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Review

Potential effects of lactoferrin as antiviral and neoadjuvant therapy in pediatric patients with viral gastroenteritis

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Abstract

Viral gastroenteritis is a prevalent disease in children. Each year, around 111 million children suffer from viral gastroenteritis. Clinical features such as fever, nausea, vomiting, and diarrhea may result in severe cases requiring hospitalization. Current therapies of this disease are symptomatic therapies, which are focused on patient rehydration. Previous studies found that lactoferrin (LF) is a milk protein known to have antiviral potential, suggesting the possibility of utilizing it as an alternative therapy for viral gastroenteritis. This literature review aims to determine the potential effects of LF in treatment and prevention, thereby reducing the incidence and severity of viral gastroenteritis. A literature search for related articles published in the past 20 years was performed on PubMed, EBSCOhost, ProQuest and another source using the main keywords "lactoferrin, viral, and gastroenteritis". There were 6 articles assessed in this review. Several clinical trials have shown that giving LF supplements could significantly reduce the duration and the severity of gastroenteritis, especially with high doses of LF (0.49-1 g). Therefore, the efficacy of LF in pediatric gastroenteritis worked in a dose-dependent manner. However, mixed results were reported in the clinical trials assessing the efficacy of LF against viral gastroenteritis, but this could be due to the low doses of LF used. In conclusion, LF could be used as a complementary treatment against pediatric gastroenteritis, but further studies using high LF doses against pediatric viral gastroenteritis need to be evaluated further.

Keywords

Antiviral, gastroenteritis, lactoferrin, neoadjuvant, pediatrics, review.

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Introduction

Viral gastroenteritis is an inflammation of the digestive tract that can cause fever, nausea, vomiting, and diarrhea. The pathogens that could cause this infection are rotavirus, norovirus, astrovirus, adenovirus, and sapovirus [1]. Each year an estimated 111 million children under the age of 5 experience mild gastroenteritis due to rotavirus infection, while another 25 million cases are moderate, and 2 million cases have severe gastroenteritis requiring hospitalization. From this number, it is estimated that 352,000 to 592,000 suffering from this infection die each year. Eighty-two percent of these death are from the poorest countries in the world [2]. In addition, norovirus contributes to about 50% of gastroenteritis cases globally and is responsible for 90% of gastroenteritis during outbreaks [3]. Adenovirus is also a reasonably frequent etiology in causing gastroenteritis [4].

The main goal of therapy in viral gastroenteritis is patient rehydration [2, 5]. In addition to rehydration, dietary changes and bowel rest are also recommended for patients suffering from viral gastroenteritis. The World Health Organization (WHO) recommends rehydration with water containing salt, sodium bicarbonate, and glucose to restore lost electrolytes and glucose [5].

In the last years, a glycoprotein has been widely studied as a potential therapy in cases of viral gastroenteritis, namely lactoferrin (LF). LF is an N-glycosyl protein that belongs to the transferrin family and is produced by several mammalians such as humans, bovines, goats, horses, dogs, and rodents. It can be found in mammalian milk, mucosal secretions, and neutrophils [6]. LF has received attention because of its ability as an antiviral [7].

In this literature review, we have summarized and discussed the activity of LF against viral gastroenteritis, especially in children. This literature review aims to provide more understanding of the current scientific evidence regarding LF as a potential complementary therapy in the management and prevention of viral gastroenteritis in pediatric patients.

Methodology

Literature searches were obtained through reference sources from PubMed, EBSCOhost, and ProQuest and another source, namely literature published in the last 20 years, without any language restrictions. The literature was searched using the keywords “lactoferrin, viral, and gastroenteritis” with their synonyms. The inclusion criteria in this literature study are as follows:

1. the literature contains current therapies related to the use of LF for viral gastroenteritis;
2. the literature assesses the effectiveness of LF therapy against viral gastroenteritis;
3. the literature has to be a clinical trial.

The results obtained from the initial search were then reviewed by reading the title and abstract to assess the relevance of the literature. Relevant studies were reviewed by reading the complete text and assessed based on compliance with the inclusion criteria. The search results were reviewed by 3 authors (R.S., A.P., and G.T.), and if there were a disagreement between the authors, it would then be mediated by 2 authors (E.D. and B.L.). All disagreements were resolved by discussion.

Results

We obtained 23 articles from PubMed, 3 articles from ProQuest, 15 articles from EBSCOhost based on the search results, with a total of 41 articles. Next, 15 duplicates were excluded using the Zotero citation manager version 5.0.89. Subsequently, title and abstract screening was carried out; 17 articles were excluded, leaving 9 articles. The authors then read each text thoroughly and obtained 4 articles that matched the inclusion criteria. An additional literature search was also carried out from another source and obtained 2 additional articles. The total number of articles included was 6. The authors then reviewed each article in this literature.

Study characteristics

There were 5 randomized controlled trials (RCTs) (n = 2,289) that assessed the effect of LF supplementation from bovine milk and breast milk on gastroenteritis in children aged 4 months to 6 years. The intervention groups were given 70-85 mg of bovine LF (bLF) [8], 490-784 mg human LF (hLF) [9], 1 g bLF [10], and 32.1-39.5 mg bLF [11] daily while in the control groups it was given a placebo, breast milk or no intervention. In RCT done by Tsukahara et al., 100 mg LF-containing yogurt was given in various frequencies while the control group received fruit jelly [12]. In addition, there was another non-RCT study (n = 234) in which children under 5 years received tablet or yogurt supplements that each contained 100 mg LF on a daily basis, and the control group was not allowed to take LF-containing products [13].

Effects of lactoferrin on the severity and incidence of pediatric gastroenteritis in clinical trials

An RCT study conducted on children aged 12-18 months by Ochoa et al. compared the incidence, duration, and severity of diarrhea experienced between the group receiving daily bLF supplement (n = 277) and the group receiving placebo (n = 278) over 6 months. Both groups consumed 0.5 g of placebo or bLF twice daily over their regular diet. There was no significant difference in the incidence of diarrhea between the LF group (5.4 events/year) and the placebo group (5.2 events/year) ($p = 0.375$). However, there were significant differences between the LF and placebo groups in the median duration of illness (4.8 days versus 5.3 days, $p = 0.046$), the incidence of moderate/severe dehydration (1.0% vs. 2.6%, $p = 0.045$), and the number of liquid stools (95/year versus 98.6/year, $p < 0.001$). In this study, the majority of diarrhea was caused by norovirus, although some were caused by other viruses and bacteria [10].

Zavaleta et al. conducted an RCT in 140 children aged 5 months to 33 months. This study measured the severity of diarrhea after treatment, which was divided into 3 groups, namely the experimental group was given the combination therapy of rice-oral rehydration solution (R-ORS), 490-784 mg hLF, and lysozyme, then the second group received R-ORS alone, and the last group was given glucose-ORS (G-ORS). The duration of diarrhea was significantly reduced in the experimental group with respect to the other groups by a mean of 3.67 days compared with the control group of 5.21 days. Next, the percentage of solid feces in the experimental group resulted in a significantly higher percentage of solid feces than the other groups, namely 85.1%, compared with the control group at 69.2%. Based on these findings, therapy with R-ORS, 490-784 mg hLF, and lysozyme was the most effective therapy among all groups in this study [9].

Similar results were also achieved by Chen et al. study in infants (n = 260) aged 4 to 6 months. Daily intake of 32.1-39.5 mg bLF was given in the form of commercially available bLF-fortified formula to the intervention group. There was a significantly lower occurrence of diarrhea-related illnesses in children who received bLF formula. Other than that, the duration of diarrhea-related illnesses was significantly lower than in the control group [11].

The RCT conducted by Tsukahara et al. demonstrated that consumption of 100 mg/day of bLF-containing yogurt at ≥ 3 days/week resulted in a significant reduction in school absences due to vomiting in children aged 3-6 years old. However, that intervention could not reduce the number of absentees due to diarrhea and gastroenteritis caused by norovirus, whereas a previous study reported by Ochoa et al. using 1,000 mg/day of bLF successfully showed a significant reduction in the severity and incidence of diarrhea caused mostly by norovirus [12].

Effects of lactoferrin on the severity of pediatric viral gastroenteritis in clinical trials

In another RCT study, by Yen et al., 172 children aged 2-6 years were divided into group A (n = 96) who received bLF and group B (n = 76) as control. It was found that the consumption of formula milk containing 70 to 85 mg bLF did not decrease the incidence of gastroenteritis due to enterovirus and rotavirus infection. However, it did reduce the duration and frequency of vomiting and diarrhea in children, although it was not statistically significant (3.1 ± 1.3 vs. 3.5 ± 1 days, $p = 0.53$) [8].

In a non-randomized trial study by Egashira et al., it was found that giving food products containing 100 mg of bLF in the form of yogurt and tablets was also shown to reduce the frequency and duration of vomiting and diarrhea, but did not decrease the duration of fever and the incidence of rotavirus-induced gastroenteritis. The results showed that LF products reduced gastroenteritis severity due to rotavirus in children [13].

Discussion

The studies that have been summarized above suggested that administration of LF may reduce duration [9, 10, 11, 13], severity [10, 13], and incidence of pediatric gastroenteritis [11]. Studies that assessed specifically rotavirus-caused gastroenteritis showed unsettled evidence [8, 13]. In addition, LF also increased stool consistency compared with controls [9, 10, 12]. From the result of these studies, it was also found that LF did not cause serious adverse effects [8-13]. These findings indicate that administration of LF to children could provide a protective effect against gastroenteritis.

The antiviral mechanism of LF is related to the structure of the protein. Although all types of LF as a whole have antiviral activity, there is a difference in the percentage value of neutralization of the rotavirus due to differences in structure and glycosylation of each, in which bLF has the highest activity level [14]. LF is able to prevent the viral primary phase of attachment by interacting with cellular membrane proteins such as heparan sulfate proteoglycans (HSPGs) [15]. *In vitro* experiments showed that bLF has anti-rotaviral activity through several mechanisms. Research has found that the N-lobes of LF can prevent the attachment of the virus to the intestinal cell receptors as well as the binding mechanism for calcium in the cells. Calcium-binding can play a role in inhibiting virus morphogenesis after going through the absorption process. In addition, there is also a binding of metal substances, removal of sialic acid, and fragments of LF after digestion plays a role in increasing anti-rotaviral activity and the immune system [16]. An *in vivo* study by Pérez-Cano et al. showed that the experimental group of mice that received additional LF supplementation had the lowest incidence, duration, and experience the mildest disease in diarrhea induced by rotavirus compared with the other groups. In addition, the immune analysis found that LF was able to accelerate the maturation process of intraepithelial natural killer cells, increasing the rate of clearance by the innate immune response in the gut mucosa [17]. *In vitro* studies also showed that bLF exhibited inhibitory function against adenovirus and norovirus by binding to cellular receptors and viral particles [18, 19]. It is also found that LF prevents adenovirus antigens from being synthesized by interacting with a penton base (polypeptide III), a protein that plays a role in attaching integrin receptors [16].

The findings in this literature suggest that LF can reduce the duration and severity of pediatric gastroenteritis, but its benefit in viral gastroenteritis is still unclear. Studies that used low doses (32.1-100 mg) of LF showed mixed results in reducing the duration, severity, and incidence of gastroenteritis. On the other hand, studies that used high doses (490-1,000 mg) of LF consistently reported that LF could lower diarrhea duration and reduce its severity. Clinical studies that specifically assessed LF against viral gastroenteritis showed mixed results, but this could be due to an inadequate dose (70-100 mg) of LF. These findings demonstrated that LF has benefits as therapy for pediatric gastroenteritis in a dose-dependent manner. Thus, the authors recommend that high doses of LF could be used as a complementary treatment for pediatric gastroenteritis. However, further clinical trials using high doses of LF against viral gastroenteritis need to be done in order to evaluate its appropriate efficacy.

The authors realized that there are several limitations to this literature study. First of all, the search for study sources was not extensive, and then the review does not assess the bias in study sources. In addition, the types and doses of LF evaluated from the included studies were different from one another, so that the data obtained were not homogeneous. Non-pure LF product was also used in one of the studies; it is possible that other components may have influenced the study results. Thus, the results described in this literature should be interpreted with caution. Nonetheless, the studies suggest that LF could help reduce the severity of diarrhea and has potential as antiviral therapy against viral gastroenteritis in pediatric patients.

Conclusions and recommendations

LF could be used as a complementary treatment against pediatric gastroenteritis in a dose-dependent manner. The administration of high doses (0.49-1 g) of LF consistently reduced the severity and duration of diarrhea in pediatric patients. However, further studies using high doses of LF are needed to truly evaluate LF's efficacy in pediatric patients with viral gastroenteritis.

Declaration of interest

The Authors declare that there are no competing interests in this study.

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