

Effects of Iron on Vitamin D Metabolism: A Systematic Review

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ABSTRACT

Vitamin D is a prohormone nutrient, which is involved in skeletal and extra-skeletal functions. Iron is another essential nutrient that is necessary for the production of red blood cells and oxygen transport. This element plays important roles in enzymatic systems including those required for Vitamin D activation. To the best of our knowledge, there is no exclusive review on the relationship between iron deficiency anemia (IDA), as the most prevalent type of anemia, and Vitamin D deficiency and the effect of recovery from iron deficiency on Vitamin D status. The aim of this study was to conduct a systematic search of observational and clinical trials in this field. The databases of PubMed, ProQuest, Cochrane Library, ISI Web of Knowledge, and SCOPUS were searched comprehensively. English-language human studies conducted on iron deficient patients or interventions on the effect of iron therapy on Vitamin D were extracted ($n = 10$). Our initial search yielded 938 articles. A total of 23 papers met the inclusion criteria. Thirteen studies were excluded because they were not relevant or not defining anemia types. The final analysis was performed on ten articles (3 cross-sectional and 7 interventional studies). Observational data indicated a positive relationship between iron status and Vitamin D, while trials did not support the effectiveness of iron supplementation on improving Vitamin D status. The mechanism underlying this association may involve the reduction of the activation of hydroxylases that yield calcitriol. Future randomized controlled trials with large sample sizes and proper designs are needed to highlight underlying mechanisms.

Keywords: Anemia, iron, iron-deficiency anemia, Vitamin D, Vitamin D deficiency

INTRODUCTION

Deficiencies in both Vitamin D and iron are recognized as two major public health concerns in the globe. Nearly

30%–50% of all age groups are Vitamin D deficient worldwide.^[1] Sun exposure is the most important source of Vitamin D for most people. The effect of sun exposure on Vitamin D synthesis depends on skin pigmentation, body size, and aging.^[2] Photosynthesized Vitamin D is transported to the liver by the Vitamin D binding protein to pass the first hydroxylation. The second

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hydroxylation in kidneys converts it to its biologically active form, 1,25-hydroxy Vitamin D ($1,25(\text{OH})_2\text{D}$). Serum phosphorus, calcium, and fibroblast growth factor (FGF-23) are the key regulators of the renal production of $1,25(\text{OH})_2\text{D}$.^[3] Although the most popular role of Vitamin D in the body is bone health, it has a wide range of functions. Vitamin D deficiency (VDD) is related to infant mortality, cardiovascular diseases, cancer, total mortality, diabetes, mood disorders, and increased risk of infections like tuberculosis and AIDS.^[4,5] When the concentration of $25(\text{OH})\text{D}_3$ is <20 ng/ml (50 nmol/L), VDD exists. A level of ≥ 30 ng/ml (≥ 75 nmol/L) is considered normal. Vitamin D insufficiency has been defined as $25(\text{OH})\text{D}$ between 21 and 29 ng/ml.^[6]

It has estimated that 2–3 billion individuals suffer from anemia worldwide.^[7] IDA is the most prevalent type of anemia. Data from US NHANES 1976–1980, have been used to estimate iron deficiency based on the prevalence of anemia in countries with a high prevalence of anemia and iron deficiency. Accordingly, when anemia is prevalent in 20% of population, iron deficiency prevalence will be 50%, and when it is $>40\%$, some degree of iron deficiency exists in whole population.^[8,9] IDA is associated with maternal mortality, prenatal infant loss, and prematurity, immune status and morbidity from infection, physical capacity and work performance, cognitive performance, and behavior.

Anemia and VDD have been observed simultaneously.^[10] Some recent studies blame IDA for VDD because of their linked metabolism.^[11-13] The results of studies in this area are inconsistent due to heterogeneity in study objectives and lack of determining the etiology of anemia. There are also several trials evaluating the effect of iron intake on Vitamin D concentration as their primary or secondary outcomes,^[14-20] but there is no exclusive review on the effect of iron deficiency or its replenishment on Vitamin D status.

To increase our understanding of this association, synthesize of the research, and generate new insights into coexistence of micronutrient deficiencies, we conducted a systematic review of the published literature investigating the development of VDD due to iron deficiency.

METHODS

Identification of studies

The PRISMA statement was used for reporting the present systematic review.^[21] Articles indexed in PubMed, ProQuest, ISI Web of Science, Cochrane Library, and SCOPUS were searched using the following MeSH terms: Anemia, iron-deficiency anemia, $25(\text{OH})\text{D}$, and VDD. We looked for these terms in the abstract, title, or keywords. No limits were used. In addition, articles referenced by those identified in this search were reviewed for relevance.

The search results were imported to endnote to find duplicates. Titles and abstracts were examined by two independent reviewers. Inclusion criteria were (1) the articles written in the English, (2) observational studies were conducted on iron deficient patients or interventions demonstrating the effect of iron therapy on Vitamin D (i.e., those observational studies on anemia without specifying its type and review articles were not included), and (3) human studies. Only papers met the inclusion criteria were reviewed [Figure 1]. Because of the limited number of eligible studies, we did not define a strict age range.

Observational studies included in this review were scored by the Strengthening the Reporting of Observational Studies in Epidemiology: Explanation and Elaboration (STROBE) criteria^[22] and trials were scored according to the Black and Downs' checklist.^[23] The STROBE checklist items relate to design, setting, participants, confounders, bias, sample size, statistical analysis, outcome measures, results, limitations, and generalizability of the study. The scoring system is as follows: 0 (not done), 1 (done partially), and 2 (done well). Score range for this tool is between 0 (lowest) to 40 (highest quality). Downs's checklist is composed of 27 items for evaluating the risk of bias, based on the adjustment of the confounders, adverse events of the intervention, patient loss, blindness, interventions compliance, and randomization. Score range is between 0 and 31 for the Black and Downs.

For each study met eligibility criteria, the first authors' name, publication year, study location, number and age of volunteers, intervention (for trials), the most relevant results, and quality score were abstracted [Tables 1 and 2].

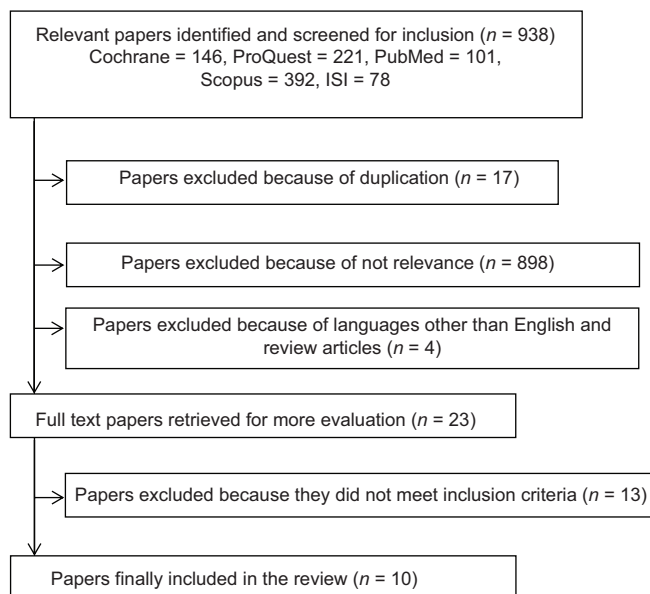


Figure 1: Flowchart describing the process of the review

Table 1: Cross-sectional studies investigating the relationship between iron deficiency anemia and Vitamin D deficiency

Authors	Year	Country	Number	Age	Findings	STROBE score
Jin <i>et al.</i> ^[11]	2013	Korea	102	3-24 months	OR of VDD in IDA patients was higher iron was a significant predictor of Vitamin D level	20
Kang <i>et al.</i> ^[12]	2015	Korea	70	4-24 months	25(OH)D was significantly lower in infants of mothers with IDA during pregnancy	21
Yoo and Cho ^[13]	2015	Korea	200	19-91 years	OR of VDD was higher in anemic patients, but not different among anemia subtypes	15

IDA=Iron deficiency anemia, VDD=Vitamin D deficiency, STROBE=Strengthening the Reporting of Observational Studies in Epidemiology, OR=Odds ratio, 25(OH)D=25-hydroxy Vitamin D

Table 2: Interventional studies investigating the effect of iron supplementation on Vitamin D concentration

Authors	Year	Country	Number of participants	Age	Intervention	Findings	Black and Down's score
Heldenberg <i>et al.</i> ^[15]	1992	Israel	17	6-24 months	Intramuscular single injection of iron dextran based on Dallmar formula	Treatment increased the serum concentrations of 25(OH)D and 24,25(OH) ₂ D	14
Prats <i>et al.</i> ^[17]	2013	Spain	47	≥ 18 years	A single 1000 mg intravenous injection of ferric carboxymaltose	1,25(OH) ₂ D level did not change	15
Wolf <i>et al.</i> ^[19]	2013	USA	200	≥ 18 years	A single 1000 mg intravenous injection of ferric carboxymaltose in comparison to iron dextran	No treatment effect was seen on 25(OH)D level in any of groups	22
Wright <i>et al.</i> ^[20]	2013	Spain	73	18-40 years	Daily intake of a 80 mg iron tablet if Hb >10 g/dL or two tablets (160 mg Fe) if Hb ≤ 10 g/dL	No significant change was observed in 25(OH)D level	23
Blanco-Rojo <i>et al.</i> ^[14]	2013	Spain	41	18-35 years	A placebo fruit juice (P) or iron-fortified fruit juice (F) containing 18 Fe	Serum 25(OH)D significantly decreased from baseline to the end of the study in both groups, without any differences between groups	24
Toxqui <i>et al.</i> ^[18]	2014	Spain	109	18-35 years	An iron (Fe) or iron and Vitamin D-fortified (Fe+D) flavored skimmed milk (iron: 15 mg/day; Vitamin D ₃ : 200 IU/day)	Serum 25(OH)D significantly increased in the Fe+D group and did not change in Fe group	25
Iguchi <i>et al.</i> ^[16]	2015	Japan	27	≥ 20 years	Intravenous single injection of ferric oxide saccharide	No significant change was observed in 1,25(OH) ₂ D concentration	15

25(OH)D=25-hydroxy Vitamin D, Hb=Hemoglobin

RESULTS

Our initial search yielded 938 articles. After duplicates were removed ($n = 17$), 898 articles were excluded because of not relevance and finally 23 articles identified for further assessment. One article that was published in language other than English and three reviews were also excluded. We also excluded studies in which iron status was not defined separately ($n = 7$). One trial did not describe the effect of the intervention on Vitamin D specifically. Finally, 3 observational studies and 7 trials were included.

Study characteristics

Of these 10 articles, 90% of them were published in recent years,^[11-20] between 2013 and 2015. All cross-sectional studies were conducted in Korea.^[11-13] Over half of the trials were conducted in Spain;^[14,17,18,20] one in

the United States;^[19] one in Japan;^[16] and one in Israel.^[15] We divided studies into two groups to specify the results (1) observational studies [Table 1] and (2) interventional studies that evaluated the effect of iron supplementation on Vitamin D status [Table 2]. We also described the relationship between iron and Vitamin D in the second category, whenever it was mentioned.

Observational studies

Table 1 shows the characteristics of cross-sectional studies evaluating the relationship between iron and Vitamin D. All three included articles^[11-13] revealed that 25(OH)D was lower in anemic cases. Kang *et al.*^[12] showed that 25(OH)D level was significantly lower in infants of mothers with medical history of anemia during pregnancy ($P = 0.011$). Although VDD had an odds ratio (OR) of 4.74 for the presence of iron deficiency, it was nonsignificant. Similarly, Jin *et al.*^[11] demonstrated that VDD was significantly

more common in anemic children (OR = 4.115, 95% confidence interval [CI] = 1.665–10.171). Serum iron was an important predictor of 25(OH)D ($P = 0.005$). The most impressive limitations of these studies were small sample size and selection bias. Yoo and Cho^[13] showed that VDD was significantly more seen in anemic individuals (OR = 3.316, 95% CI = 2.265–4.854). This study was also limited by small sample size, seasonal variation, and coexisting of other health problems in participants. The results of these studies were represented after adjustment for age, gender, estimated glomerular filtration rate, and transferrin saturation. The risk of bias in all studies was related to insufficient description of study design, potential source of bias, and generalizability of the results.

Interventional studies

Study design and baseline participant characteristics are presented in Table 2. Quality scores for these studies ranged from 14 to 25 for the Down. Vitamin D was not the main outcome in 3 studies.^[16,17,19] Four of the studies investigated other metabolites of Vitamin D.^[15-17,19] Only two studies were parallel-group double-blind randomized clinical trials.^[18,20] A total of 411 individuals were recruited, with 371 participants remaining at the end of study. Over 50% of trials enrolled premenopausal women,^[14,18-20] two enrolled elderlies,^[16,17] and one enrolling 6–24 months infants.^[15] Type, dosage and duration of supplementation varied. Four trials used single dosage of intravenous or intramuscular iron^[15-17,19] and a follow-up of 5–12 weeks. Two studies used fortified products for 16 weeks.^[18,20] One trial reported daily intake of ferrous sulfate tablets which the dose and duration were related to recovery from IDA.^[14]

Pure iron supplementation did not significantly affect the serum concentration of any of the Vitamin D metabolites in most interventions.^[16,17,19,20] Heldenberg *et al.* observed significant increases in both 25(OH)D and 24,25-dihydroxy Vitamin D levels in a group of infants with IDA and VDD.^[15] Although children took Vitamin D as a routine treatment, they were Vitamin D deficient and showed positive results after iron injection. In a group of iron-deficient women consuming a placebo fruit juice (P) or iron-fortified fruit juice (F), 25(OH)D decreased in both groups ($P < 0.001$).^[14] Toxqui *et al.* provided an iron (Fe group) or iron and Vitamin D-fortified (Fe plus D group) skimmed milk for iron-deficient women.^[18] After 16 weeks, 25(OH)D significantly increased in the Fe⁺ D group ($P < 0.001$) without any change in the Fe group. Quality assessment using Down's checklist indicated missing data about confounders, blinding, and randomization.

The relationship between iron and Vitamin D was assessed in three studies.^[14,15,20] A significant positive correlation was found between serum iron and baseline Vitamin D

concentration, hematocrit, transferrin saturation in two studies.^[14,20] In one study, infants with low 25(OH)D and low 24,25(OH)₂D had lower hemoglobin (Hb) and transferrin saturation.^[15]

DISCUSSION

In the present review, a possible association was demonstrated between iron and Vitamin D levels. Our results indicated that iron supplementation has no statistically significant effect on the improvement of VDD. Future trials should be conducted to elucidate different dimensions of this relationship.

All observational studies reported positive correlation between iron and Vitamin D in spite of some differences in adjusted cofounders, VDD and ID cut off points, age ranges, and health status of populations. This was also confirmed in two interventional studies. There are potential cofounders influencing the relationship between iron and Vitamin D including body mass index (BMI), age, dietary calcium and fat intake, ethnicity, some diseases and medications, inflammation, oxidative stress, and altitude which should be considered in future research. The most important ones are BMI and inflammation. Vitamin D is a fat soluble nutrient which is stored in body fat; so the amount of fat tissue can affect its concentration.^[24] Iron marker, ferritin, is an acute-phase protein that increases in inflammatory conditions and this can result in IDA underestimation.^[25] It is worth noting that unfortunately IDA detection was not defined accurately and number of iron deficient patients was very small in comparison with total sample size. Increased age leads to a decreased Vitamin D concentration.^[26] Premenopausal women are at increased risk of anemia because of menstruation, but menopausal females progress anemia because of inflammation and nutritional deficiencies.^[27] The final problem is cross-sectional nature of studies. Comparison of iron deficient patients with healthy controls can shed light on the mentioned relationship. However, the number of interventional studies is not efficient enough to make an accurate judgment.

Epidemiological data have shown that bone health is related to 25(OH)D status. Desirable range of 25(OH)D for fracture prevention is more than 75 nmol/L. It has been postulated that chronic iron deficiency increases bone resorption.^[28] One of the proposed mechanisms is Vitamin D deactivation.

When iron depletion takes place in tissues, the activity of iron containing enzymes decrease.^[29] As mentioned before, Vitamin D is activated in the body by two sequential steps. In the first step, 25(OH)D₃ is produced in the liver. A kind of cytochrome P450, CYP2R1, is responsible for this stage. The second hydroxylation happens in kidneys

and some other tissues by the virtue of CYP27B1 to form 1,25(OH)₂D₃. CYP2R1 requires NADPH-cytochrome P450 reductase to function properly. CYP27B1 needs two other compounds: Ferredoxin reductase and ferredoxin.^[30] Both of these enzymes contain heme group. Hence, it seems that Vitamin D metabolism is dependent on iron and its deficiency might disturb Vitamin D activation.

There are some evidences demonstrating an opposite association. On the other hand, VDD may results in anemia. A number of mechanisms have been suggested to explain this finding: (a) VDD contributes to decreasing local calcitriol production in bone marrow and increases membrane permeability of calcium. As a result, erythropoiesis declines. *In vitro* studies have shown that this happens at mRNA and protein levels;^[31,32] (b) hyperparathyroidism due to VDD raises proliferation of erythroid progenitor cells;^[33] and (c) VDD is associated with higher hepcidin level in the body. This pro-inflammatory mediator is involved in anemia of chronic disease.^[34] Previous studies have reported beneficial effects of supplementation with Vitamin D on the reduction of erythropoiesis stimulating agents requirements in patients with chronic kidney disease and increased Hb concentrations.^[35,36] In a 16-week randomized controlled trial, Toxqui *et al.* tested the effectiveness of iron versus iron and Vitamin D-fortified milk on improving iron status in 109 iron-deficient women.^[37] The group consuming Fe⁺ D, had higher levels of erythrocytes, hematocrit, and Hb at week 8 compared to the Fe group. However, most of these studies did not focus on a specific type of anemia in a healthy population. Further clinical trials are needed to explore the direction of the Vitamin D and iron association.

Almost all reviewed studies showed that iron supplementation had no effect on 25(OH)D level. However, most of these studies were inadequately powered regarding design (e.g., lack of blinding, randomization, and control group). Mostly, Vitamin D status is assessed by measuring 25(OH)D using ultraviolet detection after its separation by normal phase high-performance liquid chromatography.^[38] None of the studies used this method; this might be involved in the lack of discovering any beneficial effect of supplementation. It may also be due to the level of iron depletion and its renewal. There are several stages for iron deficiency: (a) Latent iron deficiency; (b) iron deficient erythropoiesis; (c) IDA; and (d) functional iron deficiency.^[39] In the third stage, Hb level decreases but mean corpuscular volume and mean corpuscular hemoglobin do not fall until the deficiency becomes chronic. It has shown that iron-containing enzymes including cytochromes are affected in this phase. Maybe lack of the effect of iron supplementation is caused by inadequate levels of iron deficiency to influence 25-hydroxylase. Just three interventions had recruited participants with IDA,^[15,17,20]

but only one of those showed positive results.^[15] Increased Vitamin D concentration was also observed in the other two studies, although it was not significant.

To the best of our knowledge, this is the first systematic review to address IDA and VDD relationship. This review is strengthened by the inclusion of both cross-sectional studies and trials. However, this review is also limited by the small number of studies, with many of the included trials not originally designed for the primary outcomes intended for this review. The primary objective of some of these trials was to investigate the effect of iron on FGF-23.^[16,17,19] Different types of outcome measures reported, Vitamin D dosages, duration of supplementation, and participants are the other factors producing heterogeneity. Several studies were conducted in Korean population with low generalization of the results and papers included were from very diverse age-strata. To further elucidate the role of iron supplementation on Vitamin D, future randomized controlled trials should focus on improving the quality of the study design.

CONCLUSIONS

This systematic review pointed out that the majority of the studies confirmed the existence of a relationship between iron and Vitamin D; but present data do not support a beneficial effect of iron supplementation in the management of VDD. Further studies with large sample sizes and proper designs are needed to highlight underlying cellular, molecular, and genetic mechanisms and to generate good quality evidence.

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Conflicts of interest

There are no conflicts of interest.

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