VITAMIN D STATUS IN PRESCHOOL CHILDREN WITH IRON DEFICIENCY ANEMIA

By

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ABSTRACT

Background: *lack of vitamin D (VDD) or iron may result in a number of health problems in infants and children, even if they show no symptoms. The probable link between the two is still a mystery.*

Objectives: *To study the status of vit D among preschool children suffering from iron deficiency anemia.*

Subjects and Methods: *This study was conducted in Al-Hussein University Hospital Outpatient Clinic. It comprised 50 Iron deficient anaemic patients who were investigated for their Vitamin D status.*

Result: *Out of 50 iron deficient anemic children 29 (58%) had deficiency and 14 (28%) had Insufficiency of vitamin D level. There was a statistically significant positive correlation found between PCV, MCV, Ferritin and Iron markers with serum vitamin D level (P-value < 0.01). where the mean of 25(OH) VIT D was (21.27 ± 9.86). There was a significant negative correlation between age, BMI, Platelets and TIBC with serum vitamin D level (P-value >0.05).*

Conclusion: *Our findings suggest a complex association between vitamin D and iron status in preschool children, Low vitamin D status (25(OH)D < 20ng/mL (50nmol/L); was associated with iron deficiency anemia. The positive association between vitamin D and iron deficiency in our study suggest that both conditions should be considered in relevant public health strategies where the two nutrient deficiencies coexist. There is a need for further studies to understand the mechanisms of action of the associations between vitamin D and iron deficiency.*

Key word: *Iron Deficiency Anemia; Vitamin D Deficiency.*

INTRODUCTION

Even in the absence of symptoms, vitamin D and iron deficiency may lead to many health problems in children, some of which can have long-term consequences. A possible link between iron deficiency and low levels of vitamin D in preschool children was investigated in our research.

Vitamin D deficiency affects around 30% to 50% of the world's population, regardless of age **(Palacios et al., 2014)** the most common kind of anaemia is iron deficiency anaemia, an estimated 2–3 billion people worldwide are anaemic, according to the World Health Organization **(MacDonald et al., 2010)**.

Vitamin-D are prohormone that is important for bone health and function. Play an important role in the synthesis of red blood cells and the delivery of oxygen **(Jin et al., 2013)**.

Bone metabolism is the primary function of vitamin D. As a result of vitamin D deficiency (VDD) in children, rickets may develop **(Balasubramanian., 2011)**; Osteomalacia in adolescents and adults **(Holick., 2004)**.

As a result of iron deficiency (ID), a wide range of health problems may arise, including growth and development delays, cognitive and memory issues as well as an increased risk of infection and anaemia (IDA) **(Katsumata et al., 2009)**.

In children who are deficient in iron or vitamin D, several negative impacts have been documented, Anemia and VDD have been shown to be present in the same patient **(Coutard et al., 2013)**.

Some recent researches have connected IDA and VDD because of their similar metabolic pathways **(Kartal, Gürsel., 2019)**.

AIM OF THE WORK

To study the prevalence of vit D deficiency among iron-deficient anemia at preschool children in Al-Hussein University Hospital Outpatient Clinic.

Ethical considerations:

1. Written informed consent was obtained from patients or their legal guardians.
2. An approval by the local ethical committee was obtained before the study.
3. The authors declared no potential conflicts of interest with respect to the research, authorship, and/ or publication of this article.

4. All the data of the patients and results of the study are confidential and the patients have the right to keep it.
5. The researcher explains the aim of the study to the patient.

Calculation of sample size:

The sample size estimation was done using the Epi info7 program for sample size calculation, with 0.05 alpha error, confidence interval of 0.95 and the power of the study 0.80. & An error of 5% odds ratio calculated= 1.115. The final maximum sample size taken from the Epi- Info output was 50.

Inclusion criteria:

Age: preschool children (4 - 6 years), clinical and laboratory evidence of IDA.

IDA was defined as Hb ≤ 11g/dL and ferritin ≤12ng/mL. Subjects with low mean corpuscular volume (MCV) (≤70fL) and reduced iron binding capacity (≤15%) were included in the IDA **(Al-Zuhairy et al., 2022)**.

Exclusion criteria:

Active infection, any chronic disease. eg Liver cirrhosis, Heart failure, chronic kidney disease, hemoglobinopathies, receiving iron or vitamin D supplementation and blood transfusion received within the last 6 months.

Study Procedure:

This prospective case-control study, include 50 children were selected from pediatric clinics of Al-Azhar University Hospitals during the period from 1st January 2023 till 31st July 2023.

All patients were subjected to:

1. **Complete history taking including:**
   - Personal history (name, age, sex, address).
   - Prenatal history including: Maternal illness, or maternal drug and multivitamins intake.
   - History of the present illness: common presenting history

   Fatigue, Pale skin, Poor appetite.

   Unusual cravings for non-nutritive substances, such as ice. paint or starch.

   - Detailed nutritional history including nutritional habits as consuming foods rich in iron and drinking tea.
   - Past history (eg: history of suggestive gastrointestinal bleeding).
   - Family history (anaemia, consanguinity, maternal & paternal age) **(Al-Zuhairy et al., 2022)**.

2. **Complete physical examination including:**

A. General examination:

General look to detect pallor and exclude other vitamins deficiency.

Vital signs (Respiratory rate, heart rate, temperature and blood pressure).

B. Systemic examination:

Chest and heart examination (eg: hemic murmur).

Complete abdominal examination to detect splenomegaly or any organomegaly.

3. a. Complete blood count including RBC indices will be measured using cell counter. Serum iron level will be measured using an autoanalyzer.

b. Serum iron profile (serum iron, serum ferritin, Iron binding capacity)

c. Serum vitamin D level. **(Al-Zuhairy et al., 2022)**.

- **Procedure:** Overall, 4 ml of whole blood was collected by venipuncture; 2 ml in EDTA vacutainers and 2 ml in plain vacutainers. Sample was allowed to clot and separated to obtain serum by centrifugation at room temperature.
- Specimens were stored frozen at −20°C till analysis. A commercially available kit was used for assessment of 25-OH vitamin D (total) by enzyme-linked immunosorbent assay.
- Lastly; Vitamin d deficiency will be defined as serum 25 -OH vitamin D less than 20 ng/mL; vitamin D insufficiency (VDI) will be defined as serum 25 -OH vitamin D between 20 and 30 ng/mL; and vitamin D sufficiency was defined as 25 -OH vitamin D greater than 30 ng/ml. **(Al-Zuhairy et al., 2022)**.

All children were classified after IDA is established into: iron-deficient anaemia with normal Vitamin D level and iron-deficient anaemia with insufficient or deficient Vitamin D level.

Statistical Analysis:

SPSS (Statistical Package for the Social Sciences) version 20 was used to tabulate and statistically analyses the obtained data. For numerical parametric data, descriptive statistics were performed using the mean, SD (standard deviation), minimum and maximum of the range; for numerical non-parametric data, they were performed using the median and first and third interquartile ranges; and for categorical data, they were performed using the number and percentage, when there were two independent groups and parametric data for quantitative variables **(Starbuck., 2023)**. Linear regression analysis was used to determine the obtained data. The statistical significance level was set at 5%. (P0.05). If p0.001 was found, there was a huge difference **(Schneider., 2010)**.

RESULTS

Table (1): Relation of 25 (OH) Vitamin D status with subgroup according to demographic data

		25 (OH)VIT D (ng/ml)			Test value	P-value	Sig.
		Deficiency	Insufficiency	Sufficiency			
		No. = 29	No. = 14	No. = 7			
Age (Ys)	Mean ± SD	5.19 ± 0.61	5.06 ± 0.62	4.46 ± 0.48	4.263•	0.020	S
	Range	4 – 6	4 – 6	3.9 – 5			
Sex	Male	16 (55.2%)	7 (50.0%)	5 (71.4%)	0.889*	0.641	NS
	Female	13 (44.8%)	7 (50.0%)	2 (28.6%)			

This table shows that there was a significant correlation between Age and the 25 (OH) Vitamin D status ($p < 0.05$).

Table (2): Relation of 25 (OH) Vitamin D status with anthropometric measurements

Weight (kg)	Mean ± SD	17.50 ± 1.36	17.21 ± 1.53	15.86 ± 0.69	4.200	0.021	S
	Range	14 – 20	15 – 20	15 – 17			
Height (cm)	Mean ± SD	104.17 ± 2.30	103.79 ± 2.55	101.57 ± 3.26	3.038	0.057	NS
	Range	98 – 108	99 – 108	95 – 105			
BMI (kg/m^2)	Mean ± SD	17.33 ± 1.28	17.06 ± 1.46	15.80 ± 0.65	4.086	0.023	S

This table shows that there was a significant correlation between, weight and BMI regarding the 25 (OH) Vitamin D status ($p < 0.05$).

Table (3): 25 (OH) Vitamin D of the studied patients

25 (OH)VIT D (ng/ml)	No. = 50
Deficiency	29 (58.0%)
Insufficiency	14 (28.0%)
Sufficiency	7 (14.0%)

This table shows that mean of 25(OH) VIT D was 21.27 ± 9.86, 58% had deficiency and 28% had Insufficiency **(Figure 1)**.

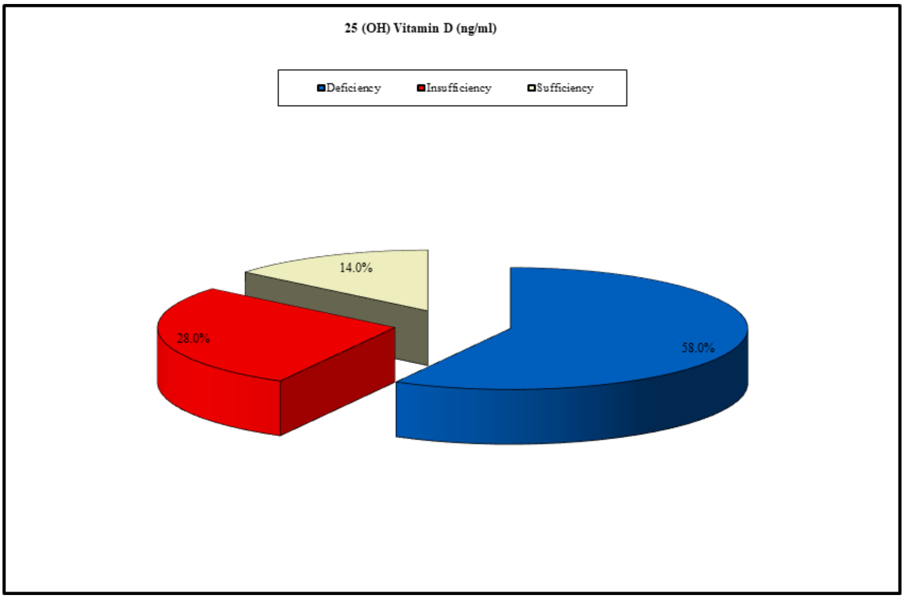

Figure (1): Incidence of 25 (OH) Vitamin D status of the studied patients

The mean of 25(OH) VIT D was 21.27 ± 9.86, 58% had deficiency and 28% had Insufficiency.

Relation of 25 (OH) Vitamin D status with BMI:

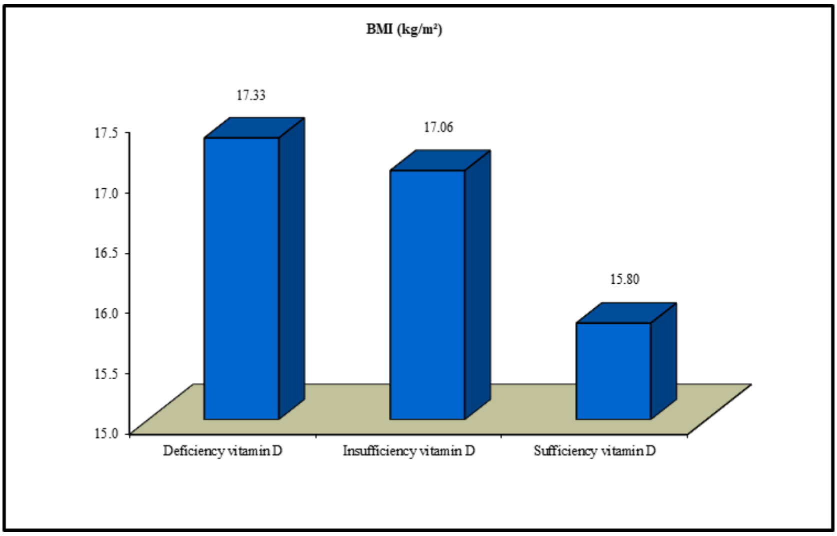

Figure (2): Relation of 25 (OH) Vitamin D status with BMI

This figure shows that there was deficiency of vitamin D with higher BMI and sufficient vitamin D with lower BMI.

Table (4): Relation of 25 (OH) Vitamin D with Haematological finding (RBCs indices)

		25 (OH)VIT D (ng/ml)			Test value	P-value	Sig.
		Deficiency	Insufficiency	Sufficiency			
		No. = 29	No. = 14	No. = 7			
PCV	Mean ± SD	33.95 ± 3.19	36.14 ± 2.71	39.00 ± 0.00	9.818	0.002	HS
	Range	24.5 – 38	28 – 38	39 – 39			
MCV	Mean ± SD	66.11 ± 2.28	65.56 ± 2.51	69.03 ± 0.56	6.232	0.004	HS
	Range	60 – 69.7	61 – 69	68 – 69.8			

This table shows that there was a highly significant correlation between PCV and MCV. (P-value< 0.01) regarding the 25 (OH) Vitamin D status.

Table (5): Relation of 25 (OH) Vitamin D with Iron Profile

		25 (OH)VIT D (ng/ml)			Test value	P-value	Sig.
		Deficiency No. = 29	Insufficiency No. = 14	Sufficiency No. = 7			
Ferritin (ng/ml)	Mean ± SD	8.76 ± 1.55	9.36 ± 1.45	11.00 ± 0.00	7.109	0.002	HS
	Range	5 – 11	7 – 11	11 – 11			
Iron (µg/dl)	Mean ± SD	34.21 ± 8.21	38.43 ± 6.31	44.71 ± 2.75	6.426	0.003	HS
	Range	18 – 45	25 – 45	39 – 48			
TIBC (µg/dl)	Mean ± SD	494.90 ± 23.72	492.07 ± 15.44	461.71 ± 14.71	7.394	0.002	HS
	Range	455 – 533	469 – 511	452 – 494			

This table shows that there was a highly significant correlation between Ferritin, Iron and TIBC (P-value< 0.01) regarding the 25 (OH) Vitamin D status.

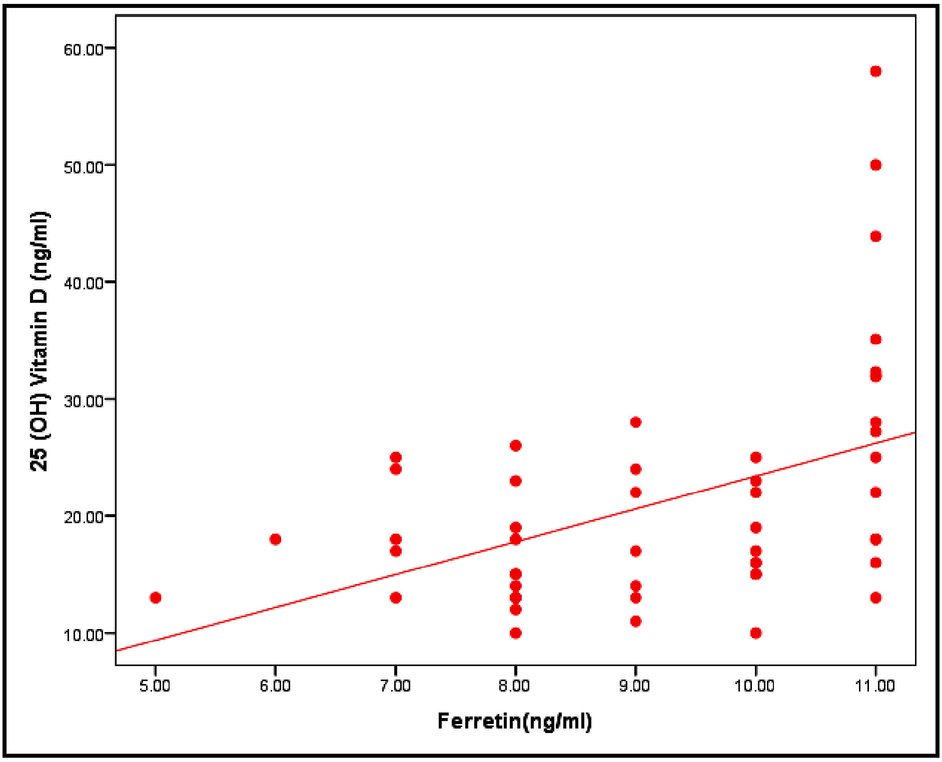

Figure (3): Correlation of 25 (OH) Vitamin D with ferretin.

Table (6): Correlation of 25 (OH) Vitamin D with age, anthropometric measurement and laboratory finding

	25 (OH) Vitamin D (ng/ml)	
	R	**P-value**
Age (Years)	-0.347*	0.014
Weight(kg)	-0.422**	0.002
Height(cm)	-0.315*	0.026
BMI (kg/m²)	-0.403**	0.004
WBCs	0.349*	0.013
Platelets	-0.398**	0.004
RBCs (milions/cmm)	-0.139	0.336
Hg(g/dl)	0.055	0.704
PCV	0.469**	0.001
MCV	0.319*	0.024
Ferretin(ng/ml)	0.452**	0.001
Iron(µg/dl)	0.521**	0.000
TIBC (µg/dl)	-0.535**	0.000

There was a statistically significant positive correlation found between PCV, MCV, Ferritin and Iron markers regarding serum vitamin D level (P-value < 0.05) and significant negative correlation between age, BMI, Platelets and TIBC with serum vitamin D level (P-value >0.05).

DISCUSSION

Vitamin D (Vit D) is well known to be important for bone health, although its mechanism of action, direct or indirect, is still a matter of debate; its effects on bone tissue and bone cells have not yet been completely clarified **(Christakos et al., 2020)**. Low levels of Vit. D also result in osteopenia or osteoporosis attributed to an increased osteoclast bone resorption. These effects depend mostly on the direct actions of 1.25 (OH) Vit. D3 **(De Martinis et al., 2021)**.

Bone metabolism is the primary function of vitamin D. As a result of vitamin D deficiency (VDD) in children, which typically develops between the ages of 3 and 18 months, rickets may develop **(Goltzman., 2018)**, Osteomalacia in adolescents and adults, as well as inhibition of immunological responses in autoimmune illnesses and cancer suppression, may be caused by it **(Minisola et al., 2011)**.

Vitamin D from diet or dermal synthesis is biologically inactive and requires enzymatic conversion to active metabolites. Vitamin D is converted to 25- hydroxyvitamin D [25(OH) D], the major circulating form of vitamin D, and then to 1,25- dihydroxyvitamin D, the active form of vitamin D, by enzymes in the liver and kidney. 1,25- hydroxyvitamin D binds to the intracellular vitamin D receptor to activate vitamin D response elements within target genes. The half-life of 1,25-dihydroxyvitamin D is 4-6h, compared with 2–3 weeks for 25(OH) D and 24 h for parent vitamin **(El-Adawy et al., 2019)**.

Iron-deficiency anemia (IDA) is a global public health problem, affecting 1.62 billion people, IDA is found to be the most common cause of anemia among Egyptian children of low socioeconomic standard, affecting 43% of them. Iron plays an important role in children's growth and development, such as brain development, cognitive function, motor function, behavior, and immunity **(Nur-Eke & Özen., 2020)**.

Iron deficiency and vitamin D deficiency (VDD) are the two most common deficiencies in young children worldwide. Health programs aimed to achieve adequate iron and vitamin D intake at an early age should be conducted to prevent deficiencies **(Prono et al., 2022)**.

Iron deficiency anemia (IDA) and vitamin D deficiency (VDD) have been observed simultaneously in infancy and young children. The relationship between these two deficiencies is unclear due to their linked metabolisms, and it is not easy to assess which of these nutrients has the most substantial effect on the other but appears to be reciprocal. Iron participates in the second hydroxylation step of vitamin D activation. The conversion is done by renal 25-hydroxyvitamin D 1α-hydroxylase enzyme, containing a cytochrome P-450 (CYP2R1 and CYP27B1 respectively), a ferredoxin, and a ferredoxin reductase. Consequently, less available iron could affect the production of the active form of vitamin D **(Saneifard et al., 2021)**.

A high degree of association between Iron deficiency anaemia and vitamin D deficiency in children has been reported, with Iron deficiency anaemia found to be a significant risk factor for low vitamin D levels in children. Vitamin D insufficiency has been linked to iron deficiency anaemia. Vitamin D insufficiency and anaemia have been linked in Korean children and adolescents.

Healthy female children and adolescents who are deficient in vitamin D are more likely to suffer from anaemia, particularly iron deficiency anaemia **(Ramagopalan et al., 2019)**.

Several mechanisms for such an association have been proposed. Vitamin D may influence Hb through a direct effect on erythropoiesis where it has a synergistic action with erythropoietin; it also increases the storage and retention of Fe and reduces pro-inflammatory cytokines **(Krajewska et al., 2022)**.

Data in our study aimed to evaluate Vitamin D status among iron deficiency anemia at preschool children. In this study we found that the mean age of studied cases was (5.05 ± 0.64), 56% were males and 44% were females **Table (1)**.

Shaheen et al., 2021 found that more than half of the children in his studied group were males (52.8%), with 50.6% of the studied children in the age group less than or equal to 6 years.

In our study we demonstrated that the mean of 25(OH) VIT D was (21.27 ± 9.86), 58% had deficiency and 28% had Insufficiency. **Table (3)**, **Figure (1)**.

This result is in agreement with studies carried out in Korea and Egypt by **Roh et al., 2016** and **El-Desouky et al., 2020**. respectively, who reported vitamin D deficiency among 59.1 and 56.7% of children, respectively.

Al-Zuhairy et al., 2022 found that the 25(OH)D levels were estimated in all subjects, and vitamin D deficiency was observed in (48.4% (92) of subjects, VDI was seen in (24.2% (46) children, while (27.4% (52)) children had normal vitamin D levels.

Shaheen et al., 2021 found that 54.4% of the children in his studied group had vitamin D deficiency, 36.7% had vitamin D insufficiency and only 8.9% had sufficient serum vitamin D levels.

Various biological and environmental factors affect the cutaneous photosynthesis of vitamin D3, including ageing, degree of skin pigmentation, occlusive clothing, duration of exposure to sunlight, and the use of topical sunscreens, cloud cover, air pollution, and season of year **(Tremezaygues., 2006)**.

In our study we found that there was negative correlation between the 25 (OH) Vitamin D status and Age (p <0.001) **Table (2)**.

In agreement with a Korean study carried out by **Baek et al., 2011** which showed a negative correlation between the age of the child and vitamin D levels by linear regression. With age, vitamin D levels decreased.

Another study carried out in Saudi Arabia by **Sultan et al., 2018** who showed an inverse relationship between vitamin D levels and bodyweight, that is increased body weight will be risk of vitamin D deficiency.

Gilbert et al., 2010 found that children with low 25(OH)D levels had a 0.1kg/m2 greater increase in BMI annually there is a consistent association in the puplished literature between increasing BMI and lower serum 25(OH)D levels **(Vanlint., 2013)**.

In our study we demonstrated that there was negative correlation between the 25 (OH) Vitamin D status and Platelet count (p=0.043) Table (5).

In agreement with **Park et al., 2017** who found that platelet count and mean platelet volume are inversly associated with Vitamin D level.

LeBlanc et al., 2012 found that subjects with lower 25(OH)D levels have higher platelet numbers, indicating that a vitamin D deficiency in obese subjects may be predictive of a higher risk of inflammation, thrombosis and cardiovascular events in this condition.

Iron deficiency Anemia perse can increase platelet count due to active bone marrow, **Kadikoylu et al., 2006** suggested that decrease iron saturation might stimulate megakaryopoieses.

These results are in line with previous findings by **Park et al., 2017** that showed an inverse association between 25(OH)D levels and platelet indices.

In our study we found that there was a significant positive correlation between PCV and MCV regarding the 25 (OH) Vitamin D status (p=0.001) **Table (4)**.

Menazie et al., 2020 found that there was a statistically significant decrease in the level of hemoglobin, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) in deficient and VDI cases than sufficient cases.

In our study we cleared that there was a significant positive correlation between Ferritin and Iron regarding the 25 (OH) Vitamin D status (p=0.001) **Table (5)**.

In agreement with a study conducted by **Jin et al., 2013** in children under 24 months of age, the mean vitamin D level was (32.7±24.3ng/ml) in healthy children and (18.1±11.4ng/ml) in children with iron deficiency anemia. Vitamin D levels were found to be insufficient in 20% of children with iron deficiency anemia.

Qader et al., 2016 demonstrated that the mean value of vitamin D was significantly lower in patient group (21.3ng/dl) in comparison to control group (37.0ng/dl), P=0.001 and the mean value of vitamin D was significantly lower in subjects who had hemoglobin (Hb) level of <11gm/dl in comparison to those with Hb of ≥11gm/dl (p <0.001).

In our study we found that there was a significant negative correlation between age, weight, Height, BMI, Platelets and TIBC regarding 25 (OH) Vitamin D **Table (6)**.

Shaheen et al., 2021 found that there was a significant negative correlation of normal weight of children with vitamin D levels.

In agreement with a Korean study carried out by **Baek et al., 2011** which showed a negative correlation between the age of the child and vitamin D levels by linear regression. With age, vitamin D levels decreased.

This result is in line with other Egyptian studies carried out by **Shebl et al., 2013** and **Abu Shady et al., 2016** which showed that the concentration of vitamin D had a significantly negative correlation with BMI.

In our study we demonstrated that there was a significant Positive correlation between PCV, MCV, Ferritin and Iron regarding 25 (OH) Vitamin D **Table (6)**.

Kartal and Gürsel., 2019 found a positive correlation between serum vitamin D level and hemogram and iron parameters similar to these findings.

Al-Zuhairy et al., 2022 found that there was a significant positive correlation (r=0.542, p=0.000) between serum ferritin and 25(OH) D.

Qader et al., 2016 demonstrated that there was a significant direct correlation between serum iron, and vitaminD level (r=0.5, P=0.001), same significant direct correlation was reported with Hemoglobin level (r=0.4, P=0.001).

Menazie et al., 2020 found that there was a statistically significant positive correlation found between vitamin D level and hemoglobin, MCV, MCH, and serum iron levels.

CONCLUSION

Our findings suggest a complex association between vitamin D and iron status in preschool children, Low vitamin D status (25(OH)D <50 nmol/L 20ng/mL (50nmol/L); was associated with iron deficiency anemia. The positive association between vitamin D and iron deficiency in our study suggest that both conditions should be considered in relevant public health strategies where the two nutrient deficiencies coexist. There is a need for further studies to understand the mechanisms of action of the associations between vitamin D and iron deficiency.

RECOMMENDATION

Vitamin D levels should be evaluated in anemic children, and they should be provided with adequate supplementation to prevent deficiencies of both nutrients.

Adequate vitamin D and iron intake should be initiated at an early age to prevent deficiency.

LIMITATIONS

There are several limitations that need to be taken. First, the sample size (Epi Info STATCALC was used to calculate the sample size) was small, as it may not be sufficiently representative to detect deficiency or to allow values lower than the average to be discriminated. Second, there was the various methods of assessment for VDD and anemia used among studies. However, the results did not significantly change.

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