Journal of Pediatric Academy

Original Article

Year: 2023 Volume: 4 Issue: 1
Doi: 10.4274/jpea.2023.202
J Pediatr Acad 2023; 4: 33-38

# Is There a Relationship Between Vitamin D Level and Iron Deficiency Anemia in Children?

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*Article Information*

**Article Type:** Original Articles
**Article Group:** Pediatric Rheumatology

**Received:** 28.11.2022
**Accepted:** 13.03.2023
**Available Online:** 31.03.2023

***Cite this article as:*** *Özdemir Kaçer E, Kılıçaslan C. Is There a Relationship Between Vitamin D Level and Iron Deficiency Anemia in Children?. J Pediatr Acad 2023; 4: 33-38*

## Abstract

Iron deficiency anemia (IDA) is the most common type of anemia in children and a major cause of morbidity and mortality. Vitamin D deficiency (VDD) is a growing public health issue that has been connected to several chronic diseases, such as osteoporosis, cancer, and metabolic syndrome. Recently, in a meta-analytic study conducted on both children and adults, it was clearly shown that there is a relationship between VDD and the risk of anemia. In this study, we wanted to review the prevalence of vitamin D insufficiency in children with IDA. We conducted a retrospective review of patient records from January 2017 to December 2019 to identify individuals aged 4 months to 18 years who had been diagnosed with IDA. Demographic data, dietary patterns, nutritional supplements, Vitamin D levels, and laboratory tests were recorded. Two hundred thirty girls and 198 boys were enrolled in the study, bringing the total number of patients to 428. The patients had a mean age of 7.24±5.1 months. The distribution of female gender according to vitamin D groups (normal, insufficient, deficient) was 85, 103, and 42, respectively; the male gender is 78, 89, and 31, respectively (p=0.745). No statistically significant difference was found between nutrition categories and vitamin D groups in different age groups (p=0.293; p=0.238; p=0.396). No statistically significant difference was found between continuous quantitative variables such as age, hemoglobin, and ferritin and vitamin D groups in different age groups (p=0.885; p=0.168; p=0.728). There was no significant association observed between the severity of anemia and VDD in children with IDA in our study. In the diagnosis of IDA, it may be useful to look at vitamin D levels by considering the time of admission. Further studies are needed for the association between vitamin D levels and IDA.

**Keywords:** Dietary pattern, Iron deficiency anemia, Pediatrics, Vitamin D deficiency

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## Introduction

Iron deficiency anemia (IDA) is the most common type of anemia in children and a major cause of morbidity and mortality.[1] Since feeding infants only with breast milk is a risk factor for IDA, iron supplementation is necessary. Anemia can be caused by various factors, such as insufficient iron intake, chronic disease, chronic blood loss, hemolysis, malabsorption or a combination of these.[2] In a study, infants who received iron supplements had higher developmental and psychomotor scores at 13 months compared to those who did not receive iron supplements.[3]

**Highlights**

- Iron deficiency anemia and vitamin D deficiency are common in childhood.
- Vitamin D measurement, which is not a routine test, should be performed in IDA patients.
- Vitamin D supplementation should be started rapidly in children with vitamin D deficiency.

Vitamin D deficiency (VDD) is a growing public health issue that has been connected to several chronic diseases, such as osteoporosis, cancer, and metabolic syndrome.[4] New information on the biological functions of vitamin D has sparked interest in the clinical consequences of VDD.[5] In a study conducted in the USA, approximately 70% of children and adolescents were found to have 25-hydroxy vitamin D [25 OH)D] deficiency.[6] Several studies have been conducted on the role of vitamin D in erythropoiesis, and it has been shown that vitamin D affects bone marrow functions[5]. Additionally, studies have shown that 1, 25(OH)D levels are several hundred times higher in the bone marrow compared to plasma.[7]

Recently, in a meta-analytic study conducted on both children and adults, it was clearly shown that there is a relationship between VDD and the risk of anemia.[8] This relationship highlighted the erythropoietic function of calcitriol, given the effects of iron on metabolism and the immune system. However, VDD has also been reported in children, adolescents, and adults with IDA, but a causal relationship hypothesis could not be established.[9,10] We think that VDD may be effective in iron metabolism and IDA.

In this study, we wanted to review the prevalence of IDA in children with VDD and we wanted to review the correlation between the severity of VDD and IDA.

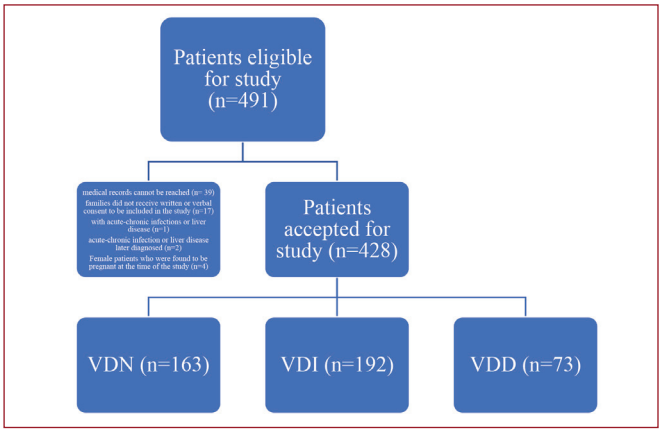
## Material and Method

### Research Strategy

This retrospective descriptive study was conducted in the pediatric department of a tertiary hospital in Aksaray, Turkey. Our study adhered to the guidelines set forth in the Declaration of Helsinki and was granted approval by the Aksaray University School of Medicine, Aksaray Education and Research Hospital Scientific Research Evaluation Committee, with decision number 2020/06-38. (Decision no: 2020/06-38. Date: 22/06/2020). We conducted a retrospective review of patient records from January 2017 to December 2019 to identify individuals aged 4 months to 18 years who had been diagnosed with IDA. Four hundred ninety one patients were eligible for study. Sixty three patients were excluded from study. Distribution of patients included and excluded from the study shown in Flowchart. Four hundred and twenty eight patients were identified and their data were recorded. Demographic data (age, gender, etc.), dietary patterns (breast milk, cow's milk, formula use, etc.), and nutritional supplements were collected from the database. Patients whose data were missing from the hospital records and who were contacted by telephone and whose data were completed were included in the study. Anemia treatment or dietary supplement given was recorded. Based on their age, the patients were categorized into three groups: 4 months to 6 years, 7 years to 12 years, and 13 years to 18 years. According to their dietary habits, the patients were grouped into three categories for the study. Patients aged 4 months to 6 years were divided into 3 groups breast-fed, formula-fed, and cow-goat milk and supplementary foods. The first group of patients aged 7-12 and 13-18 years is those who regularly eat meat, salmon, sardines, egg yolk, shrimp, yogurt, cereals, milk, and orange juice, the second group is those who are fed fast food and ready-made food, and the third group is meat and protein-poor diets or vegetarians.[11] The patients were divided into 3 groups according to their vitamin D levels; those with IDA and normal vitamin D (VDN), those with IDA and vitamin D insufficiency (VDI), and those with IDA and VDD. Fast food and ready-made food nutrition were defined as the consumption of ready, frozen, or packaged food outside the home at least 3 days a week for 1 or more meals and between meals.[12] A vegetarian diet was accepted as one that does not include meat (including fowl), seafood, or products containing those foods.[13] A protein-poor diet was accepted as 0.6-0.8 g/kg/day or less protein intake.[14]

### Inclusion and Exclusion Criteria

- IDA criteria in children;[15]
- Hemoglobin (Hb) level <11 g/dL,
- Serum ferritin level (both men and women) <12 ng/mL,
- Mean corpuscular volüme <70 fL,
- Increased red blood cell distribution width,
- Transferrin saturation <15%.




**Flowcart.** Distribution of patients included and excluded from the study

*VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency*

Serum ferritin, which is a biomarker of iron stores in the body, is also an acute-phase reactant that can increase in response to inflammatory conditions such as infection, chronic inflammation, or liver disease. For this reason, children who were healthy and had no findings at the end of the examination were included in the study.

There is currently no consensus on how to measure and define VDD in children.[16] In our study, a serum 25(OH) D level of less than 20 ng/mL was defined as VDD; a serum 25(OH)D level of 20 to 30 ng/mL was defined as VDI.[6,17] Serum 25(OH)D levels were measured with a radioimmunoassay kit from DiaSorin (Stillwater, MN, USA).

Inclusion criteria;

- Patients who meet criteria for IDA,
- Patients whose medical records can be accessed,
- Patients whose families received verbal consent to be included in the study,
- Patients without acute-chronic infections or liver disease,
- Patients aged 4 months-18 years.

Exclusion criteria;

- Patients who do not meet the criteria for IDA,
- Patients whose medical records cannot be reached,
- Patients whose families did not receive verbal consent to be included in the study,
- Patients with acute-chronic infections or liver disease.

Criteria for exclusion during or after study;

- Patients with acute-chronic infection or liver disease later diagnosed,
- Female patients under the age of 18 who were found to be pregnant at the time of the study.

### Statistical Analysis

The statistical analysis was conducted using Statistical Package for the Social Sciences version 20.0 (IBM, Armonk, NY, USA). To determine whether the variables were normally distributed, both visual methods such as histograms and probability plots, and analytical methods such as the Kolmogorov-Smirnov test, skewness, and kurtosis were used. Continuous data were reported as median (minimum-maximum) and mean ± standard deviation, while categorical variables were reported as frequencies and percentages. The chi-square or Fisher's exact test was used to compare categorical variables, while the Kruskal-Wallis and/or ANOVA tests were used to compare continuous variables for more than two independent groups.

## Results

A total of 428 patients, 230 (53.7%) girls, and 198 (46.3%) boys were included in the study. The distribution of female gender according to vitamin D groups (VDN, VDI, VDD) was 85, 103, and 42, respectively; the male gender is 78, 89, and 31, respectively (p=0.745). The mean age of all patients was 7.24±5.1 months. The mean age in patients with IDA was 7.26±5.14; in patients with VDI was 7.31±4.94, and in patients with VDD was 7.31± 4 (p=0.885).

Of 428 patients, 192 (44.8%) had VDI and 73 (17%) had VDD. Of 214 children aged 4 months to 6 years, 93 (43.46) had VDI and 37 (17.29%) had VDD. Of 132 children aged 7-12 years, 65 (49.24) had VDI and 22 (16.6%) had VDD. Of 82 children aged 13-18 years, 34 (41.46%) had VDD and 14 (17.07) had VDD (p=0.779). The chi-square test was utilized to explore the associations between variables, such as gender and age groups, and vitamin D levels. Upon examining the obtained p values, no significant difference was observed between these groups concerning the variables listed in the table. **Table 1** presents the distribution of vitamin D groups based on gender and age groups.

The examination of age groups in terms of vitamin D groups according to nutrition categories was carried out with the Mantel-Haenszel chi-square test, and no difference was observed in terms of distribution between nutrition categories and vitamin D groups in different age groups (p=0.293; p=0.238; p=0.396). Therefore, there is no conditional independence between groups (p=0.367). The distribution of vitamin D groups according to their feeding patterns shown in **Table 2**.

VDI was present in 78 (50.32%) and VDD in 25 (16.13%) of 155 patients who applied during the summer season. VDI was present in 53 (40.77) and 25 (19.23) 130 patients admitted during the winter season. Of the 77 patients admitted in the spring, 34 (44.16%) had VDI and 18 (23.38%) had VDD. Of 66 patients admitted in the autumn season, 28 (42.42%) had VDI and 5 (7.58%) had VDD. The chi-square test was utilized to examine the association between vitamin D groups and seasonal admission numbers, and after analyzing the obtained p values, no significant difference was found between these groups regarding the variables presented in the table (p=0.069). Vitamin D groups and seasonal admission numbers are shown in **Table 3**.

The mean values of hemoglobin and ferritin levels were calculated according to age groups. Continuous quantitative variables such as age, hemoglobin, and ferritin were compared between vitamin D groups and no significant difference was found (p values; 0.885;

**Table 1.**
*Comparison of the children with IDA in terms of age and gender according to the vitamin D levels*

| | | VDN (%) | VDI (%) | VDD (%) | p value |
|---|---|---|---|---|---|
| Age group | <4 months-6 years | 84 (39.25) | 93 (43.46) | 37 (17.29) | 0.779 |
| | 7-12 years | 45 (34.09) | 65 (49.24) | 22 (16.67) | |
| | 13-18 years | 34 (41.46) | 34 (41.46) | 22 (17.07) | |
| Gender | Female | 85 (36.96) | 103 (44.78) | 42 (18.26) | 0.745 |
| | Male | 78 (39.39) | 89 (44.95) | 31 (15.66) | |

IDA; Iron deficiency anemia, VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency

0.168; 0.728, respectively). The comparison of vitamin D groups in terms of age, hemoglobin, and ferritin is shown in **Table 4** and **Figure a, b, c**.

## Discussion

Our study is the first to compare our region's IDA and VDD. Of 428 patients diagnosed with IDA, 45% had VDI and 17% had VDD. Vitamin D was not sufficient in 62% of children diagnosed with IDA.

In our study, serum Hb and ferritin concentrations do not differ according to seasons and age groups, but when we look at the age groups, the number of patients with IDA between the ages of 4 months and 6 years was higher in our study. Although we expect to see more VDD in the lower age group due to reasons such as rapid growth, decreased vitamin D stores, increased vitamin D requirement and insufficient sun exposure, the prevalence of vitamin D in anemic children in our study does not statistically differ according to age.

The American Academy of Pediatrics recommended that 400 IU of vitamin D daily be given to all infants regardless of whether they are given formula or not since breast milk contains low vitamin D.[18] Our study, consistent with the literature, found that the prevalence of vitamin D in children with IDA did not differ according to their diet. According to the results of the study, daily vitamin D supplementation can prevent more than 60% of vitamin D deficiency.

Yoon et al.[9] demonstrated that VDD has a high prevalence in children with IDA. However, there are also studies showing no association with the prevalence of vitamin D in children with iron deficiency anemia.[19] In our study, no correlation was found regarding the prevalence of vitamin D in children with iron deficiency. Further studies are needed for the association between VDD and anemia.

Our study observed that most admissions in children with IDA and low vitamin D levels were in winter and summer. Previous studies have shown that serum 25(OH)D levels are significantly lower in spring and winter than in autumn and summer.[20] Although it was not statistically significant in our study, we think that the seasonal effect is important in VDD accompanying IDA. One of the important points that should not be ignored is that anemic children are generally sluggish and tired. This may cause children to go out less and be exposed to sunlight, which may predispose them to VDD.[21]

Although our study did not find a significant relationship between the severity of anemia and low serum 25(OH) D levels, previous research has suggested a role for vitamin D in erythropoiesis.[22] Another study found that people with VDD have a higher prevalence and risk of

**Table 2.**
*The distribution of the children with IDA, VDI, and VDD according to their feeding patterns*

| Age group | Diet | IDA | VDI | VDD | p1 | p2 |
|---|---|---|---|---|---|---|
| <4 months-6 years | Breast-fed | 53 (63.1) | 64 (68.8) | 25 (67.6) | 0.293 | 0.367 |
| | Fed with cow's milk or supplementary foods | 20 (23.8) | 16 (17.2) | 11 (29.7) | | |
| | Formula-fed | 11 (13.1) | 13 (14.0) | 1 (2.7) | | |
| 7-12 years | *Regular nutrition | 19 (42.2) | 36 (55.4) | 10 (45.5) | 0.238 | |
| | Fast food nutrition | 13 (28.9) | 22 (33.8) | 8 (36.4) | | |
| | Protein-poor or vegetarian diet | 13 (28.9) | 7 (10.8) | 4 (18.2) | | |
| 13-18 years | *Regular nutrition | 26 (76.5) | 22 (64.7) | 8 (57.1) | 0.396 | |
| | Fast food nutrition | 4 (11.8) | 6 (17.6) | 5 (25.7) | | |
| | Protein-poor or vegetarian diet | 4 (11.8) | 6 (17.6) | 1 (7.1) | | |

*Meat, salmon, sardines, egg yolks, shrimp, yogurt, cereals, milk, orange juice
IDA; Iron deficiency anemia, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency

**Table 3.**
*Vitamin D groups and seasonal admission numbers*

| Season | VDN | | VDI | | VDD | | p value |
|---|---|---|---|---|---|---|---|
| Summer | 52 | 33.55% | 78 | 50.32% | 25 | 16.13% | 0.069 |
| Winter | 53 | 40.77% | 52 | 40% | 25 | 19.23% | |
| Spring | 25 | 32.47% | 34 | 44.16% | 18 | 23.38% | |
| Autumn | 33 | 50% | 28 | 42.42% | 5 | 7.58% | |

VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency

**Table 4.**
*The comparison of VDN, VDI, and VDD groups in terms of age, hemoglobin, and ferritin*

| | VDN | | VDI | | VDD | | p value |
|---|---|---|---|---|---|---|---|
| Age | 7.26±5.14 | 6 (1-19) | 7.31±4,.94 | 7 (1-19) | 7.03±5.04 | 6 (1-19) | 0.885* |
| Hb | 9.57±0.85 | 9.8 (7.8-10.9) | 9.4±0.87 | 9.3 (7.8-10.9) | 9.45±0.96 | 9.3 (7.8-10.9) | 0.168 |
| Ferritin | 8.52±2.05 | 8.8 (5-11.5) | 8.67±2.15 | 8.95 (4-11.9) | 8.56±2.03 | 9 (5.2-11.8) | 0.721 |

VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency, Hb; Hemoglobin
Results as descriptive statistics mean±standard deviation and median (min.-max.)
*Shows One-Way ANOVA result, all others are Kruskal-Wallis test values

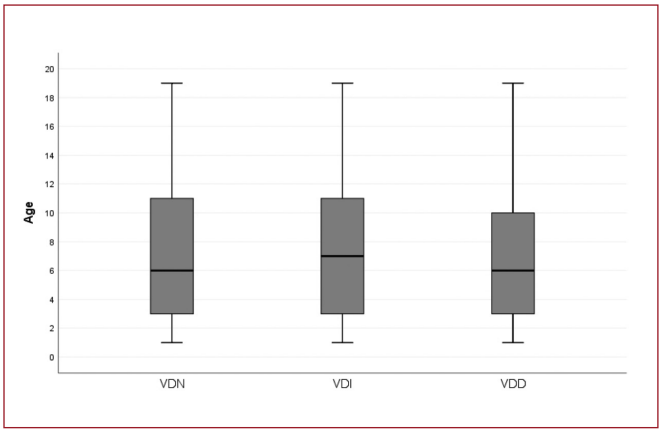



**Figure a.** Vitamin D groups and age

*VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency*

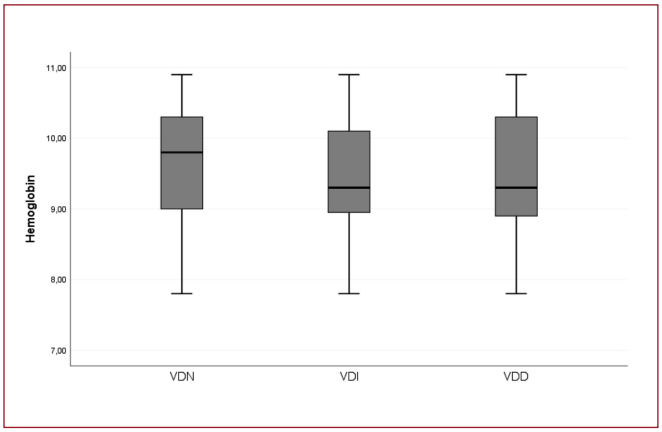



**Figure b.** Vitamin D groups and hemoglobin

*VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency*

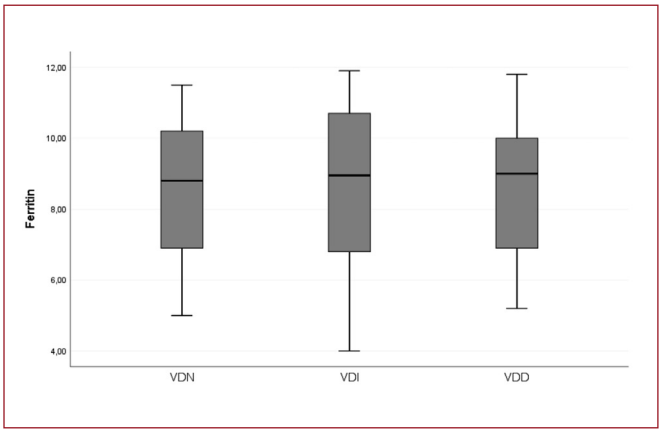



**Figure c.** Vitamin D groups and ferritin

*VDN; Normal vitamin D, VDI; Vitamin D insufficiency, VDD; Vitamin D deficiency*

anemia compared to those with VDN levels.[22] There are studies showing that VDD in children is associated with lifestyle factors such as obesity and decreased nutrition.[23] In our study, no significant correlation was found between anemia and vitamin D. More research is needed on the relationship between vitamin D and anemia in healthy children.

Kaymak Cihan and Ünver Korğalı[24] demonsrated that the longer exclusively breastfeeding is independent risk factor for IDA in children. Li et al.[25] found that infant formula intake is were protective factors for VDD and VDI. The results of our study did not demonstrate a significant relationship between feeding patterns and vitamin D levels. This may be due to regional differences and sufficient homogeneity between patient groups.

### Study Limitations

Our study had some limitations. The study population was limited as the patients consisted of children with a diagnosis of IDA and no other complaints. Additionally, we did not examine a control group of healthy children. Therefore, our results regarding the prevalence of vitamin D and IDA cannot be generalized to other populations.

## Conclusion

In conclusion, no correlation was found between the severity of anemia and VDD in children with IDA in our study. In the diagnosis of IDA, it may be useful to look at vitamin D levels by considering the time of admission. Further studies are needed for the association between vitamin D levels and IDA.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version. Özdemir Kaçer E: Designed study, collected and analyzed data, wrote and revised article, Kılıçaslan C: Analyzed and collected data, wrote article.

**Conflict of Interest:** There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients. Verbal consent from was obtained from patients and their parents.

**Ethics Committee Approval:** The study was conducted in compliance with the Declaration of Helsinki and approved by Aksaray University School of Medicine, Aksaray Education and Research Hospital Scientific Research Evaluation Committee with (Decision no: 2020/06-38. Date: 22/06/2020).

**Financial Disclosure:** The authors declared that this study received no financial support.

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