores. According to our findings, the means ΔHAZ, ΔWAZ and ΔWHZ were -0.05, -0.01 and 0.01, respectively. The mean MPO level was 71.26 ng / ml. No significant relationship was found between ΔHAZ, ΔWAZ and ΔWHZ with MPO level. Moreover, there was no significant relationship between socioeconomic status and MPO level.

MPO is produced by neutrophils and is involved in the bactericidal process by helping to generate free radicals, thus it is classified as an inflammatory biomarker of the intestine **(18, 19)**. In different studies, the relationship between fecal biomarkers including

MPO, and the growth status of children has been divergent. In some studies, a significant relationship has been demonstrated between the two, whereas, in more recent studies, the relationship between poor growth and these biomarkers has been weak **(20)**.

Campbell et al., through a study of EED biomarkers among 6 to 18- month- old Bangladeshi children found no association between the changes of height and weight Zscores with fecal MPO levels, and the mean fecal MPO was reported 4460.3 ng / ml (21). George et al., studied infants aged 6 to 30 months in Bangladesh. They showed no significant association between growth markers and fecal MPO during the 9- month follow-up **(22)**. In another study, no association was found between fecal biomarkers of EED and stunting in rural Malawian children **(15)**. In addition, Vaz Nery et al., in a randomized controlled trial on the effectiveness of community-wide water, sanitation and hygiene (WASH) intervention on EED fecal biomarkers MPO and AAT in children aged one to five years, did not find a significant association between anthropometric indices such as being underweight, stunting, thinness and wasting and these biomarkers **(20)**.

Nevertheless, there are some other studies on the association between fecal inflammatory biomarkers and growth velocity in children under 2 years of age showing a significant relationship between MPO levels and growth markers **(2, 14)**.

A significant difference in the present study with other studies in which the relationship between MPO and growth status has been examined is the mean level of MPO, as in most other studies the MPO level has been reported much higher. For instance, in a study conducted in Bangladesh, the median MPO level in children under 30 months was reported 3576.75 ng/ml **(23)**. In the present study, the mean MPO level was 71.26 ng/ml and no values reached the cut off point for myeloperoxidase (2000 ng/ml). One of the major causes of discrepancy in fecal MPO levels might be due to the higher age range of children in the current study. In a study conducted on rural Malawian children aged 1 to 5 years, fecal MPO levels decreased significantly with age, with a mean fecal MPO concentration of 290 ng/ml reported in the age range of 49 to 60 months **(15)**. Interestingly, this significant reverse relationship between fecal MPO concentrations and age has been shown in other studies **(24)**.

We studied children aged 2 to 5 years because children are completely weaned after 2 years and they have attained a considerable physical development in order to be in close contact with their environment than the first two years of their lives. Moreover, EED is a condition that can occurin all age groups (24). Colston *et al*., in a study to find out whether EED in the first two years of life could predict growth status at 5 years, showed that EED biomarkers were significantly associated with size at 5 years **(25)**. On the other hand, it seems that the effects of EED are long-lasting and permanent if left untreated.

There is evidence that close contact with animals, unsanitary disposal of animal waste, and geophagy (mouthing of soil), are significantly associated with growth failure and elevation of EED fecal biomarkers **(13, 23, 26)**. Based on the observations of the authors, in the study villages some environmental conditions (keeping farm animals like chickens, cows and sheep, and the unsanitary disposal of animal waste) were approximately in line with other studies conducted in low and middle income countries, although in this study all three villages had access to safe drinking water (faucet water), improved sanitation facilities and electricity. Additionally, regarding the household social status, more than 70% of the mothers had secondary school education or higher, more than 70% of families had family size of 4 or fewer, and the mean maternal age was 30.86 years representing a better social status than other studies **(2, 14, 21, 23)**. Therefore, another reason might be the notable difference in the environmental conditions and social status of families in our study with most of other studies.

Menzies et al., examined the functional characteristics of small intestine in healthy adults of 14 different tropical countries. They found that although EED can be observed in people of the tropical regions, interestingly it is not evident among people of some economically developed tropical countries, including Qatar and Singapore **(27)**. In the 1970s, Pakistani and Indian patients with EED who had immigrated to the New York City, showed a significant improvement in small intestine functional markers without any interventions. In contrast, the Americans who had immigrated to Pakistan, experienced changes in their small intestine functional markers, few months after emigration **(28)**. It seems that socioeconomic status of the people and environmental conditions play a more important role in predicting EED than living in tropical regions.

Moreover, it has been shown that antibiotic consumption plays a role in reducing the level of some fecal biomarkers of intestinal inflammation and permeability such as MPO and calprotectin which could be long lasting **(29)**. In a study on the effects of antibiotic use (macrolide and penicillin-type antibiotics) on the gut microbiome in 2-7 -year-old children, Korpela et al., demonstrated that there is a strong relationship between macrolide use and long-term changes of intestinal microbiota composition and reduction of microbial richness **(30)**. Although the history of antibiotic consumption was not included in the present study, many studies have revealed that antibiotic utilization in Iran is high as penicillins, cephalosporins, and macrolides are the most commonly prescribed antibiotics in outpatient settings **(31-33)**.

Conclusion

According to the results of the present study, there was no significant relationship between MPO level and growth velocity. The reported MPO levels were lower than other studies. This significant difference in fecal MPO levels might be mainly due to the better social status and environmental conditions of villages in our study compared to the children in other studies, whereas due to the negative means of ΔHAZ and ΔWAZ, the growth failure is still an important issue in this age group that should be addressed.

Limitations

This study faced some limitations. First, the low sample size that can limit the power of the current analysis, however, we included all eligible participants who could be recruited in the study period. Second, study follow-up period was short and it might have been more precise to follow up children for more than three-month periods in terms of the relationship between MPO and growth status. Not including the history of antibiotic consumption in children is another limitation. Finally, the data of household economic status was gathered through self-reporting, which might be a potential source of bias. In addition, the present study is the first survey on the relationship between fecal MPO and growth velocity of children in Iran, thus, it is impossible to compare the findings of our study with similar studies in this geographical setting. Therefore, it is recommended that further studies be conducted on this subject in Iran.

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Abbreviations:

EED: Environmental Enteric Dysfunction

WHZ: weight for height Z score

ΔWHZ: weight for height Z score changes

HAZ: height for age Z score

LAZ: Length for age Zscore

WAZ: weight for age Z score

ΔHAZ: height for age Z score changes

ΔWAZ: weight for age Z score changes

AAT: Alpha1 Antitrypsin

MPO: Myeloperoxidase

NEO: Neopterin

WASH: water, sanitation and hygiene

Conflict of Interest

The authors declare no conflict of interest.

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