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VITAMIN D AND ACUTE DIARRHEA IN CHILDREN: A META-ANALYSIS

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Vitamin D, Acute diarrhea, Children

ABSTRACT

Diarrhea remains a significant health concern worldwide, particularly in developing countries, contributing to 10% of deaths in children under 5 years. Bacterial infections, notably Shigella and Enteropathogenic Escherichia coli (EPEC), are prevalent causes. This study explores the association between vitamin D3 levels and acute diarrhea in children through a systematic literature review and meta-analysis. Ten studies, including case-control, cross-sectional, and cohort designs, were analyzed. The meta-analysis revealed a significant relationship between vitamin D3 deficiency and acute diarrhea, indicating a higher risk in children with lower vitamin D3 levels. While conflicting findings exist, this study provides valuable insights into the potential role of vitamin D3 in mitigating the risk of acute diarrhea in children.

INTRODUCTION

Diarrhea is still a major health problem in the world, especially in developing countries. Although there has been a decrease in the number of deaths caused by diarrhea, diarrhea still contributes 10% to deaths in children aged less than 5 years and also still causes around 500,000 deaths in developing countries per year. Rotavirus is the most common cause of acute diarrhea. Besides viruses, bacteria are also a common cause of acute diarrhea in developing countries. The prevalence of diarrhea due to bacteria is 34.5% - 60.7% of all diarrhea in developing countries, with the main causes being Shigella and Enteropathogenic Escherichia coli (EPEC). Lack of access to clean water, a lack of personal hygiene, and low breastfeeding rates are the main predisposing factors for acute diarrhea due to bacterial infection.(Abed et al., 2014)

Vitamin D3 is a fat-soluble micronutrient that plays a role in calcium and phosphate metabolism, calcium homeostasis, vascular health, cell differentiation and proliferation. Vitamin D3 often associated with several diseases ranging from infectious diseases to malignancy. There is evidence that shows when vitamin D3 serum is higher than needed vitamin D3 can maintain calcium homeostasis, reduce the risk of insulin resistance, obesity, metabolic syndrome, and malignancy. Vitamin D3 can cause abnormalities in the bones called rickets in children and osteomalacia in adults.(Abed et al., 2014) Prevalence of vitamin D3 in children 10.8% and insufficiency 39% in South China.(Guo et al., 2018) The prevalence of hypovitaminosis D in America is 60.4%, with 44.6% insufficiency and 15.8% deficiency.(Durá-Travé et al., 2018) In Indonesia, the prevalence of vitamin D3 (serum 25(OH)D <25nmol/L) 13%, insufficiency (25-49nmol/L) 45.1%, normal (50-74nmol/L) 49.3%, and sufficiency (≥75 nmol/L) 5,6%.(Ernawati & Budiman, 2015) In DKI Jakarta, the prevalence of vitamin D3 in elementary school children by 75.9% and vitamin D3 15%. Prevalence of vitamin D3 in Manado, North Sulawesi by 34% and vitamin D3 by 64% in adolescents aged 10-18 years.(Pangestu et al., 2016)

Vitamin D3 often occurs in patients with acute diarrhea. Research by Mahyar et al shows a significant relationship between Vitamin D3 serum and acute diarrhea.(Mahyar et al., 2019) Bener et al study on 458 children with vitamin D3 demonstrated that the incidence of diarrhea was significantly higher in children with deficiency vitamin D3. Other studies have also confirmed that vitamin D3 associated with prolongation and exacerbation of diarrhea caused by Clostridium difficile. Research from Bucak et al in 70 patients with diarrhea caused by rotavirus with controls of 60 healthy children to get serum levels of vitamin D3 which is lower in children with diarrhea compared to healthy children, which this study confirms that vitamin D3 is a predisposing factor to acute diarrhea.(Bucak et al., 2016) Vitamin D3 is an important factor in regulating the inflammatory immune response and inhibition of carcinoma via its receptor (VDR) and vitamin D3 common in acute diarrhea.

However, not all studies support a link between vitamin D3 and diarrhea. There are several studies showing conflicting results regarding the relationship between vitamin D3 serum in children with acute diarrhea. Research in Japan(Urashima et al., 2010), indicating that supplementation of vitamin D3 did not reduce the incidence of diarrhea. In addition, research in Bangladesh (Zhao et al., 2015) in children under two years shows that children with normal weight and thin with deficiency vitamin D3 more rarely experience diarrhea caused by EPEC, ETEC, and EAEC.

Meta-analysis of research on vitamin D3 serum in children with acute diarrhea has not been studied before. So this study aims to determine levels of vitamin D3 serum in children with acute diarrhea by meta-analysis method.

RESEARCH METHOD

This research is a quantitative research with a systematic literature review approach (systematic review) and meta-analyses. The literature search process was carried out on several databases. Databases are selected based on criteria is a credible and giving data base impact factor with clear criteria such as, Pubmed (Medline), Thomson Reuters, Cochrane, Embase, Scopus and Crossref. The keywords used included Diarrhea OR Diarrhoea OR Gastroenteritis OR gastrointestinal infection then combined with the search terms for vitamin D (set operator AND), namely vitamin D OR 25(OH)D OR vitamin D deficiency. Search terms for cohort, control studies, cut latitude (set operator AND), namely cohort study, cohort retrospective, case control study, cross sectional study. Search terms for children (set operator AND), namely children OR childhood OR child OR teenager OR adolescent OR adolescence OR children under 18 years old.

Titles and abstracts of literature that have been found based on keywords will be filtered manually to determine relevant literature. Published or unpublished studies and research in journals that do not have data impact factor at Thomson Reuters or Scopus were not included in this meta-analysis. Elimination of studies for meta-analysis was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram.10

The keyword gastroenteritis combined with the search term for vitamin D (AND) Vitamin D OR 25(OH)D OR Vitamin D deficiency resulted in the title the correlation between vitamin D and bacterial diarrhea in children. If the search is limited from 2011 to 2022, there will be 21 entries.

Inclusion Criteria (Selecting)

After all the literature was found, the researcher then sorted the literature based on the inclusion criteria as follows:

1. The research design included in the meta-analysis was an observational study namely cohort, case control, and controlled trials. These criteria were set to screen research that includes data on the vitamin D3 with acute diarrhea in children.
2. Participants in the study were children under 18 years of age. The studies that we used as the background for preparing this research proposal show that the average age of research respondents is 0-18 years.
3. Outcomes in both studies are in the form of dichotomous data namely Odd Ratio (OR) or the mean difference or the average difference. This study aims to see the relationship between vitamin D3 and acute diarrhea in children, thus an observational study that provided data that allowed for the calculation of OR (number of cases and samples in each exposed and non-exposed group) and mean difference (mean and standard deviation) of the vitamin D3 with acute diarrhea in children will be extracted and meta-analyzed according to the type of data.
4. The main outcome data to be extracted is vitamin D3 in children with acute diarrhea
5. Additional outcomes in this study were the incidence of diarrhea and duration of diarrhea in children with vitamin D3.

Assessing the Risk of Bias

In the observational study, after all the literature that complied with the inclusion criteria was determined, the researcher then conducted a risk assessment of bias using the guidelines of The Newcastle-Ottawa Scale (NOS) where the things considered included: bias in the randomization process (bias arising from the randomization process), bias due to missing data (bias due to missing outcome data), bias in the assessment of the outcome (bias in measurement of outcome) and bias in the results reported (bias in selection of the reported results).11

Data Extraction

After the researcher assesses the risk of bias, the researcher selects literature with a low risk of bias. Information about these literatures is then summarized in a summary table containing the name of the researcher and the year of publication, the title of the study, the country where the research was conducted, the research method, the population, the number of samples for cases and controls or exposed and non-exposed, case diagnoses, mean and standard deviation of vitamin D3 in exposed and non-exposed cases and controls.

Analysing

Outcomes in this study are presented in the form of mean difference and Odd Ratio (OR) to see the relationship between vitamin D3 serum in children with acute diarrhea. Calculation pooled effect size mean difference and OR using Review Manager software Version 5.3 with a standard of 95%Confidence Interval (CI). Effect size is a quantitative index used to summarize the results of meta-analytic studies. Then the I2 statistic was used to evaluate the heterogeneity between studies. If the value of I2 ≥50% then the pooled effect size will be calculated using the model Random-effect (DerSimonian-Laird Method). Meanwhile, if the value of I2 <50% then the modelfixed-effect (Mantel-Haenzel method) will be used to calculate pooled effect size.12

Interpretation of Results

The results of the meta-analysis will be presented in forest plots and pooled Odd Ratio (OR) and mean difference. The results of the analysis will be interpreted by taking into account the heterogeneity of the study.

RESULTS AND DISCUSSION

An article search was performed on database Pubmed, Google Scholar, Cochrane, Pediatrica Indonesiana to the EBSCO database. Use advanced builder by entering keywords, we get 1180 articles consisting of 195 articles from database Pubmed and 985 from Google Scholar. By using the Mendeley application, 210 articles were found that had duplicates, leaving 970 articles. Manual screening based on suitability of titles and abstracts found 949 irrelevant studies, leaving 21 studies examining acute diarrhea with vitamin D3. From these articles, the researcher excluded 11 studies with the reason that they did not have the required outcome (n = 6), adult patient respondents (n = 2), trial study designs (n = 2), and articles that could not be accessed in full (n=1). Thus, there were 10 articles included in the qualitative assessment and meta-analysis. All articles were then screened in depth and inclusion criteria which included age, year of publication, and completeness of data and analysis were applied. Article covering incidence and deficiency outcomes of vitamin D3 (n=2), the article includes outcomes of vitamin D3 deficiency and incidence and mean vitamin D3 in diarrheal and non-diarrheal patients (n=2), the article includes the mean vitamin D3 in patients with diarrhea as cases and patients without diarrhea as controls (n = 1), articles include diarrhea outcomes (n = 2), and cohort articles (n = 3).

7 studies that were analyzed, 4 studies used a case-control research design namely (Abed et al., 2014), (Bucak et al., 2016), (Hassam et al., 2019) and (Mahyar et al., 2019), and 3 studies used cross-sectional research design (cross sectional) namely (Bener et al., 2009), (Talachian et al., 2015), and (Chowdhury et al., 2017). The study sites represent the continents of Asia (Iran, Turkey, India, Qatar, Qalbia, Columbia and Bangladesh) and Africa (Egypt, Tanzania). The age of the participants ranged from 0 – 15 years. Acute diarrhea in some studies is defined as liquid bowel movements that occur with a frequency of 3 or more times in 24 hours, semisolid or liquid consistency and lasts for less than 14 days. Vitamin D3 a serum level of 20-29 ng/mL is defined as vitamin D3 whereas <20 ng/mL is defined as vitamin D3. The number of samples ranged from 25 to 331 respondents in the case group and between 20 to 629 respondents in the control group.

Research by (Bener et al., 2009) and (Chowdhury et al., 2017) in children with vitamin D3. In the study of (Chowdhury et al., 2017) deficiency of vitamin D3 defined as a serum level of 25(OH)D <10ng/mL. Research by (Abed et al., 2014), (Thornton et al., 2013), (Talachian et al., 2015), (Ahmed et al., 2016), (Bucak et al., 2016), (Palframan et al., 2018), (Hassam et al., 2019) and (Mahyar et al., 2019) with children with diarrhea as a case sample. (Bucak et al., 2016)'s study was conducted only on children with diarrhea caused by rotavirus. There is a difference in the proportion of cases of diarrhea in the (Bener et al., 2009) and (Chowdhury et al., 2017) studies, in (Bener et al., 2009)'s study of vitamin D3 more in children with diarrhea while in the (Chowdhury et al., 2017) study more in children without diarrhea.

A meta-analysis of 10 articles found that vitamin D3 lower in children with acute diarrhea and the incidence of acute diarrhea is higher in children with vitamin D3 seen from the mean (SD), median (range) or the median (quartile). The results of the study also showed a p-value which stated that there was a relationship between vitamin D3 with cases of acute diarrhea in children.

Table 2. Mean and Standard Deviation of 25(OH)D Serum Levels (ng/mL) in Children with Acute Diarrhea and Non Diarrhea

No.	Author, year of publication	Total sample		Mean (SD) serum 25(OH)D (ng/mL) levels	
		Cases	Control	Cases	Control
1.	Bener et al, 2009	315	143	13.4 ± 8.9	27.5 ± 8.3
2.	Abed et al, 2014	60	20	19.95 ± 13.12	47.36 ± 20.73
3.	Talachian et al, 2015	25	25	36.01(26.28)	52.8(25.39)
4.	Bucak et al, 2016	70	67	14.6 ± 8.7	9.06 ± 6.51
5.	Hassam et al, 2019	47	141	20.77 ± 6.8	17.88 ± 7.9
6.	Mahyar et al, 2019	60	60	19.3 ± 7.8	22.4 ±7.3

The mean and standard deviation of serum levels of 25(OHD (ng/mL) samples are briefly summarized in Table 2. From Table 2, it can be seen that in the studies of Bener et al (2009)(Bener et al., 2009), Abed et al (2014)(Abed et al., 2014), and Talachian et al (2015)(Talachian et al., 2015) mean serum levels of vitamin D3 in the case group was found to be lower compared to the control group. While in the research of Bucak et al (2016)(Bucak et al., 2016), Hassam et al (2019)(Hassam et al., 2019), and Mahyar et al (2019)(Mahyar et al., 2019) it was found that the average level of serum vitamin D3 in the case group was slightly higher than the control group.

Table 3. Proportion of Vitamin D3 Deficiency/Insufficiency Cases in Children with Acute Diarrhea and Non Diarrhea

Author, year	Number of Samples		Number of cases of Vitamin D Deficiency/Insufficiency	
	Acute Diarrhea	Non Diarrhea	Acute Diarrhea	Non Diarrhea
Talachian et al, 2015	25	25	Deficiency: 9 (36%)	Insufficiency: 5 (20%)
Bucak et al, 2016	70	67	Deficiency: 59 (84.2%)	Deficiency: 4 (6%)
Hassam et al, 2019	47	141	Deficiency: 20 (42.6%)	Deficiency: 81 (57.4%)
Mahyar et al, 2019	60	60	Severe deficiency: 7 (11.6%) Deficiency: 23 (38.3%) Suboptimal: 25 (41.6%) Optimum: 5 (8.3%)	Severe deficiency: 2 (3.3%) Deficiency: 21 (35%) Suboptimal: 26 (43.3%) Optimum: 11 (18.3%)

Based on the table of proportions of cases of vitamin D3 deficiency and insufficiency in children with acute diarrhea and non-diarrhea illustrates that cases of vitamin D3 deficiency and insufficiency more in the group of children with acute diarrhea than the group of healthy or non-diarrheal children.

Table 4. Results of Research Quality Assessment Based on NOS

Studies	Selection				Comparability		Exposure/Output			Total points
	1	2	3	4	1	2	1	2	3	
Bener et al, 2009	★	★	★	-	-	-	★	★	-	5
Thornton et al, 2013	★	★	★	-	★	★	★	★	★	7
Abed et al, 2014	★	★	-	-	★	★	★	★	-	6
Talachian et al, 2015	★	★	★	-	-	-	★	★	-	5
Bucak et al, 2016	★	★	★	-	-	-	★	★	-	5
Ahmed et al, 2016	★	★	★	-	★	★	-	★	-	6
Chowdhury et al, 2017	★	★	★	-	-	-	★	★	-	5
Palframan et al, 2018	★	★	★	-	★	★	★	★	-	8
Hassam et al, 2019	-	★	★	★	-	-	★	★	-	5
Mahyar et al 2019	★	★	-	★	★	★	★	★	-	7

Assessment of the quality of research that will be analyzed using Newcasttle-Ottawa Scale (NOS). All included studies received ≥ 5 points out of a total of 9 points for cross-sectional and case-control studies. Table 4 is a table of bias risk assessments for articles included in the meta-analysis, there are 5 articles with 5 stars, 2 articles with 6 stars, 2 articles with 7 stars, and 1 article with 8 stars. Studies by Abed et al (2014)(Abed et al., 2014), Ahmed et al (2016)(Ahmed et al., 2016), Bucak et al (2016)(Bucak et al., 2016), Hassam et al (2019)(Hassam et al., 2019) and Mahyar et al (2019)(Mahyar et al., 2019) use NOS criteria for case-control study designs. Research by Bener et al (2014)(Bener et al., 2009), Talachian et al (2015)(Talachian et al., 2015) and Chowdhury et al (2017)(Chowdhury et al., 2017) used NOS criteria for a cross-sectional study design. Thornton et al (2013)(Thornton et al., 2013) and Palframan et al (2018)(Palframan et al., 2018) used NOS criteria for cohort research design.

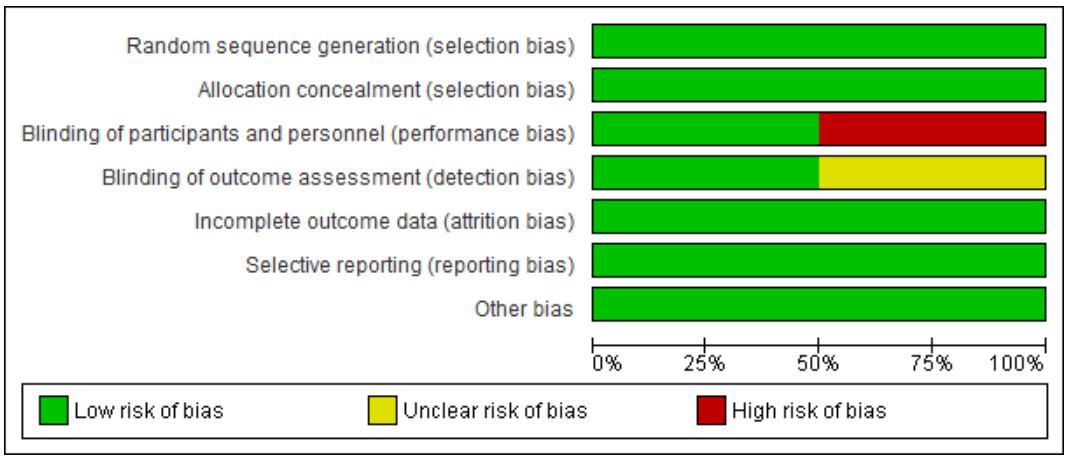

Figure 1. Chart Biased Risk

In the selection criteria, selection of cases and non-cases as well as assessment of exposure was given 1 star while in the fourth (4) assessment, namely the explanation of whether there was an outcome at the time the study was conducted was not given a star because in a cross-sectional study, exposure and outcome were studied at the same time. On the comparability criterion, there is no control for certain variables such as age and gender or their

absence matching for cases and non-cases. In the exposure assessment, there is no explanation regarding the assessment response-rate between cases and non-cases.

In the case-control study design, according to the selection criteria, all studies except the study by Hassam et al (2019)(Hassam et al., 2019) reported a representative sample where the sample came from hospital medical records. Furthermore, on the control selection criteria, all patients come from the same community. In selecting controls, research by Mahyar et al (2019)(Mahyar et al., 2019) used a combination of hospital controls and community controls. In terms of comparability criteria, research by Abed et al (2014)(Abed et al., 2014) controlled for age and gender variables and Mahyar et al (2019)(Mahyar et al., 2019) controlled for age, gender, family size and income variables. On exposure assessment, no articles reported response-rate in cases and controls. In the assessment of the article with the cohort study design it did not explain the outcome being studied, namely acute diarrhea occurred before or after the study began.

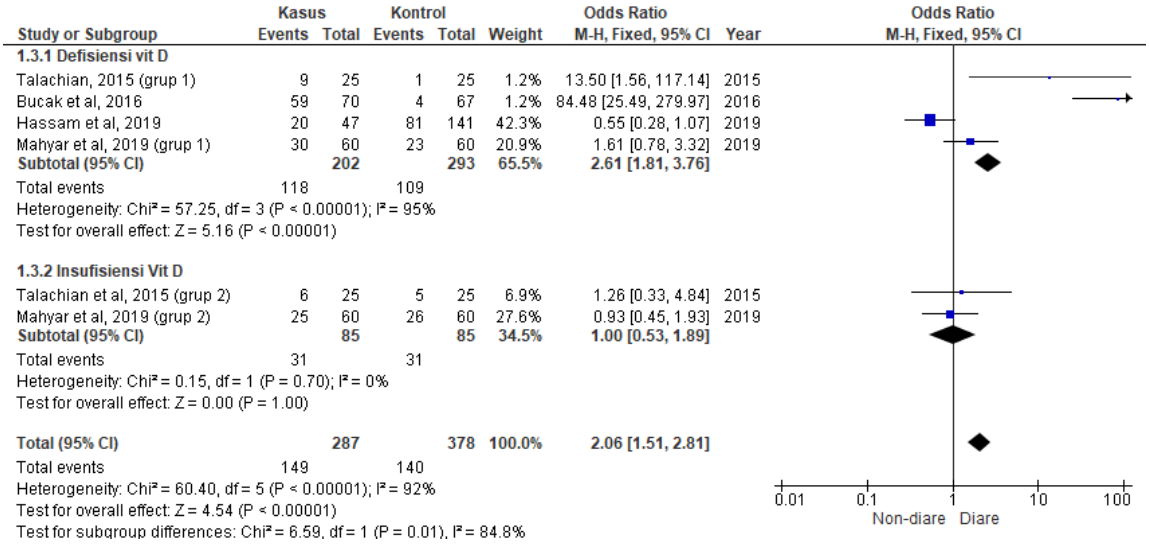

Figure 2. Forest Plots OR Value of Acute Diarrhea in Children with Vitamin D3 Deficiency and Insufficiency

Based on Figure 2, the case group is a group of children with acute diarrhea with a total of 287 responses and the control group is a group of children without acute diarrhea with a total of 378 responses. The heterogeneity value is indicated by the chi^2 value and I^2 which showed high heterogeneity (chi=60.40 and I^2=92%) until used random effect. The results of the analysis showed that there was a significant relationship between acute diarrhea and the incidence of vitamin D3 and vitamin D3 with an OR value of 2.06 (95% CI 1.51; 2.81). After the subgroup analysis was carried out by separating the vitamin D3 insufficiency group and the vitamin D3 deficiency group, it was found that there was a relationship between acute diarrhea and the incidence of vitamin D3 deficiency with an OR value of 2.61 (95%CI 1.81; 3.76) with p-value (p <0.00001), namely the group of children with vitamin D3 deficiency have a 2 times greater risk of experiencing acute diarrhea compared to children with high levels of vitamin D3 normal.

However, there is no relationship between acute diarrhea and the incidence of vitamin D3 insufficiency with an OR value of 1.00 (95%CI 0.53; 1.89) with p-value (p = 1.00).

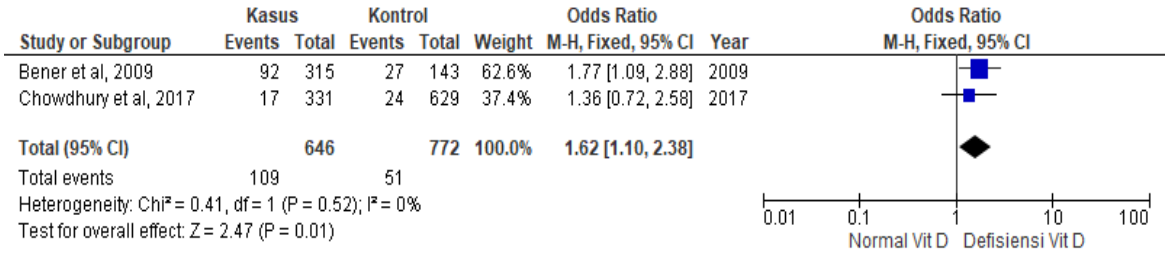

Figure 3. Forest Plots Vitamin D3 Deficiency OR Value in Children with Acute Diarrhea

Based on Figure 3, there are 646 cases of vitamin D3 deficiency and 772 controls with chi^2 heterogeneity values = 0.41 and I2 = 0% until used model fixed effect. The results of the analysis showed that there was a significant relationship between vitamin D3 deficiency3with the incidence of diarrhea in children with an OR value of 1.62 (95%CI 1.10; 2.38) with a p-value (p = 0.01), namely the group of children who experienced acute diarrhea at the time of examination of vitamin D3 more likely to have a vitamin D3 deficiency compared to healthy children.

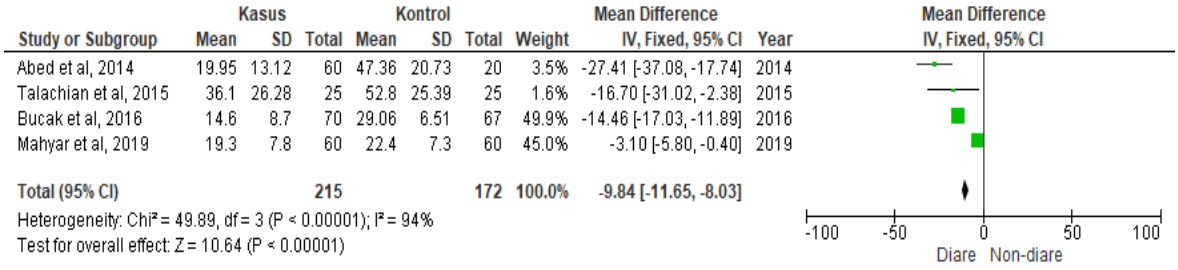

Figure 4. Forest Plots Differences in Vitamin D3 Serum in Children with Acute Diarrhea and Non Diarrhea

Based on Figure 4, there are 215 respondents with acute diarrhea and 172 respondents in the control group. The heterogeneity value is indicated by the chi^2 value = 49.89 and I^2 = 94% which shows high heterogeneity so that model random effect used. The results of the analysis showed that there was a significant difference in the mean levels of vitamin D3 in the acute diarrhea and non-diarrhea groups with an average difference of -9.84 (95% CI -11.65; -8.03) where a minus value indicates the average vitamin D3 in the group of children with acute diarrhea lower than the group of children without diarrhea, with a p-value (p < 0.00001). So it can be concluded that there is a significant difference in vitamin D3 children with acute and non-acute diarrhea.

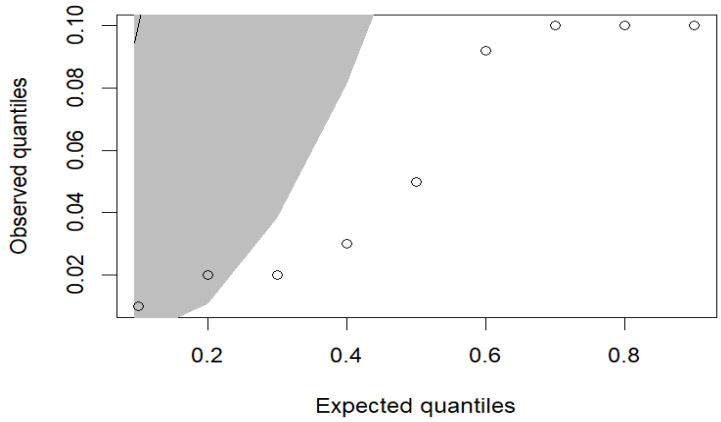

Figure 5. Probability of the Vitamin D3 Cohort Study with acute diarrhea

The results of the meta-analysis using chi square method for cohort studies showed that there was a significant relationship between vitamin D3 with the incidence of acute diarrhea in children with a p value <0.001.

DISCUSSION

This study is the first systematic review and meta-analysis to analyze vitamin D3 serum on the incidence of acute diarrhea in children. There were 10 studies included in the analysis to look at differences in vitamin D3 serum consisting of 4 case-control studies, 3 cross-sectional studies, and 3 cohort studies. Meanwhile, to look for OR deficiency of vitamin D3 there were 3 studies included in the analysis which were cross-sectional studies. Due to limited articles regarding the relationship of vitamin D3 and acute diarrhea in children, this meta-analysis includes articles with outcomes such as incidence of deficiency, vitamin D3 insufficiency, incidence of acute diarrhea, average vitamin D3 deficiency in the acute diarrhea and non diarrhea groups, as well as rate incidence of acute diarrhea per child per year.

The results of this meta-analysis study showed a significant association between vitamin D3 deficiency and acute diarrhea. However, the thing to note is that a cross-sectional study conducted by Bener et al (2014)(Bener et al., 2009) and Chowdhury et al (2017)(Chowdhury et al., 2017) found contradictory outcomes with the incidence of acute diarrhea where Bener et al (2014)[14] found a significant relationship between the incidence of diarrhea and vitamin D3 deficiency, on the other hand Chowdhury et al (2017)[16] found no such relationship. This can be due to the definition of vitamin D3 deficiency in the study Bener et al (2014)(Bener et al., 2009) and Chowdhury et al (2017)(Chowdhury et al., 2017) differed in that Bener et al (2014)(Bener et al., 2009) defined vitamin D3 deficiency is the level of 25(OH)D <20 ng/mL whereas in the study Chowdhury et al defined vitamin D3 deficiency as 25(OH)D <10 ng/mL.

Research conducted by Mahyar et al (2019)(Mahyar et al., 2019) and Talachian et al (2015)(Talachian et al., 2015) reported the occurrence of acute diarrhea in cases of vitamin D3 insufficiency. The results of the analysis showed that there was no significant difference in the proportion of incidents of vitamin D3 insufficiency against cases of acute diarrhea and non-diarrhea. In the study of Mahyar et al (2019)(Mahyar et al., 2019) and Talachian et al (2015)(Talachian et al., 2015) vitamin D3 insufficiency defined as 25(OH)D levels between 21-30 ng/mL. Based on the analysis in this meta-analysis found that there are differences in the definition of vitamin D3 where studies with significant outcomes define vitamin D3 deficiency status3with 25(OH)D levels (<20 ng/mL) compared to studies with no significant results between vitamin D3 deficiency with acute diarrhea (<10 ng/mL). This gives an indication that research with a definition of vitamin D3 deficiency with levels (<20 ng/mL) will be more

common in cases of acute diarrhea than studies with a definition of vitamin D3 deficiency at levels (<10 ng/mL).

Furthermore, the results of a meta-analysis of average levels of vitamin D3 in cases of acute diarrhea and non-diarrhea showed significant results where patients with acute diarrhea had an average level of vitamin D3 which was lower than the group of healthy children with a mean difference of -9.84 (95%CI -11.65:-8.03). However, the average levels of vitamin D3 in cases of acute diarrhea can be categorized as normal or insufficiency where the average level of vitamin D3 in cases of acute diarrhea conducted in the Talachian et al (2015)(Talachian et al., 2015) study 36.01 ± 26.28 and in the Hassam et al (2019)(Hassam et al., 2019) study 20.77 ± 6.8.42.

The study by Bucak et al (2016)[7] specifically determined the cause of acute diarrhea by rotavirus and found the incidence of vitamin D deficiency3 which was very high in cases of acute diarrhea caused by rotavirus with an incidence proportion of 84.2% and OR 84.48 (95% CI 25.49:279.97). Whereas in the Talachian et al (2015)(Talachian et al., 2015) study which did not report the cause of acute diarrhea reported a lower incidence proportion of 36% with OR 13.50 (95% CI 1.56:117.14). This illustrates that a deficiency of vitamin D3 can make a child more susceptible to acute diarrhea caused by viruses or bacteria compared to acute diarrhea caused by other factors.

Acute diarrhea is often clinically unable to distinguish the causative agent. Acute diarrhea is characterized by three or more loose or liquid bowel movements per day or decreased consistency and increased frequency for less than 2 weeks. Acute diarrhea can heal itself but not infrequently also causes complications that cause death. Deaths mainly due to dehydration and acute diarrhea are most common among children in low- and middle-income countries.

Mechanisms of vitamin D3 deficiency to the incidence of acute diarrhea is not fully understood. However, there are several assumptions regarding the pathogenesis of vitamin D3 deficiency and acute diarrhea. First, vitamin D3 plays a role in immunomodulatory adjustment and anti-inflammatory and anti-bacterial properties. This is due to its function in the manufacture of antibacterial peptides such as cathelicidin and β-defensins in the epithelium of the digestive system and increased macrophage activity. This defense mechanism enhances resistance against invading intestinal pathogenic organisms such as Shigella and Salmonella.(Hewison, 2011; Liu et al., 2006) In case of vitamin D3 deficiency, this defense mechanism cannot be carried out so that the risk of diarrhea increases.(Wu et al., 2010; Zasloff, 2006) Animal studies have shown that VDR expression is associated with reduced Salmonella invasion and furthermore, vitamin D3 regulated antimicrobial peptides have an anti-bactericidal effect on E. coli.(Iimura et al., 2005; Wehkamp et al., 2007; Wu et al., 2010)

Vitamin D3 plays an important role in intestinal mucosal barrier homeostasis and in maintaining the integrity of epithelial junctions in the intestine.(Kong et al., 2007; Zhang et al., 2013) The complex and healthy intestinal mucosal barrier acts as the first line of defense against microorganisms that invade the gut.(Antoni et al., 2014) Vitamin D3 deficiency causes disturbances in the expression of proteins involved in barrier formation in the intestinal mucosal defense system, so that a large number of microorganisms can easily penetrate the intestinal mucosal defense system causing inflammation. Recent animal studies have shown that a deficiency in vitamin D3 can lead to increased susceptibility of intestinal mucous membranes to damage and significantly increase the risk of acute diarrhea.(Waterhouse et al., 2019)

Significant relationship between vitamin D3 and gut microbiota have been noted in various studies.(Waterhouse et al., 2019) The gut microbiota acts as a metabolic organ and alterations in the composition of the gut flora are implicated in various disease pathologies. In a recent study, Schaffler et al. found that administration of vitamin D3 significantly affect the

bacterial composition in samples with Crohn's disease.(Schäffler et al., 2018) Other studies confirmed these findings, observing changes in the gut microbiota with vitamin D3 supplementation in patients with multiple sclerosis.(Cantarel et al., 2015)

Pregnancy is a unique stage of life and there is an increased need for vitamin D3 and calcium needed for the development of mineral structures in the fetus and to maintain vitamin D3 levels mother within normal limits. Vitamin D deficiency in pregnant women is associated with pregnancy complications such as preeclampsia, gestational diabetes, and premature birth. Low vitamin D status during pregnancy can lead to vitamin D3 insufficiency because 25(OH)D can cross the blood-placenta barrier. Wang et al, investigated the relationship between vitamin D3 status during three trimesters of pregnancy and on the umbilical blood of newborns found that newborn 25(OH)D levels had a relationship with vitamin D3 mother during pregnancy and the strongest relationship was found in the third trimester. Attention should be paid to vitamin D3 status in pregnant women to prevent vitamin D3 in neonates.(Wang et al., 2021)

This meta-analysis aims to investigate vitamin D3 in children with acute diarrhea and found that vitamin D3 in children with acute diarrhea is lower than in children without diarrhea. This study also analyzed the incidence of vitamin D3 deficiency and insufficiency found more frequently in children with acute diarrhea. So the results of this study support the hypothesis which states that there is a relationship between levels of vitamin D3 in children with acute diarrhea, where there is deficiency or insufficiency of vitamin D3 may be a risk factor for acute diarrhea in children.

CONCLUSION

The conclusion of this study, among others, is that there is a relationship between vitamin D3 with acute diarrhea. In addition, the results of the meta-analysis support vitamin D3 as a risk factor for acute diarrhea in children. Children with vitamin D3 deficiency are twice as likely to have acute diarrhea. Then, there is a significant difference between the mean levels of vitamin D3 in children with acute diarrhea which is lower than in healthy children or non-diarrhoea with a difference of 9.84 ng/mL and it is necessary to evaluate the levels of vitamin D3 in children with acute diarrhea.

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