

REVIEW ΑΝΑΣΚΟΠΗΣΗ

Association between vitamin D and gastrointestinal disease Diarrhea in infancy and childhood

Vitamin D is a steroid hormone that plays a primary role in bone health. In addition to this well-known role in skeletal health, recent studies have shown that vitamin D directly or indirectly regulates many genes, contributing to a range of extra skeletal functions like immunomodulation. One of the main causes of hospitalization in young children is infectious diseases. Gastroenteritis is one of the most common infectious diseases affecting young children in developing countries and a significant cause of hospitalization. Vitamin D deficiency has been associated with increased risk, severity and duration of diarrhea, possible due to a weakened immune response and reduced antimicrobial activity in the gut. However, findings are inconsistent and supplementation trials have not demonstrated preventive benefits. The aim of this review is to summarize recently published data investigating possible associations between vitamin D and gastrointestinal infections in childhood, combined with the possible health benefits from its supplementation.

1. INTRODUCTION

Infancy is a time of increased infectious disease susceptibility and severity, as infants have reduced proinflammatory responses to defend against pathogens. Infections can be generalized or localized to systems like the upper and lower respiratory tract, central nervous systems, skin, gastrointestinal and urinary tract system.¹ Infectious diseases in childhood are a leading cause of morbidity and mortality worldwide, with diarrhea being one of the most common infections affecting children under the age of five worldwide. According to the World Health Organization (WHO) the total number of deaths in the ages of less than five years worldwide have declined from 12.8 million in 1990 to 4.8 million in 2023 and neonatal deaths from 5.2 million in 1990 to 2.3 million in 2023. Leading causes of death in children under five years are pneumonia, diarrhea and malaria along with preterm birth and intrapartum-related complications. Nearly half of these deaths are in newborns.²

The immature infant system develops gradually after birth until after the first years of life, with the contribution of its environmental exposure to pathogens. Breastfeeding, vaccinations, adequate nutrition –after ending breastfeeding– and proper hygiene contributes to the development of infants' immune system.³ Nowadays, some evidence-

based research has also revealed the beneficial effect of vitamin D (VitD) on the maturation and strengthening of the defensive system of infants and young children.^{4,5} The first known function of VitD was the regulation of calcium and phosphate metabolism, essential for the growth and maintenance of the skeletal system. Later it was discovered that in addition to its classical function it had non-skeletal functions involving other systems, one of which is the immune system.^{6,7} Hence, it has been of great interest to explore whether VitD may play a role in the innate immunity of childhood.⁶ Studies have shown that VitD might play a significant immunomodulatory role in improving the incidence or severity of bacterial and viral infections.⁸ Therefore, the purpose of this review is to present evidence-based data of the VitD contribution in the incidence or severity of gastrointestinal infections-diarrhea, and the possible role of VitD supplementation in either prevention and or help in improving the outcome in childhood.

2. VITAMIN D

Vitamin D (VitD) is a fat-soluble vitamin which can be found in two compounds, cholecalciferol (Vit-D2) and ergocalciferol (Vit-D3). In the human body it can be obtained from exposure to the sun or absorbed from food sources.

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Συσχέτιση της βιταμίνης D
και της γαστρεντερικής
νόσου-διάρροιας στη βρεφική
και στην παιδική ηλικία

Περίληψη στο τέλος του άρθρου

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Then it undergoes two hydroxylations, one into the liver to become 25(OH)D (25-hydroxy vitamin D) and a second one in the kidneys where it is converted into 1,25(OH)₂D (calcitriol).⁹ Initially, VitD was for the homeostasis of calcium and phosphate in the human body and its role in bone health, particularly during childhood. Rickets was the first disease recognized to be caused by its deficiency in infants and children and VitD administration was found to be the cure during the 19th and 20th century.¹⁰ Ever since, many studies have reported multiple health benefits of VitD beyond its classical role in all age groups. Although 1,25(OH)₂D is the active metabolite of VitD, 25(OH)D is the circulating marker of VitD status but the reference standards used are not clearly defined. The wide variability between lower and upper limits of healthy serum 25(OH)D levels is the reason why there is not an international consensus on the optimal concentrations in children and adults. VitD guidelines issued by major organizations worldwide recommend optimal serum 25(OH)D levels to be in the range of 50 to 75 nmol/L (20–30 ng/mL).^{11,12} However, varying recommendations from different societies arise from evaluating clinical or public health approaches.¹³ Currently, recommendations for VitD supplementation are based on ensuring serum levels capable to support skeletal health for infants, children and adults.

Also, recommendations for VitD supplementation vary from one country to another adapted to their climate conditions. Countries in Europe establish their own recommendations according to their regional latitude, weather conditions, cultures, dietary and dress habits, as well as food fortification policies.¹⁴ The global consensus recommendations for VitD supplementation is consistent with the suggestions from the Institute of Medicine (IOM) and US Centers for Disease Control and Prevention (CDC). They recommend that for infants from birth up to 12 months, 400 IU/day (10 µg) is adequate, independent of their mode of feeding. Infants, children, adults, pregnant and lactating women need to meet their nutritional requirements for vitamin D through their diet and/or supplementation which is at least 600 IU/day (15 µg).^{12,15,16} In agreement with the above, various international scientific societies recommend VitD supplementation of 400 IU daily during the first year of life, starting from birth, as being safe and effective for VitD status for all infants, independently of their mode of feeding.^{17–21}

Since the immunomodulatory effects of VitD were recognized, many studies have begun to explore its possible relationship to the incidence and severity of infections in infants and young children. Many epidemiologic studies and reviews have demonstrated a correlation between VitD

deficiency and increased incidence of respiratory infections,^{22–24} urinary tract infections^{26,27} and higher mortality in acute and critically ill children.²⁸ Moreover, it is known that VitD plays an important role in the enhancement of innate immunity such as the production of gut antimicrobial peptides.^{29,30} Due to that association with enteric immunologic function, its role in infectious diarrheas is now under research for its use in improving their outcomes.

3. GASTROINTESTINAL INFECTION-DIARRHEA

Gastroenteritis is an inflammation of the gastrointestinal tract involving both the stomach and the small intestine and it is quite frequent in infants. Symptoms include diarrhea with or without vomiting and frequent fever and abdominal pain.³¹ World Health Organization (WHO) describes diarrhea as “the passage of three or more loose or watery stools per day”.³² Diarrhea is one of the most common causes of hospitalization in children and could be due to infections by viruses, bacteria, parasites, and fungus. Worldwide, 3–5 billion cases of acute gastroenteritis and nearly 2 million deaths occur each year in children under 5 years.³³ Rotavirus gastroenteritis occurs almost exclusively in infants and young children, with nearly every child having been infected by the age of 5 years³⁴ and with the majority of serious infections occurring between the age of 4 and 24 months.³⁵

Globally, there is insufficient data on the association between VitD levels and diarrhea in children. Different studies have investigated the role of vitamin D in children with gastrointestinal infections. Four studies carried out in Columbia, Egypt and Iran showed VitD deficiency to be associated with an increased incidence of diarrhea in infants and school aged children.^{36–39} In 2013 one of the largest sample studies reported that VitD deficiency was associated with frequent episodes of gastrointestinal infections in children. The authors followed 475 school-aged children 5–12 years old, during one academic year and checked them for diarrhea. They concluded that VitD deficient and insufficient children had a higher number of diarrhea episodes.³⁶ Two more studies with school aged children (<14 years old) are in agreement with the above results. Children with recurrent diarrhea were deficient of VitD, higher rate of diarrheal attacks, vomiting and abdominal pain.^{37,40} A recent systematic review and meta-analysis found an association between VitD deficiency and diarrhea in children living in developing countries and added that “*VitD deficiency should be considered as a comorbid that can be present in children with diarrhea*”.⁴¹ Moreover, other studies in infants and children less than 5 years also indicated correlation

between VitD deficiency/insufficiency and increased episodes and risk for acute diarrhea.^{42,43} A prospective study from Turkey which enrolled children less than 4 years, found that serum VitD levels were significantly lower in the patient group than in the healthy controls ($p < 0.001$) suggesting that low VitD may be a potential risk factor for rotaviral diarrhea for this age.⁴⁴

However, there are some studies that did not find any correlation between VitD levels and the incidence of diarrhea. A study by Hassam et al in 188 children younger than 5 years found that although all children in all groups (patients with diarrhea, sick controls without diarrhea and healthy controls) found to be VitD deficient, this deficiency was not necessarily related to the incidence of diarrhea in this age group.⁴⁵ Similarly, another study reported no correlation between VitD status and the incidence or severity of diarrhea in very young children aged less than one year.⁴⁶

Also, in the existing literature, only a few clinical trials have assessed the effects of vitamin D supplementation on gastrointestinal illnesses. One trial concerning VitD supplementation of 1,200 IU daily in school-age children (6–15 years old) did not seem to reduce the incidence of gastroenteritis.⁴⁷ Similarly, another small study by Alam et al in Dhaka, Bangladesh assessed hospitalized children with acute diarrhea, aged 6 to 36 months who were daily given 1,000 IU of VitD for a short duration, only for five days. This supplementation was not found to reduce the time of recovery from the diarrhea.⁴⁸ Likewise, another trial, larger in sample size and using controls, investigated the

effects of quarterly supplementation of 100,000 IU VitD on diarrheal incidence in children aged 1 to 11 months followed for up to 18 months. Their findings also showed no benefits in preventing or having any effect on the risk of recurrent diarrhea.⁴⁹

4. CONCLUSIONS

In summary, some studies included in this review suggest a possible association between inadequate VitD levels and the risk of gastrointestinal infections-diarrhea. VitD deficiency or insufficiency may contribute to the pathogenesis of gastrointestinal infectious diseases in childhood. Most infants and children-patients had significantly decreased serum VitD levels associated with increased rates of diarrhea. However, studies with VitD supplementation on young children produced negative results. Supplementation of VitD did not seem to reduce the risk of childhood infectious diarrhea. The controversial results between the studies reviewed could be attributed to conditional differences such as seasonal, personal or racial differences, dietary habits, study design, methods of measuring VitD and different cut-off values. And the studies with VitD supplementation are only few. Hence, there is still need for larger well-designed clinical trials in order to explore whether serum 25(OH)D concentrations are truly associated with gastrointestinal infections-diarrhea. Even longer lasting and dose response data testing, whether VitD supplementation would be beneficial for reducing the diarrhea incidence risk in the pediatric population are needed for unequivocal results.

ΠΕΡΙΛΗΨΗ

Συσχέτιση της βιταμίνης D και της γαστρεντερικής νόσου-διάρροιας στη βρεφική και στην παιδική ηλικία

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Η βιταμίνη D είναι μια στεροειδής ορμόνη που διαδραματίζει πρωταρχικό ρόλο στην υγεία των οστών. Εκτός από αυτόν τον γνωστό ρόλο στην υγεία του σκελετού, πρόσφατες μελέτες έχουν δείξει ότι η βιταμίνη D ρυθμίζει άμεσα ή έμμεσα πολλά γονίδια, συμβάλλοντας σε μια σειρά από εξω-σκελετικές λειτουργίες, όπως η ανοσορρύθμιση. Μια από τις κυριότερες αιτίες νοσηλείας σε παιδιά μικρής ηλικίας είναι οι μολυσματικές ασθένειες. Η γαστρεντερίτιδα αποτελεί μια από τις πιο συχνές λοιμώξεις που προσβάλλουν μικρά παιδιά στις αναπτυσσόμενες χώρες και συνιστά σημαντική αιτία νοσηλείας. Η ανεπάρκεια βιταμίνης D έχει συσχετιστεί με αυξημένο κίνδυνο, σοβαρότητα και διάρκεια της διάρροιας, ενδεχομένως λόγω εξασθενημένης ανοσιακής απόκρισης και μειωμένης αντιμικροβιακής δράσης στο έντερο. Ωστόσο, τα ευρήματα είναι αντικρουόμενα και οι μελέτες με συμπληρώματα δεν έχουν δείξει προληπτικά οφέλη. Στόχος της παρούσας ανασκόπησης είναι η σύνοψη πρόσφατων δημοσιευμένων δεδομένων που εξετάζουν πιθανές συσχετίσεις μεταξύ βιταμίνης D και γαστρεντερικών λοιμώξεων της παιδικής ηλικίας, καθώς και τα πιθανά οφέλη για την υγεία από τη συμπληρωματική χορήγησή της.

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