



## The effect of iron on vitamin D level in children with combined iron and vitamin D deficiency

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### Abstract

**Introduction:** Iron deficiency (ID) and vitamin D deficiency (VDD) are two common nutritional problems. Recently, an association between these two disorders has been suggested that remains to be definitely confirmed.

**Objectives:** Our aim was to compare treatment with iron, vitamin D, and their combination on serum levels of vitamin D in children with ID and vitamin D insufficiency (VDI).

**Patients and Methods:** A total of 90 patients with low levels of ferritin and vitamin D were assigned to three groups of 30 each: treatment with iron for ID, treatment with vitamin D, and co-treatment with vitamin D and iron. Levels of vitamin D and ferritin were measured before and 3 months after treatment. Data analysis was entirely conducted by paired t-test, one-way ANOVA using SPSS 19.

**Results:** Serum vitamin D levels significantly changed 3 months after treatment in the vitamin D and iron+ vitamin D groups ( $P < 0.01$ ), but not in the iron group ( $P = 0.68$ ). Comparison of mean changes in serum vitamin D levels was not significantly different between the iron+ vitamin D and vitamin D groups ( $P = 0.774$ ).

**Conclusion:** Iron supplementation alone could not significantly increase vitamin D levels in studied children. Vitamin D supplementation and vitamin D+ iron supplementation caused similar effects on serum vitamin D levels, and management of ID did not have any incremental effect on vitamin D levels in children. It is necessary to use vitamin D supplementation to control and treat VDD.

**Keywords:** Vitamin D insufficiency, Iron deficiency, Vitamin D deficiency.

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### Introduction

Iron deficiency (ID) and vitamin D deficiency (VDD) are two of the leading nutritional disorders worldwide (1,2) that cause a spectrum of health-related problems in children, with potential long-lasting effects even in the patients that do not present with any symptom (3). Approximately 30%–50% of the people at any ages suffer from VDD globally (4).

Vitamin D and iron are important nutrients that are necessary for growth and development in childhood (5) but are frequently disregarded. In young children, ID and VDD can cause impaired neurodevelopment and rickets, respectively. Risk factors for ID and VDD are various in different populations (6).

One billion people worldwide have VDD and vitamin D insufficiency (VDI) (7).

Health programs aimed at helping to achieve adequate iron and vitamin D intake at an early age should be conducted

to prevent deficiencies (6). In Europe, the prevalence of ID in young children has been reported to be 0%–85% (8) and that of VDD between 0% and 64% (9).

Vitamin D is a prohormone starting to synthesize in the skin and is then converted from inactive to active metabolite through liver and kidney. It is a necessary nutrient for bone mineralization and its deficiency can cause rickets in childhood and osteomalacia in adulthood (10).

VDD has been reported to be associated with increased risk of many chronic diseases such as cancer, autoimmune diseases, cardiovascular disease, and infectious diseases including acquired immune deficiency syndrome (HIV/AIDS) and tuberculosis (11).

In addition, evidence reported by animal and human studies shows the role of vitamin D in iron metabolism and erythropoiesis (5,12). Erythroid precursors are directly stimulated by vitamin D, which suggests the great

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### ■ Implication for health policy/practice/research/medical education

In a study on 90 cases, we found vitamin D supplementation and vitamin D+ iron supplementation caused similar effects on serum vitamin D levels, and management of iron deficiency did not have any incremental effect on vitamin D levels in children. It is necessary to use vitamin D supplementation to control and treat vitamin D deficiency.

contribution of vitamin D to erythropoiesis (13).

ID and ID anemia (IDA) is highly prevalent in children, adolescents, and women in industrial and non-industrial countries (14). It is likely that VDD is associated with different anemia such as IDA, anemia due to chronic kidney disease, and inflammation-associated anemia (15). ID not only decreases physical activity but also increases the risk of infection (16).

Recently, an association between these two deficiencies has been suggested that remains to be definitely confirmed (2,5). Iron-deficient children are more likely to develop VDD (17).

Serum 25-hydroxyvitamin D level is considered to be an index of vitamin D status in the body and represents the synthesized vitamin D in the skin and the absorbed dietary vitamin D (18).

In IDA, depletion of tissue iron stores and decrease in serum ferritin levels occur. In the absence of inflammatory diseases, serum ferritin levels represent serum iron stores in the body. Ferritin blood test is probably the most useful laboratory test to measure iron levels and is directly a fraction of iron stores (19). However, ferritin, as an acute-phase protein, increases independent of iron levels in acute and chronic inflammations (5).

It has been reported that Asian children with decreased serum levels of vitamin D have comparatively lower hemoglobin and serum iron levels (19). A study with 9400 children aged 2 to 8 years at Johns Hopkins University, reported that children with vitamin D levels below 20 ng/mL were at 50% higher risk of anemia, and the risk of anemia decreased by 3% per 1ng/mL increase in vitamin D levels. This study showed an association between VDD and anemia (20).

In Iran, a study by Rouyani et al at Golestan University of Medical Sciences reported that 75% of the people with ID suffered from VDD, while in the control group, 45% had VDD (21).

### Objectives

Given the prevalence of VDD and ID in developing countries including Iran (due to economic and cultural issues and inadequate and inappropriate diet) as well as its importance for children's growth and development, conducting additional studies on diagnosis and early treatment of these deficiencies, are important.

Additionally, an unconfirmed association between these ID and VDD has recently been reported and treatment

with iron has been suggested to be effective on vitamin D levels. Thus, it is essential to investigate the potential association between these two variables.

We were therefore sought to conduct a comparative study treatment with iron, vitamin D, and their combination on serum levels of vitamin D in children with ID and VDI. The results of our study may determine whether ID treatment can improve vitamin D levels. Inconsistent with previous studies, the current study was conducted with 3 groups, treated with iron, treated with vitamin D, and treated with the combination of iron+ vitamin D. Participants suffered from both ID and VDD.

### Materials and Methods

#### Study design

In this cross-sectional study was conducted in 2015. Around 90 children aged 2 to 12 years with low ferritin and vitamin D levels hospitalized in the pediatric ward of Hajar hospital, Shahrekord. Subjects selected by convenience sampling. While during this study, one of the groups did not receive vitamin D, thus only the people with VDI were enrolled to observe ethical considerations and those with VDD were excluded. In addition, ferritin is an acute-phase reactant and increases in certain diseases, then the individuals with severe infectious diseases, malignancy, thalassemia, liver disease, chronic disease, and hyperthyroidism who may have high ferritin levels were also excluded from the study.

Accordingly patients with impaired vitamin D metabolism were also excluded from the study.

#### Laboratory tests

Ferritin levels were measured by chemiluminescence immunoassay (Monobind kit) and serum vitamin D levels (25-hydroxyvitamin D) by enzyme-linked immunosorbent assay (ELISA) using DS kit. Then, patients were assigned to 3 groups of 30 for each. Treatment with standard iron for ID (group 1), treatment with vitamin D (group 2), and co-treatment with vitamin D and iron (group 3).

To assure appropriate consumption of iron in sufficient amounts, patients were followed up for 3 months. In the iron-treated group, patients' vitamin D levels were examined thus they were excluded from the study if they developed VDD. At completion of 3 months follow-up, the serum levels of ferritin and vitamin D were measured. ID was defined as serum ferritin level of <12 ng/mL for patients aged ≤ 5 years old and < 15 ng/mL for those aged >5 years old (22). VDD was defined as 25(OH) D level < 20 ng/mL, VDI as 25(OH) D of 21 to 29ng/mL, and vitamin D sufficiency (VDS) as 25(OH) D ≥ 30 ng/mL (23,24).

#### Ethical issues

The research followed the tenets of the Declaration of Helsinki. After the study protocol was approved by the Ethics Committee of Shahrekord University of Medical Sciences (# IR.SKUMS.REC.1394.174), the participants

or their parents provided informed consent to participate in the study. All participants were informed about the objectives of the study and assured that the information will remain confidential.

### Statistical analysis

Data analysis was conducted by paired *t* test, one-way ANOVA, and descriptive statistics in SPSS 19. A *P* value of <0.05 was considered significant.

### Results

In this study, 90 cases with decreased vitamin D and iron levels participated. Table 1 shows the demographic data of the participants.

The average vitamin D level in vitamin D group was  $24.66 \pm 2.57$  ng/mL and  $49.2 \pm 17.43$  ng/mL before and after treatment, respectively ( $P=0.01$ ). In the vitamin D+ iron treated group, the serum vitamin D levels before and after treatment were significantly different ( $P=0.04$ ). However, in the iron-treated group, the mean changes in vitamin D levels before and after treatment were not significantly different ( $P=0.68$ ; Table 2).

The mean changes in serum vitamin D levels after treatment were compared among the 3 groups (Table 3). The mean difference in vitamin D levels after treatment with iron was statistically significant compared to the other groups. Vitamin D levels improved more markedly in the iron+ vitamin D-treated group than the iron-treated group. Similar findings on the comparison of the average changes in the vitamin D-treated group and the iron-treated group were obtained that indicated the greater effect of vitamin D in increasing serum vitamin D levels than that of iron. The comparison of average changes in serum vitamin D levels after treatment in vitamin D+ iron treated group with those in the vitamin D-treated group did not show any statistically significant difference ( $P=0.744$ ).

### Discussion

VDD is one of the serious nutritional disorders in the communities. Given the role of this vitamin in different organs, it is essential to suggest modalities to improve VDD. Our study on children suffering from both ID and VDD, showed that vitamin D supplementation, but not iron supplementation, was effective in increasing serum vitamin D levels. This indicates that improving ID with iron supplementation cannot improve low levels of vitamin D. The prevalence of simultaneous ID and VDD has

been observed in different populations and it is therefore possible that these two deficiencies are associated. It has been argued that iron can be a predictor of decrease in vitamin D levels (3,17).

A study showed that 92% of Spanish women aged 18–35 years with ID suffered from VDD or VDI (1). In populations of 102 infants aged 3–24 months (3), 160 children aged 1–5 years (17) and 79 cases aged 4 month–13 years (25), VDD was more prevalent in the IDA/ID groups. In a study with a population of children aged 3 months to 12 years in northern India, 66% of the children with anemia and 35% of healthy children, were found to have VDD (5). In a study in Korea, 58% of the children aged four months to 11 years with IDA had low vitamin D levels. They showed around 39% of their study population had VDD. However, children with VDD and VDI did not have comparatively lower serum levels of hemoglobin, ferritin, and iron than those with normal serum vitamin D levels. They could not detect an association between IDA and the severity of VDD (25). However, that study was conducted on the people with IDA and no comparison with controls was made. In the other studies in Korea, VDD was associated with increased risk of IDA especially in women (22,26).

In most studies, decreased vitamin D level was found to be independently associated with decreased serum hemoglobin level and subsequently increased risk of IDA (27,28). In a study in the groups receiving vitamin D3, changes in the serum ferritin, hemoglobin, and iron levels and transferrin saturation were not significantly different compared to the placebo group. Lack of such differences in that study was attributed to most participants having adequate levels of iron with only 1% of them with anemia (2). A study showed that vitamin D could improve iron status if consumed with iron (16). However, the aim of the present study was not to investigate the effect of vitamin D on iron levels but instead the effect of iron on vitamin

**Table 2.** Mean changes in vitamin D levels before and after treatment in groups

Groups	Vitamin D (ng/mL)		P value
	Before treatment	After treatment	
Iron	25.56±2.26	35.8±11.07	0.68
Vitamin D	24.66±2.75	49.2±17.43	0.01*
Iron+ vitamin D	25.5±2.5	51.24±18.60	0.04*

\*Significant.

**Table 1.** Frequency distribution of participants by age, gender, and place of residence in groups

Groups	Number	Gender		Age (y)	Place of residence	
		Male No. (%)	Female No. (%)		Rural No. (%)	Urban No. (%)
Iron	30	18(60%)	12 (40%)	5.05±2.8	14(46.7)	16(53.3)
Vitamin D	30	16(53.3%)	14 (46.7%)	5.95±2.81	11(36.7%)	19(63.3%)
Iron+ vitamin D	30	14(46.7%)	16(53.3%)	5.06±2.53	12(40%)	18(60%)

**Table 3.** Mean difference in vitamin D levels after treatment in groups

	Comparison to groups	Mean difference	P value
Iron	Vitamin D	-6.25	0.011*
	Iron+ vitamin D	-7.69	0.001*
Vitamin D	Iron	6.25	0.011
	Iron+ vitamin D	-1.44	0.774
Iron+ vitamin D	Iron	7.69	0.001
	Vitamin D	1.44	0.774

\*Significant.

D levels.

It has been argued that vitamin D influences iron metabolism and erythropoiesis through influencing inflammatory pathways and hepcidin (12). Heparin is known as a regulator of iron absorption, tissue distribution, and extracellular concentration that causes decrease in the plasma concentration and bioavailability of iron through inhibiting ferroportin and exerts an inhibitory effect on erythropoiesis. This pro-inflammatory mediator prevents iron from exiting macrophages.

It has been reported that vitamin D treatment is associated with decreased hepcidin expression *in vitro* and *in vivo*, and therefore is a potential regulator of iron and has been considered a new potential approach to manage anemia in the patients with low vitamin D levels (13,29). A study reported that VDD was not a risk factor for IDA (30), while decreased vitamin D levels were not observed to be significantly associated with serum ferritin and hemoglobin levels (1).

In Saudi children aged 6.14 years, VDD was not associated with IDA (10), which is consistent with the current study conducted in Iran. It is worth mentioning that vitamin D status in European, Middle-East, and Asian countries is completely different, which could be attributed to difference in diet, air pollution, and limited exposure to the sunlight (31,32). In a study on 105 patients aged one to 18 years, the prevalence of anemia, VDI, serum iron and ferritin levels, and transferrin saturation were not significantly different among VDI, VDD, and healthy groups (12).

In 263 children aged 3 months to 12 years in North India, no difference was observed in mean levels of ferritin among VDD, VDI, and normal groups (5).

A systematic review reported that the relationship between iron and vitamin D. However trials do not confirm any benefit of iron supplementation in VDD management (33).

A pilot study with pregnant women aged 20 to 45 years suffering from both VDD and IDA, showed that administration of iron and vitamin D did not affect the increase of hemoglobin levels significantly than administration of iron alone (34).

Consistently, in our study, co-treatment of vitamin D and iron, compared to vitamin D treatment alone, did not cause better impact to improve VDD. Therefore, not only iron alone did not suffice to improve VDD but

also iron+ vitamin D supplementation did not lead to any incremental effect in improving patients' conditions. Some studies showed that iron supplementation alone did not cause any significant change in serum vitamin D levels (1,35).

Sooragonda et al also reported that vitamin D supplementation in the people with IDA after iron improvement did not cause any significant increase in hemoglobin and ferritin concentrations compared to the control group (36).

Inconsistent with our study, a study showed that iron supplements caused an increase in serum iron and vitamin D levels in infants. They concluded that the increase in serum vitamin D levels could be due to the role of iron supplement in converting 25(OH)D to 1,25(OH)<sub>2</sub>D (active form of vitamin D) and also the role of iron in intestinal absorption of vitamin D (37). However, their study was conducted in infants aged 6 to 24 months, while our study contained the children aged 2 to 12 years.

Factors influencing vitamin D status and anemia including measurement method, malnutrition, age, low socioeconomic status, drugs, infections, and race should be taken into consideration to explain an association between vitamin D and anemia (28,38,39).

### Conclusion

Although vitamin D and blood ferritin levels have been reported to be associated, iron supplementation alone did not have a significant effect in increasing vitamin D levels in the children in this study. In addition, adding iron to vitamin D supplementation also did not cause any incremental effect in improving vitamin D levels in children. It is necessary for the people with both ID and VDD to undergo separate, rather than combined, therapies for ID and VDD.

### Limitation of the study

This investigation was conducted on a limited proportion of children. Thus larger studies on this feature of patients are necessary.

### Authors' contribution

NR, SMKN and MB designed the project. NR collected the data. NN and NR analyzed the data. NR and NN wrote the manuscript. MB and SMKN edited the final draft. All authors read and signed the final manuscript.

### Conflicts of interest

None.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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