Relation between vitamin D deficiency and recurrent acute diarrhea in children under the age of five years in Qena university hospitals

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Abstract

Background: Worldwide, children have a very high prevalence of vitamin D deficiency. Epidemiological evidence connects vitamin D deficiency to immune system dysfunction and an elevated risk of infections. For the therapy of acute diarrhea in children, it may be useful to know how vitamin D deficiency affects the severity of the condition.

Objectives: To study the relation between vitamin D deficiency and recurrent acute diarrhea in children.

Patients and Methods: A Hundred Egyptian children (1 month to 5 years old) with a history of recurrent attacks of acute diarrhea were enrolled in the study. They were subjected to complete history, clinical examination and laboratory investigation including vitamin D assays.

Results: we found a positive correlation between vitamin D deficiency and recurrent acute diarrhea. Vitamin D deficiency was deficient in 15%, insufficient in 17%, and sufficient in 68% of children with recurrent acute diarrhea. There was a significantly decreased percentage of vitamin D supplementation in deficient patients (20%) when compared with insufficient patients (64.7%) and sufficient patients (63.2%). There was a highly significantly increased total number of diarrhea episodes in deficient patients (5.6 ± 1.1) when compared with insufficient patients (4.3 ± 1.5) and sufficient patients (2.2 ± 0.9).

Conclusion: This study pays attention to the role of vitamin D in the susceptibility to infection-related illness in children.

Keywords: Vitamin D; Recurrent Acute Diarrhea; Children.

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Introduction

The World Health Organization (WHO) describes diarrhea as "the passage of three or more loose or watery stools per day (or more frequently than is normal for the individual)" **(WHO Diarrheal disease, 2017).** Diarrhea may be acute which lasts less than two weeks or chronic which continues for more than two or three weeks. Any big volume of faeces or frequently loose stools that develop and resolve repeatedly are considered to be recurrent diarrhea **(Chris, 2015).**

The body requires optimal levels of micronutrients for effective immunological function, with variable needs at different stages of life **(Maggini et al., 2018).** widely known that overt (clinical) micronutrient deficiencies harm the immune system which predisposes individuals to infections **(Alpert, 2017**). For instance, a lack of certain micronutrients has been linked to a higher risk of morbidity and mortality from measles, pneumonia, and diarrheal disease **(Hemilä, 2017; Prentice, 2017).** Calcitriol controls the antimicrobial proteins cathelicidin and beta-defensin, which are in charge of improving the composition of the intestinal microbiota and preserving the gut barrier **(Biesalski, 2016; Clark and Mach, 2016)**. The current study aimed to assess sociodemographic risk factors and clinical manifestations associated with recurrent acute diarrhea and to evaluate the relationship between vitamin D deficiency and recurrent acute diarrhea in Children.

Patients and methods

Type of the study: a Cross-sectional study.

Study setting: the study was conducted in pediatric outpatient Clinics of the Pediatric department at Qena University hospitals.

Study period: March 2020 To March 2021.

Sample size: Hundred Egyptian children with a history of recurrent attacks of acute diarrhea were enrolled in the study.

Inclusion criteria: Children who suffered from recurrent acute attacks of diarrhea aged from 1 month to 5 years.

Mild diarrhea means having a few diarrhea stools in a day. **Moderate diarrhea** means having more than a few but not more than 10 diarrhea stools in a day. **Severe diarrhea** means having more than 10 loose, watery stools in a single day (24 hours).

Exclusion criteria: Children with diseases commonly cause chronic diarrhea such as cystic fibrosis, celiac disease, Mal absorption syndrome, intestinal tuberculosis, immune deficient diseases, corticosteroid intake, ulcerative colitis, food allergies, milk intolerance, giardiasis, rickets, and severe malnutrition.

Ethical considerations: The study was approved by the Institutional Ethical Committee of South Valley University. **Ethical approval code:** SVU/MED/ PED025/1/148. Parents of subjects involved in the current study were informed about the nature and details of the current work and written consent was obtained from each participant.

Methodology

All patients were subjected to the following:

1. A complete history was taken from the parents of the children.
2. Full clinical examinations: Anthropometric measurements for body weight, height, BMI, and head circumference.
3. Systemic examination to exclude the presence of any chronic illness.
4. Laboratory investigations:
   a) complete blood count using cell dyne Ruby (Abbott diagnostic – Santa Clara - Ca – UAS).
   b) Parathyroid hormone (PTH) by an automated immunoassay system from TOSOH Bioscience
   c) Quantitative colorimetric estimation of total calcium and phosphorous levels

using automated chemistry analyzer Pentra (Horiba, France).

d) Quantitative estimation of serum 25(OH) vitamin D level using VIDAS-France (automated enzyme-linked immunoassay).

There are three levels of vitamin D deficiency: in mild deficiency, vit D level ranges from 20 to 10 ng/ml, in moderate deficiency vit D level ranges from 10 to 5 ng/ml, while in severe deficiency vit D is less than 5ng /ml **(Gani, 2015).** Vitamin D sufficiency (level more than 30 ng/mL), insufficiency (level between 20 to 30 ng/mL) and deficiency (level less than 20ng /ml) (**Häusler and Weber, 2019).**

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 24. Quantitative data were expressed as mean ±SD. Qualitative data were expressed as frequency and percentage. **A one-way analysis of variance (ANOVA):** when comparing more than two means (for normally distributed data). **Kruskal Willis test (KW):** when comparing more than two means (for abnormally distributed data). **Chi-square test:** was used when comparing non-parametric data. P-value < 0.05 was considered significant.

Results

Description of demographic data in all studied patients. **Table (1)**

There was no statistical significant relation between vitamin D status and (weight and height).**Table (2)**

Description of vitamin D level in all studied patients.There were 15 patients (15%) of deficient level, 17 patients (17%) on insufficient level and 68 patients (68%) of sufficient level.**Table (3)**

There was a decreased percentage of vitamin D supplementation in deficient vit D status patients when compared with insufficient and sufficient vit D status patients.**Table (4)**

There was no significant relation between vitamin D status and number of mild episodes of diarrhea . There was Significant increased the total number of diarrhea episodes in deficient patients when compared with insufficient patients and sufficient patients. There was Significant increased number of moderate diarrheal episodes in deficient patients when compared with insufficient patients and sufficient patients. There was Highly statistical significant increased number of severe diarrheal episodes in deficient patients when compared with insufficient patients and sufficient patients .**Table (5)**

There was no significant relation between vitamin D status and malnutrition. There was Statistically significant decreased percentage of dysentery in sufficient patients when compared with insufficient patients and deficient patients There was Statistically significant decreased percentage of distension in sufficient patients when compared with insufficient patients and deficient patients.

There was statistically significant decreased percentage of pallor in sufficient patients when compared with insufficient patients and deficient patients . There was Statistically significant decreased percentage of pallor in sufficient patients when compared with insufficient patients and deficient patients. There was Statistically significant decreased percentage of vomiting in sufficient patients when compared with insufficient patients and deficient patients.

There was Statistically significant decreased percentage of abdominal pain in sufficient patients when compared with insufficient patients and deficient patients.**table (6)**. There was no statistical significant relation between vitamin D status and WBCs. Statistically significant increased PTH in deficient patients when compared with insufficient and sufficient patients . Statistically significant decreased Ca and PO4 in deficient patients when compared. **table (7)**. There was no significant relation between vitamin D status and (gestational age, birth weight, feeding history, breast feeding duration & weaning age). Statistically decreased percentage of sun exposure in deficient patients when compared with insufficient and sufficient patients.**table (8)**

Table 1. Demographic data in all studied patients

Variables		Studied patients (N = 100)	
Age (months)	**Mean ±SD**	13.3 ± 12.5	
	Min – Max	1 – 60	
Sex	**Male**	55	55%
	Female	45	45%
Residence	**Rural**	52	52%
	Urban	48	48%
Socioeconomic status	**Low**	48	48%
	Moderate	52	52%
Vitamin D supplementation	**No**	43	43%
	Yes	57	57%

Table 2. Relation between vitamin D status and (weight & height).

Variables		Vitamin D status						Stat. test	P-value
		Deficient (n = 15)		**Insufficient (n = 17)**		**Sufficient (n = 68)**			
Weight (kg)	**Mean**	9.5		9.3		8.7		KW = 2.2	0.325 NS
	±SD	2.9		3.6		2.6			
Weight categories	**Normal**	9	60%	12	70.6%	57	83.8%	X^2 = 4.7	0.094 NS
	Under weight	6	40%	5	29.4%	11	16.2%		
Height (cm)	**Mean**	74.8		73.3		71.5		KW = 1.62	0.443 NS
	±SD	11.6		14.04		11.1			
Height (cm)	**Normal**	8	53.3%	12	70.6%	56	82.4%	X^2 = 6	0.050 NS
	Short	7	46.7%	5	29.4%	12	17.6%		

Table 3. Vitamin D levels in all studied patients

Variables		Studied patients (N = 100)	
Vitamin D (ng/ml)	Mean ±SD	39.3 ± 19.9	
	Min – Max	7 – 97.8	
Vitamin D status	Deficient	15	15%
	Insufficient	17	17%
	Sufficient	68	68%

Table 4. Relation between vitamin D status and demographic data.

Variables		Vitamin D status						Stat. test	P-value
		Deficient (n = 15)		Insufficient (n = 17)		Sufficient (n = 68)			
Age (months)	Mean	16.5		14.3		12.3		F = 0.74	0.478 NS
	±SD	12.2		17.5		11.1			
Sex	Male	3	20%	8	47.1%	34	50%	X^2 = 4.5	0.105 NS
	Female	12	80%	9	52.9%	34	50%		
Residence	Rural	6	40%	9	52.9%	37	54.4%	X^2 = 1.03	0.598 NS
	Urban	9	60%	8	47.1%	31	45.6%		
Socio-economic status	Low	9	60%	8	47.1%	31	45.6%	X^2 = 1.03	0.598 NS
	Moderate	6	40%	9	52.9%	37	54.4%		
Vit. D supplementation.	No	12	80%	6	35.3%	25	36.8%	**X^2 = 9.8**	**0.007 S**
	Yes	3	20%	11	64.7%	43	63.2%		

Table 5. Relation between vitamin D status and Number of episodes of diarrhea.

Variables		Vitamin D status			KW	P-value
		Deficient (n = 15)	Insufficient (n = 17)	Sufficient (n = 68)		
Total No. of diarrheal episodes	Mean	5.6	4.3	2.2	**52.7**	**< 0.001 HS**
	±SD	1.1	1.5	0.9		
No. of mild episodes	Mean	1.0	1.1	1.1	0.077	0.962 NS
	±SD	0.7	0.6	0.7		
No. of mod. Episodes	Mean	1.4	0.7	0.5	**15**	**0.001 S**
	±SD	0.8	0.6	0.6		

No. of severe episodes	**Mean**	3.2	2.5	0.6	**51.2**	**< 0.001 HS**
	±SD	1.0	1.2	0.8		

In mild episodes of diarrhea, no significant relation between vitamin D status and number of mild episodes of diarrhea. Significant increased the total number of diarrhea episodes in deficient patients when compared with insufficient patients and sufficient patients (**p < 0.001**). Significant increased number of moderate diarrheal episodes in deficient patients when compared with insufficient patients and sufficient patients. Highly statistical significant increased number of severe diarrheal episodes in deficient patients when compared with insufficient patients and sufficient patients

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Table 6. Relation between vitamin D status and clinical data.

Variables	Vitamin D status						X^2	P-value
	Deficient (n = 15)		Insufficient (n = 17)		Sufficient (n = 68)			
Dysentery	5	33.3%	5	29.4%	7	10.3%	**6.8**	**0.032 S**
Distention	10	66.7%	8	47.1%	21	30.9%	**7.2**	**0.028 S**
Dehydration	11	73.3%	12	70.6%	13	19.1%	**26.3**	**< 0.001 HS**
Pallor	9	60%	8	47.1%	16	23.5%	**9.2**	**0.01 S**
Vomiting	12	80%	11	64.7%	22	32.4%	**14.5**	**0.001 S**
Abdominal pain	13	86.7%	9	52.9%	28	41.2%	**10.2**	**0.006 S**
Malnutrition	6	40%	5	29.4%	12	17.6%	3.9	0.139 NS

No significant relation between vitamin D status and malnutrition. Statistically significant decreased percentage of dysentery in sufficient patients when compared with insufficient patients and deficient patients Statistically significant decreased percentage of distension in sufficient patients when compared with insufficient patients and deficient patients.Statistically significant decreased percentage of pallor in sufficient patients when compared with insufficient patients and deficient patients .Statistically significant decreased percentage of pallor in sufficient patients when compared with insufficient patients and deficient patients.Statistically significant decreased percentage of vomiting in sufficient patients when compared with insufficient patients and deficient patients.Statistically significant decreased percentage of abdominal pain in sufficient patients when compared with insufficient patients and deficient patients.

Table 7. Relation between vitamin D status and studied laboratory data

Variables		Vitamin D status			KW	P-value
		Deficient (n = 15)	Insufficient (n = 17)	Sufficient (n = 68)		
PTH (pg/ml)	**Mean**	54.2	55.6	29.7	**12.8**	**0.002 S**
	±SD	41.8	40.7	17.5		
Total. Ca (mg/dl)	**Mean**	7.1	8.3	8.6	**13.6**	**0.001 S**
	±SD	1.4	1.1	1.2		

PO4 (mg/dl)	**Mean**	4.6	5.9	5.8	**8.2**	**0.016 S**
	±SD	1.5	1.6	1.1		
Hb (g/dl)	**Mean**	9.8	10.6	11.5	**9.8**	**0.007 S**
	±SD	2.0	2.1	1.6		
WBCs (cells/ µl)	**Mean**	8.1	8.4	7.8	0.8	0.668 NS
	±SD	2.2	2.0	2.3		

No statistical significant relation between vitamin D status and WBCs. Statistically significant increased PTH in deficient patients when compared with insufficient and sufficient patients . Statistically significant decreased Ca and PO4 in deficient patients when compared.

Table 8. Relation between vitamin D status and (gestation age & post-natal data).

Variables		**Vitamin D status**						**Stat. test**	**P-value**
		Deficient (n = 15)		**Insufficient (n = 17)**		**Sufficient (n = 68)**			
G. Age (weeks)	**Mean**	37.0		37.6		37.5		KW = 5.1	0.077 NS
	±SD	0.8		0.8		0.7			
Birth weight (kg)	**Mean**	3.1		3.1		3.0		KW = 0.48	0.786 NS
	±SD	0.2		0.3		0.3			
Feeding history	**Breast feeding**	5	33.3%	5	29.4%	35	51.5%	X^2 = 3.6	0.162 NS
	Comp.	10	66.7%	12	70.6%	33	48.5%		
B. feeding duration (months)	**Mean**	10.0		8.1		9.5		KW = 1.72	0.423 NS
	±SD	5.7		4.4		4.9			
Weaning age (months)	**Mean**	5.4		5.2		5.2		KW = 0.05	0.976 NS
	±SD	1.0		0.8		0.9			
Sun exposure	**No**	11	73.3%	6	35.3%	24	35.3%	**X^2 = 7.6**	**0.022 S**
	Yes	4	26.7%	11	64.7%	44	64.7%		

No significant relation between vitamin D status and (gestational age, birth weight, feeding history, breast feeding duration & weaning age).

Statistically decreased percentage of sun exposure in deficient patients when compared with insufficient and sufficient patients .

Discussion

Diarrhea is One of the most prevalent illnesses among children under five in developing countries and is also the second most common infectious cause of morbidity and mortality in this age range. Low vitamin D levels are linked to increased risk and severity of acute infections as well as unfavorable outcomes of some chronic infections **(Yin and Agrawal, 2014).**

Our study aimed to evaluate whether vitamin D was associated with diarrheal incidence and severity in children. In our study ,we found an increase in the total number of diarrheal episodes in patients with deficient vit D

level when compared with insufficient patients and sufficient patients that was in agreement with Abed et al., the study conducted on 80 randomly chosen children aged 4 to 12 years. These findings provide evidence that vitamin D deficiency increases children's susceptibility to infection-related illness **(Abed et al., 2014).**

Our results showed that there is an increase in the total number of diarrheal episodes in patients with deficient vit D levels when compared with insufficient patients and sufficient patients that comes in agreement with **El-Desouky et al.** who demonstrated a significant correlation between low serum vitamin D and recurrent acute diarrhea in children. There was a statistical difference in regards to the number of acute diarrhea attacks and vitamin D deficiency. Hemoglobin level decreased below normal in (55%) of children with deficiency. Seventy-five percent of the studied children were supplemented with vitamin D which significantly decreases the number of diarrheal attacks (**El-Desouky et al., 2020**).

As revealed by a study by Thornton et al. on 475 school-aged children, 10% of the children had vitamin D deficiency, while 47% had inadequate levels. Children with vitamin D insufficiency have a higher incidence of diarrhea, according to the results of the one-year follow-up **(Thornton et al., 2013).** According to **Bener et al**. study on 458 Qatari youngsters, vitamin D deficiency affected 61.6% of those aged 11 to 16 as well as 28.9% of those aged 5 to 10 and 9.5% of those under 5 years old. They claimed that children with vitamin deficiencies have a considerably higher prevalence of diarrhea **(Bener et al., 2009).**

The involvement of vitamin D deficiency in the prolongation and exacerbation of diarrhea brought on by Clostridium difficile has also been supported by additional investigations (6.1 days vs. 4.2 days, P = 0.01) **(Wong et al., 2016).** According to a study by **Talachian et al.,** children with diarrhea have considerably lower serum 25 (OH) vitamin D concentrations than children without diarrhea (25 children with acute diarrhea and 25 healthy children) **(Talachian et al., 2015).**

Serum levels of vitamin D are much lower in children with diarrhea than in children without diarrhea, according to a study by **Bucak et al,** that included 70 patients with rotavirus diarrhea and 60 healthy children as a control group (14.6 + 8.7 ng/mL vs. 29.06 + 6.51 ng/mL). These studies revealed that vitamin D deficiency is a risk factor for rotavirus diarrhea **(Bucak et al., 2016).**

The serum 25(OH)Vitamin D concentrations of 60 children with acute bacterial diarrhea and 60 healthy children were compared by Mahyar and colleagues. The amount of serum 25(OH) vitamin D was found to be significantly correlated with acute bacterial diarrhea by the authors **(Mahyar et al., 2019)**.

In contrast to our results, Ahmed et al stated that vitamin-D status was not associated with the incidence and severity of diarrhea in study children **(Ahmed et al., 2016).**

In a similar vein, 3046 high-risk 1- to 11-month-old infants were randomly assigned to receive 6 doses of oral vitamin D3 (cholecalciferol 100 000 IU) every three months in a double-blind placebo-controlled trial. Supplemental vitamin D3 was found to have no impact on the likelihood of developing recurrent diarrheal illness **(Aluisio et al., 2013).**

Vitamin D levels were not shown to be specifically associated with diarrhea in children under the age of five in a study of 188 children under the age of five **(Hassam et al., 2019).**

The discrepancy in the results between the previous studies can be attributed to differences in the study population or study design. Also, this variability may be influenced by ethnicity, race, sex, disease duration, and age at onset.

These findings contrasted with those of a Brazilian study by Almeida et al., which found no differences in newborns' mean 25(OH) D serum concentrations based on the amount of time or length of sun exposure **(Almeida et al., 2018).**

Contrary to the current study, **Coutard et al** conducted among hospitalized patients in France aimed to investigate the relationship between vitamin D deficiency and anemia. Vitamin D (25[OH]D) and hemoglobin levels were estimated. Interestingly, after adjustment for other factors, anemia was not significantly associated with vitamin D deficiency.

Conclusion

Based on the results obtained in this study, vitamin D insufficiency was linked to an increase in the frequency of diarrheal bouts, also there is a link between hypocalcemia and a rise in PTH levels in the blood.

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