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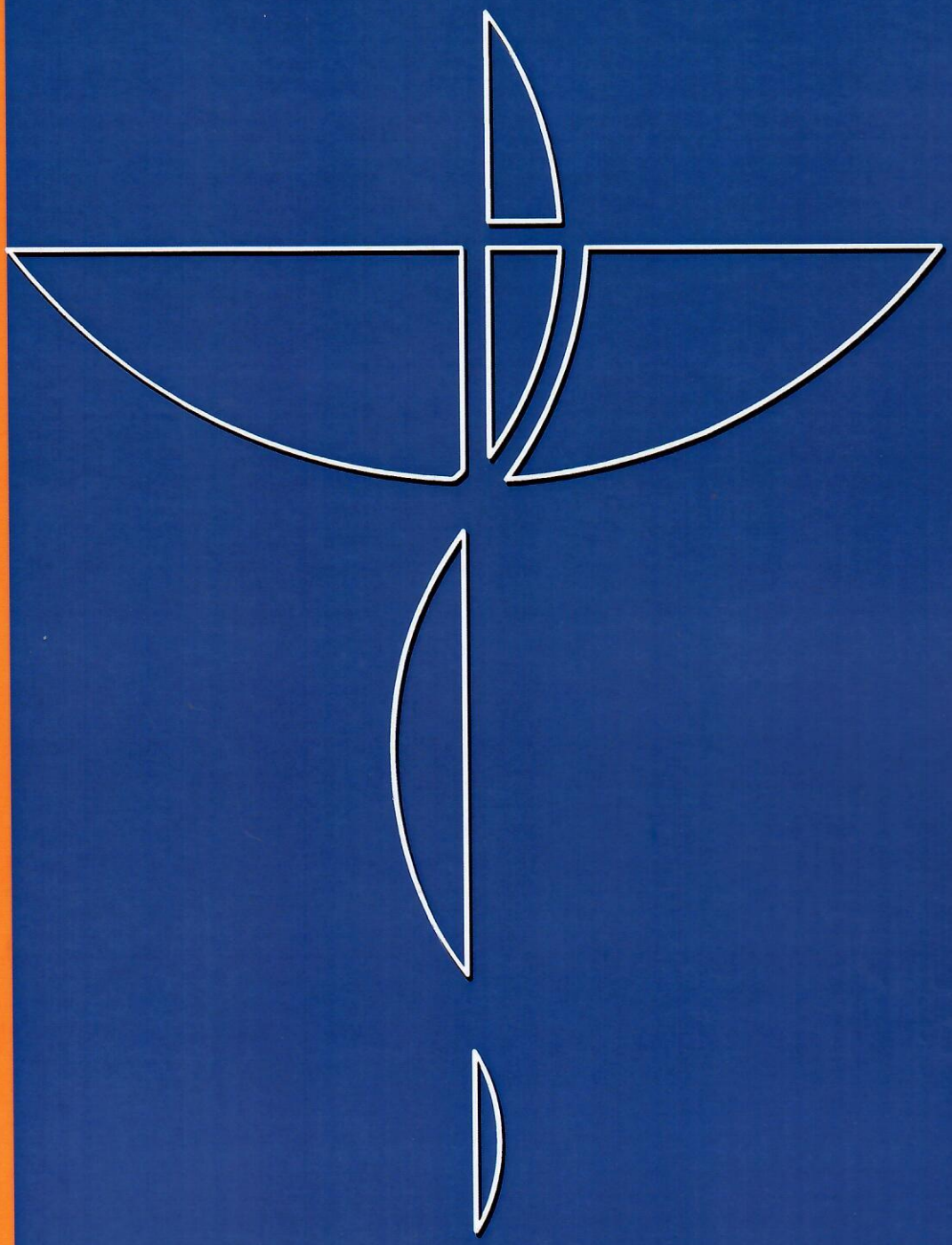

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EVALUATION OF BREAST MILK sIgA PROTECTIVE ROLE VERSUS ALPHA GLUTATHIONE S TRANSFERASE IN INFANTS ACUTE GASTROENTERITIS

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Abstract

Aim: The aim of this study was to assess whether mucosal integrity measured by stool sIgA values is a protective factor against epithelial damage measured by serum α-GST values in infants with acute gastroenteritis and their association with the type of nutrition.

Material and Methods: A total of 23 infants with acute gastroenteritis divided in 2 groups based on the feeding patterns (type of milk) were included in the study. Investigated indicators were severity of symptoms, dehydration degree and the need for parenteral rehydration. Stool sIgA and serum α-GST levels were tested and compared between the groups.

Results: A statistically significant association was identified between group affiliation and the sIgA levels in stool (p=0.001346). The most common cause of acute gastroenteritis in infants was *Rotavirus*. Our study has shown that exclusive breastfeeding reduces the risk of Rotavirus infection especially in the first 6 months of life OR=0.0758, 95%CI(0.0071-0.8074). It was found a statistically significant association between group affiliation and the α-GST levels in serum (p=0.002260). It was revealed that Rotavirus can cause erosion of the intestinal epithelium through the positive values of α-GST in *Rotavirus* positive cases. It was found that stool sIgA negatively correlates with serum α-GST for p=0.002.

Conclusion: Breastfeeding is important, especially in the first two years of a child's life, because breast milk provides high concentrations of sIgA that protects the intestinal epithelium of infants from damage in the presence of intestinal pathogens, as in this case it protects it from damage caused from *Rotavirus* acute gastroenteritis.

Key words: acute gastroenteritis; infants; secretory Immunoglobulin A; alpha Glutathione S Transferase; breastfeeding

ЕВАЛУАЦИЈА НА ЗАШТИТНАТА УЛОГА НА СЕКРЕТОРНИОТ ИМУНОГЛОБУЛИН А ОД МАЈЧИНОТО МЛЕКО НАСПРОТИ ALPHA GLUTATHIONE S TRANSFERASE КАЈ ДОЕНЧИЊА СО АКУТЕН ГАСТРОЕНТЕРИТ.

Апстракт

Цел: Целта на оваа студија беше да се покаже дали мукозниот интегритет мерен преку вредностите на sIgA во столицата е заштитен фактор од епително

оштетување мерено преку вредностите на α-GST во серум кај доенчиња со а
гастроентерит и нивната поврзаност со начинот на исхрана.
Методи и материјал: Во студијата беа вклучени 23 доенчиња со а
гастроентерит поделени во 2 групи според типот на исхрана. Испит
индикатори беа тежината на симптомите, степенот на дехидратација и пот
од парентерална рехидрација. Нивоата на sIgA во столица и α-GST во сер
испитани и е направена нивна споредба помеѓу групите.
Резултати: Се најде статистички сигнификантна асоцијација помеѓу припа
на група и вредностите на sIgA во столицата (p=0.001346). Најчестиот изо
патоген беше *Rotavirus*. Оваа студија покажа дека ексклузивното дое
намалува ризикот за *Rotavirus* дијареа посебно во првите 6 месеци од жи
OR=0.0758, 95%CI(0.0071-0.8074). Покажана е статистички сигнифи
поврзаност помеѓу припадност на група и серумските вредности на
(p=0.002260). Се докажа дека *Rotavirus*-от може да предизвика интести
епителна ерозија преку покачените серумски вредности на α-GST во *Ro*
позитивните случаи. Во студијата се покажа дека дека sIgA во сто
негативно корелира со α-GST во серум за p=0.002
Заклучок: Доењето е многу значајно во првите две години од животот б
мајчиното млеко обезбедува високи концентрации на sIgA кој го заш
цревниот епител на доенчињата од оштетување при присуство на ентe
патогени, како што во овој случај го заштитува од оштетување предизвик
Rotavirus акутен гастроентерит.

Клучни зборови: акутен гастроентерит; доенчиња; секреторен Имуноглобу
alpha Glutathione S Transferase; доење

Introduction

Although often considered a benign disease, acute gastroenteritis remains a majo
of morbidity and mortality in children under 3 years of age. Worldwide, ab
billion cases of acute gastroenteritis occur in children under 5 years of age [1].
gastroenteritis can be particularly dangerous in the first 12 months of life with a
risk of increased water and electrolyte loss with consequent moderate to
dehydration, especially in infants who are not exclusively breastfed.
gastroenteritis mortality may be higher in children in the first 12 months than in c
older than one year [2]. Acute gastroenteritis management is based on the
findings, with a focus on dehydration correction and optimization of fluid an
intake. The incidence of acute gastroenteritis ranges from 0.5 to 2 episodes per ch
year in children younger than three years. At this age, acute gastroenteritis is th
common cause of hospitalization [3]. Acute gastroenteritis is defined as a decr
stool consistency and/or an increase in the frequency of discharges (≥ 3 in 24
with or without fever and vomiting. *Rotavirus* is the most common cause o
gastroenteritis, rarer causes are *Adenovirus*, *Norovirus*, and *Astrovirus*. B
pathogens include *Salmonella*, *Shigella*, and less commonly *Escherichi*
Campylobacter jejuni, and *Yersinia enterocolitica*. Enterocyte infection leads
death, lumen extrusion, and atrophy of the intestinal villi, resulting in reduced in
surface area, with impaired digestive and absorption functions and acute tr
malabsorptive diarrhea.

The secretory Immunoglobulin A (sIgA) is the first line of defense for the intestinal epithelium from pathogenic microorganisms and intestinal toxins. It prevents the binding of microorganisms to epithelial receptors by binding it to the Fc receptor on the surface of the pathogen, trapping microorganisms in the mucus and enabling their removal by stimulating peristalsis and mucociliary activity [4, 5]. sIgA is able to directly reduce bacterial virulence and it has an effect on the composition of the intestinal microflora [4]. IgA is a weak activator of complement and it poorly opsonizes [4].

Breast milk is not only a source of energy, but also a very complex dynamic biological fluid that has a protective and immunomodulatory role [6]. Human milk is a link between the mother's immune system and the infant's one. When infants come in contact with new microorganisms they remain unprotected although they have received antibodies transplacentally from the mother. This risk can be reduced by antibodies present in breast milk that may affect the infant's immune, metabolic and micro flora systems [6]. sIgA is the most important immunoglobulin in breast milk not only because of its high concentration but also because of its biological activity [7,8]. A number of studies have confirmed that exclusive breastfeeding has a protective role and reduces the risk of diarrhea, especially in infants up to 6 months of age [9,10]. Natural and specific sIgA antibodies in breast milk are capable of binding to commensal bacteria and may be involved in establishing of the intestinal micro flora of the newborn, which in turn stimulates the maturation of intestinal lymphatic tissue, resulting in the production of sIgA with limited affinity of recognition and removal of pathogenic microorganisms [4]. The intestinal mucosa is involved in the digestion and absorption of nutrients, in the protection against infectious, toxic and carcinogenic substances ingested in the digestive tract. For this purpose, a complex defense system is involved: mucosal barrier, epithelial cells with short life (several days), which have a complex enzyme system capable of metabolizing harmful substances in a way that allows their excretion through the bile, stool and urine. One of the most important classes of enzymes that perform this function is Glutathione S Transferase (GST) enzymes. They are involved in binding, transporting and detoxifying these harmful substances by binding them to glutathione (GSH) [11]. Kelly et al. 2004 [12] demonstrated that the GSH detoxification system is important in maintaining the integrity of the intestinal mucosa. According to Kong et al. 2019 [13] and Coles et al. 2002 [14] alpha Gluthatione S Transferase (α-GST) is isoform of GST enzymes and is a highly active structural enzyme in intestinal mucosal epithelial cells, although it is also present in the liver and kidneys [11]. The aim of this study was to assess whether mucosal integrity measured by stool sIgA values is a protective factor against epithelial damage measured by serum α-GST values in infants with acute gastroenteritis and their association with the type of nutrition.

Material and Methods

Study design

This was a prospective cohort study started in the period November 15, 2018 until December 31, 2019. The study included newborns and infants from birth to 6 months of age who were diagnosed with acute gastroenteritis. All infants were hospitalized at the Children's Department in Clinical Hospital - Shtip. Parents' written consent was obtained for each infant included in the study after extensive communication with them. An appropriate survey questionnaire was designed and responses were obtained from

the infants' mothers. The questionnaire covered the following segments: infant age, nutrition (breast milk, milk formula or cow's milk) and weaning practice. Information on the onset of symptoms of acute gastroenteritis in the last 24 hours before admission, as well as information on the nutrition and health status of the nursing mother were included. Infants were divided in 2 groups according to age in months and according to milk nutrition and introduction of complementary food. Group I included newborns and infants from birth to 6 months who were exclusively breastfed. Group II included newborns and infants from birth to 6 months of age who weren't exclusively breastfed and were on mixed milk nutrition.

Exclusively breastfed were infants who were fed only with breast milk and didn't receive additional food or fluids (excluding oral rehydration solution, vitamins, minerals, and medications). The clinical picture and degree of dehydration were determined by physical examination and the degree of dehydration was graded as mild, moderate and severe through the use of a clinical scoring system. (World Health Organization: Integrated management of childhood illness-Module 4, Diarrhea). For each infant included in the study, a record sheet was filled and according to the severity of the clinical signs the need for parenteral rehydration was assessed during the hospital stay. The study didn't include infants whose diarrhea was due to a surgical or extra-intestinal cause, as well as infants who had received immunosuppressive therapy.

Laboratory methods

From each infant included in the study, two samples of diaper stool were taken with a plastic spatula. One sample stool was collected in a sterile plastic cup with the general data of the patient and the code written on it and within 30 minutes was brought to the Microbiological Laboratory in the Center for Public Health (CPH) - Shtip. In this stool sample the presence of Rotavirus and Adenovirus with Immunochromatographic test (DUO ROTA-ADENOVIRUS - Check-1 VEDA.LAB, Alencon-France) was analyzed. From the same stool sample, a coproculture was performed which was supposed to identify the presence of enteropathogenic bacteria by sowing the stool sample on a suitable substrate.

The second stool was frozen at -80 °C and in that sample the sIgA level was determined quantitatively by ELISA method with ELISA kit test by Immundiagnostik Bensheim, Germany.

From each infant 2.5 ml venous blood was taken and the serum was obtained following centrifugation. In that serum sample α-GST level was determined quantitatively by ELISA method with ELISA kit test by CUSABIO (CSB-E08906h).

Statistical analysis

The collected data were processed using the statistical program SPSS 20 and the following statistical methods:

- Descriptive method: attributive statistical series were analyzed by determining percentages and numerical series with central tendency measures and with data dispersion measures.
- Statistical significance of the probability between the distributions of the frequencies of two attributive variables was estimated by the Difference test, and between the numerical series exploring the Student t-test.
- With Shapiro-Wilk's test the normality of variable distribution was tested.
- Correlative relations were realized using Pearson's correlation coefficient (r).

- The Odds ratio-OR cross-correlation is used to determine the relationship between the dependent and independent – criterion variables. For CI (confidence interval 95% CI) statistical significance was defined at the level of standard error less than 0.05 (p). The results are shown in tables and figures.

Results

The analysis included 23 hospitalized infants from birth to 6 months of age with a diagnosis of acute gastroenteritis, divided in two groups. The first group included 7(30.4%) infants and the second group included 16(69.6%) infants, divided by age expressed in months and type of nutrition.
Table 1 presents the infants with acute gastroenteritis by gender and sex.
The average infant age in the first group was 2.1±0.9 months, and in the second group was 3.4±1.5 months.

Table 1 Distribution of the infants according to the gender and age

Group	**I**		**II**	
Gender	Number	%	Number	%
Male	4	57.1	9	56.25
Female	3	42.9	7	43.75
Age in months	Number	Mean ! SD	Number	Mean ! SD
	7	2.1 ! 0.899735	16	3.4 ! 1.454877

SD: Standard deviation

The distribution of the clinical signs in both groups is presented in Table 2, which included the average number of vomiting, average number of liquid stools, fever, degree of dehydration, number of days of parenteral rehydration and length of hospital stay. The average number of vomiting 24 hours before admission in infants in the first group was 0.3±0.5, in the second group was 4.6±3.3, the difference was statistically significant (p=0.002669). The average number of liquid stools in infants 24 hours before admission in the first group was 3.7±0.8, in the second group 10.4±4.9, and the difference was statistically significant (p=0.002152). Fever was reported in 14.3% of infants in the first group and in 81.25% in the second group, with statistically significant percentage difference (p=0.0025). All infants from the first group had mild degree of dehydration, in the second group a mild degree of dehydration was registered in 25.0%, moderate in 43.75% and a severe degree of dehydration in 31.25% of infants. The average number of liquid stools during treatment in the first group was 9.0±2.2, and in the second group was 21.2±8.5, the difference between the average number of liquid stools was statistically significant (p=0.001419).

The average number of vomiting during treatment in the first group was 0.3±0.8, and in the second group was 3.0±2.4, the difference between the average number of vomiting was statistically significant (p=0.008516). The average number of parenteral rehydration days in the first group was 0.7±0.8, and in the second group it was 2.0±1.0, the difference between the average number of parenteral rehydration days was statistically

significant (p=0.005246). The average number of hospital days (length of stay) in the first group was 4.1±1.6 and in the second group it was 4.9±1.8, the difference between the average number of hospital days was statistically insignificant for p>0.05 (p=0.318302).

Table 2 Clinical condition 24 hours before admission and during the hospitalization

Group	Average I	Average II	t-test	p	N I	N II	SD I	SD II
No. of vomiting 24 hours before admission	0.285714	4.56250	-3.40460	0.002669	7	16	0.487950	3.265348
Number of stools 24 hours before admission	3.7	10.4	-3.49610	0.002152	7	16	0.755929	4.951431
Number of stools during the hospitalization	9.0	21.2	-3.67211	0.001419	7	16	2.236068	8.549610
Number of vomiting during the hospitalization	0.3	3.0	-2.90250	0.008516	7	16	0.755929	2.394438
Number of parenteral rehydration days	0.7	2.0	-3.11436	0.005246	7	16	0.755929	0.966092
Number of hospitalization days	4.1	4.9	-1.02224	0.318302	7	16	1.573592	1.768945

SD Standard deviation; N Number

Rotavirus was positive in 12 stool samples. In the first group *Rotavirus* was positive in one (14.3%) infant and in the second group *Rotavirus* was positive in 11(68.75%) infants. In one infant from the second group was isolated *Shigella flexneri* and in one infant from the same group was isolated *Adenovirus* (Figure 1).

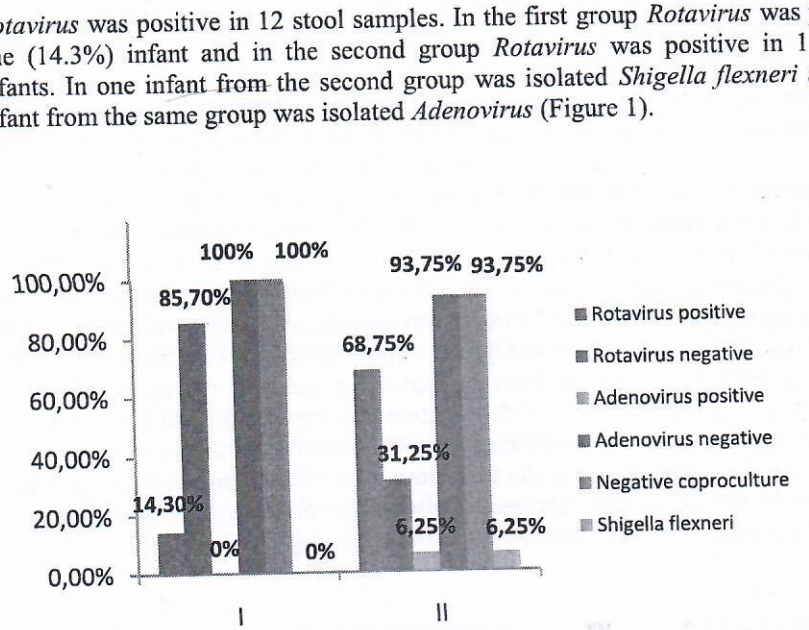
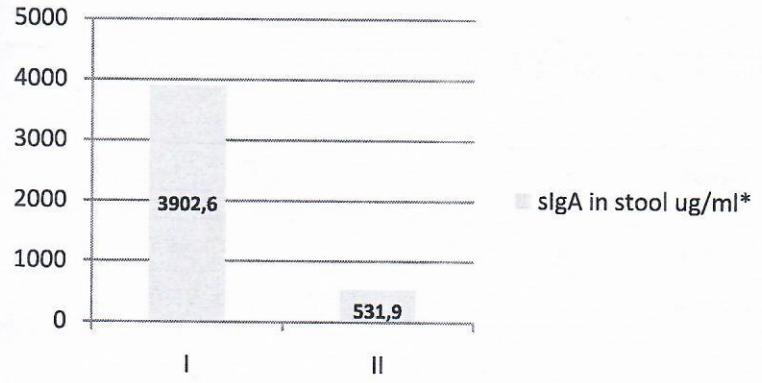


Figure 1 Microbiological findings in stool

The mean value of sIgA in infants diagnosed with acute gastroenteritis in the first group was 3902.6 ± 1496.8 ug/ml, and in the second group it was 531.9 ± 506.2 ug/ml, the difference between the mean values was statistically significant for $p < 0.05$ ($p = 0.000000$) (Figure 2).



sIgA: secretory Immunoglobulin A; t-test= 8.198331; p= 0.000000 (statistically significant)

Figure 2 Average value of sIgA in infants with Acute gastroenteritis

Table 3 shows the effect of sIgA on the degree of dehydration, vomiting symptom and fever in infants with acute gastroenteritis. It was found a statistically significant association between dehydration rate, vomiting frequency and fever between the first and second group. Infants who were sIgA positive had a significantly lower degree of dehydration, lower vomiting frequency and fever.

Table 3 Effect of sIgA on the clinical condition in infants with Acute gastroenteritis

-	Negative sIgA	Positive sIgA	p
Dehydration degree	**N=12**	**N=11**	
Mild	2 (16.6%)	9(81.8%)	p=0.004708
Moderate	5 (41.7%)	2 (18.2%)	
Severe	5 (41.7%)	0	
Fever	**N=12**	**N=11**	p=0.036074
No	2 (16.7%)	7 (63.6%)	
Yes	10 (83.3%)	4 (36.4%)	
Vomiting	**N=12**	**N=11**	p=0.000383
No	1 (8.3%)	9 (75.0%)	
Yes	11 (91.7%)	2 (25.0%)	

N: number; sIgA: secretory Immunoglobulin A

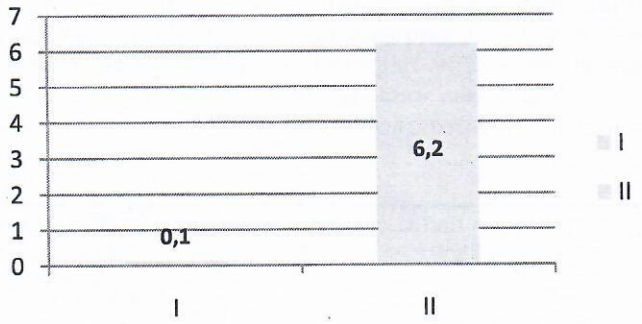
α-GST in serum was positive in 16 infants (69.6%) from the whole of infants. In the first group, positive α-GST in serum (≥ 0.156 ng/ml) was registered in only one infant (14.3%), and in 85.7% it was negative. In the second group, α-GST in serum was negative (<0.156 ng / ml) in one infant (6.25%) and positive (≥ 0.156 ng/ml) in 93.75% of infants. A statistically significant association between group affiliation and serum α-GST test for p <0.05 (p= 0.000460) was confirmed (Table 4).

Table 4 Distribution of α-GST positive and α-GST negative infants

Group α GST	I		II	
	Number	%	Number	%
Negative	6	85.7	1	6.25
Positive	1	14.3	15	93.75

α-GST: alpha Glutathione S Transferase

The mean value of α-GST in serum in infants diagnosed with acute gastroenteritis in the first group was 0.1 ± 0.03 ng/ml, and in the second group it was 6.2 ± 4.5 ng/ml, the difference between the mean values was statistically significant for p <0.05 (p = 0.002260) (Figure 3)



α-GST: alpha Glutathione S Transferase ; t-test=-3.47531; p= 0.002260

Figure 3 Average value of α-GST in infants with Acute gastroenteritis

Of the 16 infants with acute gastroenteritis who had positive alpha GST values in serum, 12 had Rotavirus (75.0%)

The Perason value of the linear correlation coefficient (r) showed that stool sIgA is negatively correlated with serum α-GST, the p value as statistically significant confirms the correlation. Correlation was negative, indicating that increasing the value of sIgA in

stool reduces serum concentrations of α-GST and vice versa (Figure 4). It has also been shown that exclusive breastfeeding is effective in preventing Rotavirus infection by reducing the risk of Rotavirus infection in children, especially in the first 6 months of life OR=0.0758, 95% CI (0.0071-0.8074).

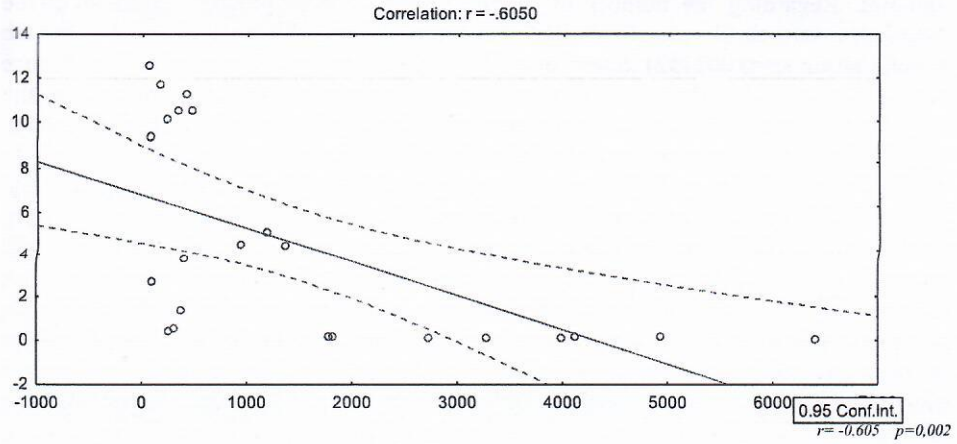


Figure 4 Correlation between sIgA in stool and serum concentration of α-GST

Discussion

Several studies have confirmed that breastfed infants have significantly higher concentrations of sIgA in the stool than those who have been formula-fed, concluding that breast milk provides large amounts of sIgA for infants and plays a major role in protection and promotion of the immune function of the infant's digestive tract [15,16,17]. The results of sIgA in stool in infants with acute gastroenteritis from our research correlate with the results of the above studies. We observed a statistically significant association between group affiliation and the sIgA levels in stool between the first and the second group. Numerous studies have shown that sIgA from breast milk has a protective effect against diarrhea in the first 6 months of life. Dialo et al. 2019 [18] noticed that breastfeeding discontinuation before the third month was found to be significantly associated with a high incidence of diarrhea at 6 months of age and between 6 and 12 months. Breastfeeding discontinuation (weaning) before the sixth month was also associated with a higher incidence of diarrhea at 6 months of age. Infants who were on milk formula for ≥ 3 months had a higher incidence of diarrhea between 6 and 12 months. Krawczyk et al. 2016 [19] and Plenge-Bönig et al. 2010 [20] have found that exclusive breastfeeding is effective in preventing Rotavirus infection by reducing the risk of Rotavirus infection in children, especially in the first 6 months of life. A few studies have shown that rotavirus is a more common cause of acute gastroenteritis in infants than Adenovirus [21,22]. These results support our findings that the most common cause of acute gastroenteritis in infants was *Rotavirus*. In the study by Sherif et al. 2015 [23] is shown that most of the breastfed infants with Rotavirus gastroenteritis had positive sIgA values in stool as opposed to those who were

on milk formula. Those infants who were positive for sIgA in stool had a milder clinical picture and a lower frequency of vomiting. In this research a statistically significant difference (p=0.002669) for the average number of vomiting 24 hours before admission was registered between the first and second group with less frequent vomiting in exclusively breastfed infants in the first group, where sIgA was positive in all stool samples. Regarding the number of liquid stools 24 hours before admission to the hospital, a statistically significant difference was registered between the first and the second group (p=0.002152). Sherif et al. 2015 [23] didn't prove statistical significance for the degree of dehydration between groups but in our study the effect of sIgA on the degree of dehydration in infants showed a statistically significant association between the first and second group for (p=0.004708). Similar results were obtained in the study of Fuchs et al. 1996, [24] which found that infants who were not breastfed were at higher risk of dehydration than those who were exclusively breastfed (p=0.006). In our study vomiting during the treatment was less common in infants in the first group versus the second group with a statistically significant difference between the average number of vomiting by $p<0.05$. Regarding the average number of stools during the treatment, there was also a statistical significance for $p<0.05$ between the first and second group. In the study of Eaton-Evans & Dugdale, 1987 [25] has been shown that infants up to 6 months of age have a lower number of liquid stools and a lower frequency of vomiting in those who are breastfed compared to those who were fed with other types of milk, indicating that breast milk has a protective effect on the intestines of infants younger than 6 months. In our study, we observed statistical significance for the number of days of parenteral rehydration between the first and second group. For the number of hospital days, no statistical significance was proved either between the first and the second group. In contrast to our results in a study by Boccolini et al. 2012 [26] was shown that the increase in the prevalence of exclusive breastfeeding in infants younger than 4 months with acute diarrhea has a negative correlation with the duration of hospitalization (Rho = -0.483, p=0.014).

Serum biomarkers that reflect damage of the intestinal mucosal barrier have been identified in several clinical and animal studies [13]. Peters et al. 1989 [27] and Khurana et al. 2002 [28] examined the activity of GST enzymes in the small and large intestines and proved that intestinal epithelial cells have a high content and activity of cytosolic GST and when the cell membrane of intestinal epithelial cells is damaged, these enzymes are released and their serum levels correlate with the degree of intestinal epithelial damage. According to Kong et al. 2019 [13] and Coles et al. 2002 [14] α-GST is isoform of GST enzymes and is a highly active structural enzyme in intestinal mucosal epithelial cells. α-GST is a potential biomarker for intestinal epithelial damage for a variety of reasons such as gastroenteritis, intestinal ischemia, chronic inflammatory bowel disease. It can be used as screening in patients at risk for intestinal pathology [29,30]. In this study, the level of serum α-GST in infants with acute gastroenteritis was determined, comparing patients on different type of milk nutrition. A statistically significant association between group affiliation and serum α-GST test was registered for $p<0.05$. As for the mean value of serum α-GST it was also observed a statistically significant difference between the first and second group ($p<0.05$). The results from this study showing striking difference in the level of α-GST could be related to the study of van Oudheusden et al. 2013 [31] where it was described that enterocytes are rapidly degraded in the early stages of intestinal damage and this can be easily detected by determining the α-GST values in plasma taking it as a marker for early detection of intestinal damage. In the study of Sherif et al. 2015 [23] GST was significantly positive

in cases that were Rotavirus positive compared to those that were Rotavirus negative. Very similar results were obtained in this study. Rotavirus was detected in 12 infants whereas only one infant was on exclusive breastfeeding. Also, majority of the infants with positive α-GST values in serum, had Rotavirus in their stool. These findings might suggest that *Rotavirus* can cause erosion of the intestinal epithelium producing higher levels of α-GST in Rotavirus positive cases.

In addition α-GST has been shown to be significantly lower in sIgA-positive stool cases compared to sIgA-negative cases of p=0.002, confirming that the presence of sIgA in infant intestines protects against epithelial damage. It has also been shown that exclusive breastfeeding is effective in preventing Rotavirus infection by reducing the risk of Rotavirus infection in children, especially in the first 6 months of life OR = 0.0758, 95% CI (0.0071-0.8074).

Conclusion

This study has shown that the presence of breast milk sIgA in infants has an effect on the severity of the clinical signs of acute gastroenteritis by reducing the vomiting frequency, the number and severity of diarrheal episodes, the risk for moderate and severe dehydration and fever frequency. It was found that α-GST is a biomarker for early intestinal epithelial damage in infants primarily with Rotavirus acute gastroenteritis. α-GST serum values were significantly lower in infants who were exclusively breastfed compared with infants who were not exclusively breastfed. This study confirmed that stool sIgA negatively correlates with serum α-GST in infants with acute gastroenteritis. Infants who had higher stool sIgA values had lower serum α-GST values, and thus milder clinical signs. Therefore, it is promising to explore the determination of α-GST in infants' acute gastroenteritis as a marker of intestinal damage and plan clinical interventions to minimize the negative consequences.

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