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Conflict of Interest

The authors have no financial conflicts of interest.

Difference in Vitamin D Levels Between Children with *Clostridioides difficile* Enteritis and Those with Other Acute Infectious Enteritis

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ABSTRACT

Purpose: A steady increase in *Clostridioides difficile* enteritis (CDE) has been reported recently. CDE is associated with intestinal dysbiosis, and vitamin D receptors are known to play an important role in this microbial imbalance as immunological regulators. We investigated the difference in vitamin D levels between children with CDE and those with other acute infectious enteritis.

Methods: This retrospective study was conducted on children below 18 years of age who visited the Gil hospital, underwent investigation to assess vitamin D levels, and had confirmed gastrointestinal infection between January 2015 and December 2018. Patients were divided into two groups: the “CDE group” (n=18) and the “other infectious enteritis group” (n=88); their clinical characteristics, other laboratory results, and vitamin D levels were analyzed.

Results: There was no difference in gender, age, and seasonal distributions between the CDE and other infectious enteritis groups. Other laboratory results were not significantly different between two groups, excluding serum albumin level (4.52±0.45 g/dL vs. 4.31±0.28 g/dL, $p=0.011$). The mean 25-hydroxy vitamin D level in the CDE group was higher than that in the control group (18.75±8.11 ng/mL vs. 14.50±6.79 ng/mL, $p=0.021$).

Conclusion: Vitamin D levels in the CDE group were lower than normal but higher than the other infectious enteritis group. These results suggested that CDE has a different mechanism or susceptibility associated with vitamin D in children, and even marginal changes in vitamin D levels can act as a risk factor for infection.

Keywords: *Clostridioides difficile*; Children; Vitamin D; Receptors, calcitriol

INTRODUCTION

Clostridioides difficile is an anaerobic gram-positive spore-forming bacillus that is known to occur in both toxic and non-toxic forms. *C. difficile* enteritis (CDE) can cause symptoms that range from mild diarrhea and toxic megacolon to death [1].

C. difficile is the cause of both hospital- and community-acquired infections worldwide, with hospital-acquired infections being the most common. Toxinotype V is one of the hypervirulent strains of *C. difficile*, and is the common cause of death associated with hospital-

acquired *C. difficile* enteritis (HA-CDE) [2]. Almost all hospital-acquired infections are associated with the use of broad-spectrum antibiotics that disrupt the indigenous intestinal microbiota. CDE is the most common cause of diarrhea in hospitalized patients [3]. CDE in adults and children is accompanied by general digestive symptoms, the most common being mild to moderate diarrhea. Asymptomatic *C. difficile* carriage rates are significantly high in the first year of life [4]. The duration and severity of symptoms are shorter and weaker in children than in adults, and the recurrence rate is 10% lower in children [5].

CDE incidence has been reported to increase with age and the increasing use of antibiotics [3,6]. However, regardless of the use of antibiotics, incidence of community-acquired *C. difficile* enteritis (CA-CDE) is steadily increasing in the pediatric population [6-8]. Although not yet proven, CA-CDE appears to be acquired through food, such as meat, seafood and raw products. Moreover, zoonosis and environmental factors have been reported to have an impact on the condition [9].

Recent studies have suggested that vitamin D is associated with the innate immune response of the body [10]; 1,25-dihydroxy vitamin D, the metabolized form of vitamin D, plays a significant role in innate and adaptive immune responses and is known to induce cathelicidin and beta-defensin proteins [11]. Based on the relationship between cathelicidin and vitamin D, a study reported that a lower concentration of 25-hydroxy vitamin D (25-OH vitamin D) was associated with the risk of CDE in patients with inflammatory bowel disease, and the mean plasma 25-OH vitamin D level was remarkably lower in CDE patients [12]. Although the mechanism of CDE in children is not clearly defined, its prevalence in this population has increased in recent years [13]. Additionally, most CDE cases in children have atypical features, regardless of prior antibiotic treatment.

A recent study identified that vitamin D deficiency impairs the gut microbiota and intestinal mucus barrier in a mouse model [14]. Moreover, in patients with Crohn's disease, vitamin D can modulate the composition of intestinal microbiota. These results suggest a relationship between vitamin D levels and intestinal dysbiosis [15].

The aim of the present study is to investigate the relationship of vitamin D levels with CDE compared to that with other acute infectious enteritis in children.

MATERIALS AND METHODS

Study design

This retrospective study was conducted in the department of pediatrics, Gachon University Gil Medical Center between January 2015 and December 2018. Children under 18 years of age with gastrointestinal symptoms who underwent investigation to assess vitamin D levels, and were identified to have gastrointestinal infection due to *C. difficile* or other bacteria and viruses were included. A total of 384 patients who underwent investigation to assess vitamin D levels were enrolled. Of these, 278 patients were excluded as follow subjects, and the remaining patients were namely divided into 2 groups: the "CDE group (n=18)" and "other infectious enteritis group (n=88)" (Fig. 1). Subjects were excluded if (1) they were younger than one year of age [4]; (2) informed consent was not provided; (3) there was insufficient clinical data; (4) they were diagnosed with chronic gastrointestinal disease, such as inflammatory bowel disease; or (5) they were diagnosed with both CDE and other acute infectious enteritis.

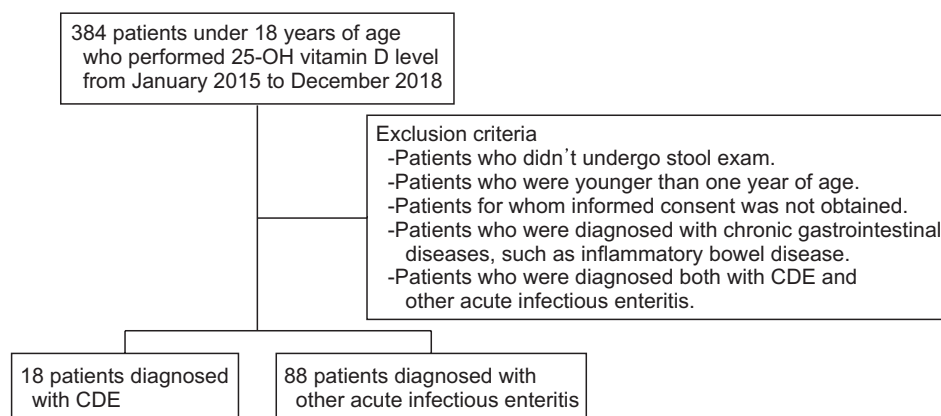


Fig. 1. Selection algorithm for CDE enteritis group and other infectious enteritis group.
CDE: *C. difficile* enteritis, 25-OH vitamin D: 25-hydroxy vitamin D.

Clinical data, such as sex, age, predisposing factors, presence of underlying diseases, prior antibiotic use within three months, treatments, and laboratory findings (complete blood count, serum albumin [g/dL], serum creatinine [mg/dL], and vitamin D level), were obtained. CDE was defined as identified antigens of *C. difficile* toxin A or B infections and/or positive PCR and/or culture assays. Other bacterial infections were confirmed with multiplex real-time PCR assays (*GeneXpert*; Cepheid Xpert *C. difficile* assay, Cepheid, CA, USA) or stool cultures. Viral infection was diagnosed using multiplex real-time PCR (xTAG GPP; Luminex System LX200, Luminex, Toronto, ON, Canada).

To detect toxins A and B in *C. difficile*, VIDAS *C. difficile* toxin A and B (bioMérieux, Marcy-l'Étoile, France) was used, and for culture analysis, a culture medium containing a selective antibiotic was used (cycloserine cefoxitine fructose egg yolk agar). Anaerobic incubation was performed for 24 to 48 hours by inoculating the growth medium.

Patients were classified as those with CA-CDE if symptoms occurred within two days of hospitalization, or if they had never been hospitalized in the last three months. In contrast, patients were considered to have HA-CDE if symptoms occurred after two days of hospitalization in the last three months.

The Institutional Review Board (IRB) of Gachon University Gil Medical Center (IRB No. C2017042) waived the need for informed consent and approved this study.

Statistical analyses

Means with standard deviations or medians with interquartile ranges were used for continuous variables, while numbers with percentages were used for categorical variables. Among the epidemiological and clinical characteristics of patients, continuous variables were compared using Student's *t*-test, while categorical variables were compared using Chi-square or Fisher's exact tests. IBM SPSS Statistics for Windows, version 24.0 (IBM Co., Armonk, NY, USA) was used for analyses, and *p*-values <0.05 were considered to indicate statistical significance.

RESULTS

Comparison of laboratory results and characteristics between *C. difficile* enteritis and other infectious enteritis

No differences were observed between the groups with respect to sex and age. Seasonal distribution was observed in all patients in the CDE group, with six patients acquiring the infection in spring (March–May) (33.3%), six in summer (June–August) (33.3%), two in autumn (September–November) (11.1%) and four in winter (December–February) (22.3%). Similarly, in the other infectious enteritis group, 13 patients (14.8%) acquired the infection in spring, 29 in summer (33.0%), 21 in autumn (23.9%) and 25 in winter (28.4%). There was no difference in seasonal distributions between the two groups. Laboratory findings, such as white blood cell count and creatinine levels, were not different between the two groups ($p>0.05$), but albumin levels were higher in the CDE group than in the other infectious enteritis group (4.52 ± 0.45 g/dL vs. 4.31 ± 0.28 g/dL, $p=0.011$) (Table 1).

In the other infectious enteritis group, 26 cases were viral enteritis, 61 cases were bacterial enteritis, and one case included duplicated infections. Causative agents of viral enteritis were rotavirus ($n=20$) and norovirus ($n=6$). *Campylobacter* ($n=21$) was the most common bacteria enteritis and others were as follows: *Salmonella* ($n=19$), *Clostridium perfringens* ($n=11$), *Aeromonas* ($n=3$), *Escherichia coli* ($n=2$), *Shigella* ($n=2$), *Yersinia* ($n=2$), and *Vibrio species* ($n=1$).

Medical characteristics of children with *C. difficile* enteritis

The number of outpatients ($n=9$, 50.0%) was the same as that of inpatients ($n=9$, 50.0%). The mean age of patients was 4.83 ± 4.50 years and most patients ($n=16$, 88.9%) were under 9 years of age (Table 2).

Diarrhea was the most common symptom ($n=13$, 72.2%), and other symptoms were as follows: abdominal pain ($n=11$, 61.1%), hematochezia ($n=9$, 50.0%), vomiting ($n=5$, 27.8%), fever ($n=4$, 22.2%), and nausea ($n=1$, 5.6%).

CA-CDE ($n=13$, 72.2%) was more common than HA-CDE ($n=5$, 27.8%).

A predisposing factor was identified in 5 patients (27.8%), of which 3 patients (16.7%) had prior history of antibiotic use and 2 (11.1%) had underlying diseases, including intussusception and hydronephrosis.

Table 1. Comparison of laboratory results and characteristics between CDE and other infectious enteritis

Variable	CDE group (n=18)	Other infectious enteritis group (n=88)	p-value
Sex			0.609
Male	11 (61.1)	48 (54.5)	
Female	7 (38.9)	40 (45.5)	
Age at diagnosis (yr)	4.83 ± 4.50	7.37 ± 5.09	0.052
Seasonal distribution			0.274
March to May	6 (33.3)	12 (14.8)	
June to August	6 (33.3)	8 (33.0)	
September to November	2 (11.1)	6 (23.9)	
December to February	4 (22.3)	25 (28.4)	
White blood cells (/mm ³)	10.31 ± 6.09	10.89 ± 5.40	0.685
Albumin (g/dL)	4.52 ± 0.45	4.31 ± 0.28	0.011
Creatinine (mg/dL)	0.34 ± 0.15	0.39 ± 0.18	0.232

Values are presented as number (%) or mean±standard deviation.
CDE: *C. difficile* enteritis.

Table 2. Medical characteristics of children with CDE

Characteristic	Value (n=18)
Associated symptoms	
Diarrhea	13 (72.2)
Nausea	1 (5.6)
Vomiting	5 (27.8)
Fever	4 (22.2)
Abdominal pain	11 (61.1)
Hematochezia	9 (50.0)
Community/Hospital-acquired CDE	
CA-CDE	13 (72.2)
HA-CDE	5 (27.8)
Predisposing factor	
Prior use of antibiotics	3 (16.7)
Underlying disease*	2 (11.1)
Treatment	
Observation or discontinuation of antibiotics	13 (72.2)
Metronidazole for initial therapy	3 (16.7)
Other antibiotics for initial therapy	2 (11.1)

Values are presented as number (%).

CDE: *C. difficile* enteritis, CA-CDE: community-acquired *C. difficile* enteritis, HA-CDE: hospital-acquired *C. difficile* enteritis.

*Underlying diseases; intussusception and hydronephrosis.

The majority of patients were managed with conservative care without the use of antibiotics (n=13, 72.2%). Three patients (16.7%) were prescribed metronidazole for initial therapy, and two (11.1%) were treated with other antibiotics.

Comparison of mean 25-OH vitamin D levels between the groups

Vitamin D levels were different between the groups (**Fig. 2**). Mean 25-OH vitamin D levels were higher in the CDE group than in the other infectious enteritis group (18.75±8.11 ng/mL vs. 14.50±6.79 ng/mL, $p=0.021$) (**Fig. 2**).

Comparison of mean 25-OH vitamin D levels between groups according to the type of infection

Mean 25-OH vitamin D levels were not different between the viral (n=26, 16.05±6.83 ng/mL) and bacterial enteritis groups, except the CDE group (n=61, 13.69±6.65 ng/mL). Mean 25-OH

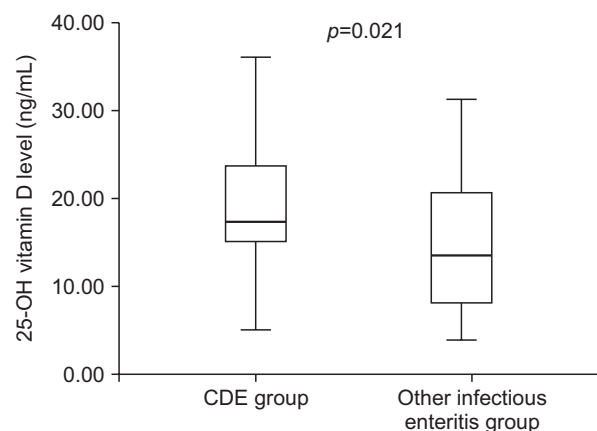


Fig. 2. Comparison of mean 25-OH vitamin D levels between the groups. Mean 25-OH vitamin D level in the CDE group was 18.75±8.11 ng/mL and mean 25-OH vitamin D level in the other infectious enteritis group was 14.50±6.79 ng/mL. $p=0.021$.

25-OH vitamin D: 25-hydroxy vitamin D, CDE: *C. difficile* enteritis.

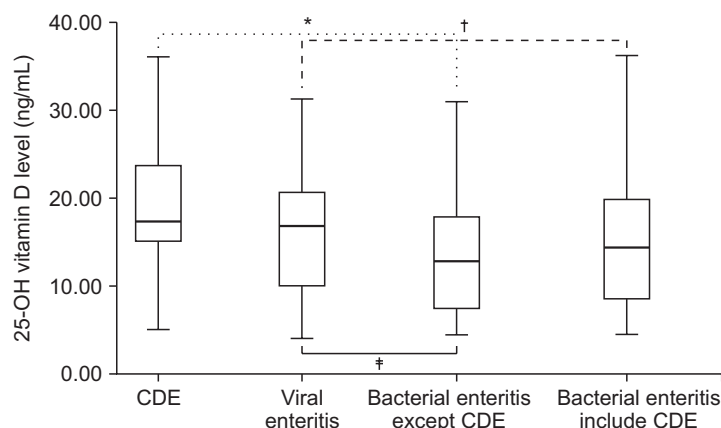


Fig. 3. Comparison of mean 25-OH vitamin D levels between groups according to the type of infection. *CDE (n=18, 18.75±8.11 ng/mL) vs. bacterial enteritis except CDE (n=61, 13.69±6.65 ng/mL) ($p=0.009$). †Viral enteritis group (n=26, 16.05±6.83 ng/mL) vs. bacterial enteritis group except CDE (n=61, 13.69±6.65 ng/mL) ($p=0.137$). ‡Viral enteritis group (n=26, 16.05±6.83 ng/ml) vs. bacterial enteritis group including CDE (n=79, 14.84±7.27 ng/mL) ($p=0.458$).
25-OH vitamin D: 25-hydroxy vitamin D, CDE: *C. difficile* enteritis.

vitamin D levels also were not different between the viral (n=26, 16.05±6.83 ng/mL) and the bacterial enteritis groups, including the CDE group (n=79, 14.84±7.27 ng/mL). The mean 25-OH vitamin D levels of the CDE group were higher than those of the bacteria enteritis group, except for the CDE group (n=18, 18.75±8.11 ng/mL vs. n=61, 13.69±6.65 ng/mL, $p=0.009$) (Fig. 3).

DISCUSSION

The mean vitamin D levels in the CDE group were higher than other bacterial and viral enteritis groups. Moreover, when comparing CDE groups with other bacterial enteritis except CDE groups, the difference between vitamin D levels was greater. These results suggest that the susceptibility to vitamin D Levels may differ between the CDE and other infectious enteritis groups.

Previous studies have reported the effects of vitamin D on the severity, recurrence, and outcomes of CDE, as well as on intestinal microbiota [16-18]. The importance of gut microbiota in the pathogenesis of *C. difficile* infection is well recognized, and marked decreases in microbial diversity have been reported in CDE patients [19]. Jin et al. [20] reported that intestinal dysbiosis in CDE could be related to a decrease in the expression of vitamin D receptors (VDR). VDRs appear to be an important immunological regulator in the human body, and the impairments of which result in the dysbiosis of the gut microbiome [21]. In the normal intestine, VDRs regulate bacterial invasion and suppress inflammatory responses. Intercellular complexes of receptors physically interact with NF-κB in osteoblasts and suppress inflammatory responses to a common invasive enteric bacterial pathogen [22].

Contrary to prior studies in adults, the our study showed that vitamin D levels in the other infectious enteritis group were lower than that in the CDE group among children [17]. These results suggest that intestinal dysbiosis, which was related to a decrease in VDR expressions, is a more sensitive factor in children than adult patients [20]. Impaired VDRs in CDE patients could be associated with variations in vitamin D levels, and even marginal changes in such levels can act as a more risk factor for infection. However, in the other acute infectious enteritis

patients with normally expressed VDR, the risk of infection will increase only in cases of significant variation in vitamin D levels in children. This may support our findings regarding the difference in vitamin D levels between the CDE and other infectious enteritis groups.

There were no differences between the groups with respect to sex and age. Several studies have found a co-seasonality of CDE and respiratory tract infection. Spring is associated with increased CDE incidence due to increases in the use of antibiotics [23]. Although there was no statistical significance, in this study, more CDE cases were reported in spring and summer. However, this could be due to the small sample size in the CDE group (n=18).

Diarrhea (n=13, 72.2%) was the most common symptom in patients with CDE, which is consistent with the findings reported in previous studies [24].

Vitamin D levels in the CDE group were compared with a control group only in adult patients in previous studies [10,17]. However, vitamin D deficiency is more common in children, and low levels of vitamin D are associated with various infections in children. The present work is the first retrospective study to compare vitamin D levels between patients with CDE and other infectious enteritis in a pediatric population.

There are several limitations of the present study. First, the sample size of the CDE group was small. Second, the study was retrospective in design and hence could not compare vitamin D levels between healthy individuals and patients with CDE. Third, the patients in the other infectious enteritis group could not be analyzed by categorizing them based on the individual bacteria and viruses. Therefore, prospective studies are needed to compare the difference in vitamin D levels between CDE and healthy control groups in a large pediatric population.

In conclusion, vitamin D levels in patients with CDE were lower than normal but higher than those with other infectious enteritis. In particular, patients with CDE had higher levels of vitamin D than those with other bacterial enteritis. These results suggested that CDE has different mechanism or susceptibility associated with vitamin D in children, and even marginal changes in vitamin D levels can act as a risk factor for infection.

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