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Vitamin D and Anemia: Insights into an Emerging Association

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Abstract

Purpose of review—This review highlights recent findings in the emerging association between vitamin D and anemia through discussion of mechanistic studies, epidemiologic studies, and clinical trials.

Recent findings—Vitamin D has previously been found to be associated with anemia in various healthy and diseased populations. Recent studies indicate that the association may differ between race and ethnic groups and is likely specific to anemia of inflammation. The mechanism underlying this association involves the reduction of pro-inflammatory cytokines by vitamin D as well as the direct suppression of hepcidin mRNA transcription. There is also evidence that vitamin D may be protective against anemia by supporting erythropoiesis. Other calciotropic hormones, fibroblast growth factor 23 (FGF-23) and parathyroid hormone (PTH) have also been found to be involved in iron homeostasis and erythropoiesis.

Summary—Recent advances in our understanding the association between vitamin D and anemia suggest that maintenance of sufficient vitamin D status may be important in preventing anemia, particularly in diseases characterized by inflammation. Early clinical trials have been promising, but further research is needed to define the efficacy of vitamin D as a future approach for the treatment of anemia.

Keywords

vitamin D; anemia; hepcidin; inflammation

Introduction

As the role of vitamin D in health continues to be defined, particularly in terms of extra-skeletal functions, an association between vitamin D and anemia has emerged in recent

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Conflicts of interest

None

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years, indicating potential roles for vitamin D in iron homeostasis and erythropoiesis. This association has been described in several observational studies in various healthy and diseased populations [1–7], and recent *in vitro* studies suggest that the mechanism underlying this association involves the action of vitamin D on inflammatory cytokines and the antimicrobial peptide, hepcidin (the hormone responsible for regulating systemic iron concentrations) [8**, 9**, 10*].

Anemia is a common nutritional problem in public health, and may further complicate chronic diseases including kidney and heart disease, resulting in fatigue, shortness of breath, and decreased physical capacity, and if severe enough, cardiovascular morbidity and mortality. Several factors may contribute to anemia including nutrient deficiencies, namely iron, but also folate, vitamins B₁₂ and B₆, as well as blood loss, infection, hemoglobinopathies, and inflammation. Given the multifactorial etiology of anemia, it can be classified into different subtypes such as iron deficiency anemia or anemia of nutrient deficiency, and anemia of inflammation (also called anemia of chronic disease). Vitamin D, through its down-regulatory effects on inflammatory cytokines and hepcidin may favorably impact anemia, particularly anemia of inflammation. This review will highlight recent advances in our understanding of the vitamin D-anemia association through mechanistic studies, epidemiologic studies, and early clinical trials.

Mechanism of action in the vitamin D – anemia association

Studies have suggested that vitamin D, by down-regulating pro-inflammatory cytokines and hepcidin, may increase iron availability, and there is also evidence that vitamin D may support erythropoiesis (Fig. 1). Through these potential mechanisms of action, vitamin D may therefore improve anemia, in particular, anemia of inflammation [11**].

Inflammation and hepcidin

Vitamin D has well-described anti-inflammatory functions [12], and has recently been shown to act directly on the antimicrobial peptide hepcidin, which is responsible for the regulation of systemic iron concentrations. Hepcidin, which prevents further iron absorption and iron release from cells during times of iron sufficiency by binding to and inducing the degradation of the cellular iron exporter, ferroportin, is also up-regulated by pro-inflammatory cytokines, interleukin-6 (IL-6) and interleukin-1 β (IL-1 β) [13,14]. This is a protective mechanism during times of acute infection to reduce bioavailable iron necessary for growth of invading microorganisms, in which iron absorption through enterocytes is decreased and iron release from macrophages in the process of iron recycling is diminished [15]. However, in chronic diseases which may carry a prolonged inflammatory stimulus, iron is pathologically sequestered within cells of the reticuloendothelial system and despite adequate iron stores, anemia may result due to impairments in iron recycling yielding insufficient iron available for erythropoiesis and hemoglobin synthesis [16].

Findings by Zughaier *et al.* support the proposed anti-inflammatory mechanism of action of vitamin D on the hepcidin-ferroportin axis, demonstrating a dose-dependent decrease in release of IL-6 and IL-1 β from a cultured human monocyte cell line in the presence of increasing concentrations of hormonally active 1,25-dihydroxyvitamin D (1,25(OH)₂D),

along with suppressed hepcidin mRNA expression and increased ferroportin mRNA expression [10*]. Bacchetta *et al.* extended these findings, showing that treatment of human monocytes and hepatocytes with 25-hydroxyvitamin D (25(OH)D) or 1,25(OH)₂D resulted in significantly decreased expression of mRNA for the hepcidin antimicrobial peptide gene (HAMP) [9**]. Vitamin D response elements (VDREs) in the promoter region of the HAMP gene were subsequently identified, providing a strong mechanistic basis for the direct action of vitamin D on hepcidin. In healthy volunteers who received a bolus oral dose of 100,000 IU ergocalciferol, significant reductions in serum hepcidin were observed by 24 hours. Similar results were obtained in a second paper by Bacchetta *et al.* in which treatment of peritoneal macrophages obtained from non-infected chronic kidney disease (CKD) dialysis patients with 25(OH)D or 1,25(OH)₂D suppressed expression of HAMP. The HAMP expression was further suppressed in peripheral blood macrophages obtained from subjects with CKD and peritoneal infection. In translating these findings to patients who had received ergocalciferol as part of a pilot trial, HAMP mRNA expression in peritoneal macrophages was significantly reduced one month after supplementation [8**].

Based on the above studies, the association between vitamin D and anemia is likely through anemia of inflammation, in which the underlying mechanism involves the direct suppression of hepcidin mRNA expression by vitamin D as well as the reduction of hepcidin-stimulatory pro-inflammatory cytokines. Additionally, early *in vivo* pilot studies in humans indicate that vitamin D supplementation may be effective in suppressing hepcidin mRNA expression and lowering serum hepcidin concentrations. The subsequent influence on markers of iron status needs to be elucidated in larger, longer-term studies.

Erythropoiesis

Another pathway contributing to anemia of inflammation is through depressed erythropoiesis and reduced red blood cell (RBC) lifespan [11**]. This may occur through inflammation- and hepcidin-mediated disruptions in iron recycling as described above, leaving insufficient iron available to support erythropoiesis. Alternatively, inflammatory cytokines may impair erythropoiesis by inhibiting the production of erythropoietin and the differentiation and proliferation of erythroid progenitor cells [17]. In addition to decreasing pro-inflammatory cytokines, vitamin D has been shown to support erythropoiesis by increasing burst-forming unit-erythroid proliferation (BFU-E) and having a synergistic effect with erythropoietin to further enhance erythroid progenitor cell proliferation [18, 19].

In a recent pre-clinical study of ribavirin-induced anemia, Refaat *et al.* found that the addition of vitamin D₃ to chronic hepatitis C therapies, pegylated interferon- α and ribavirin, maintained RBC counts and hemoglobin concentrations and increased erythropoietin concentrations compared to rats who received ribavirin therapy alone [20*]. Hemoglobin, RBC count, and erythropoietin concentrations were all positively correlated with serum 25(OH)D concentrations. These findings are suggestive of a protective role of vitamin D against drug-induced disturbances in erythropoiesis.

Studies in CKD patients have shown that vitamin D may reduce erythropoiesis stimulating agent (ESA) requirements [21, 22]. In a study of children with CKD on dialysis, Rianthavorn *et al.*, found that treatment with high-dose ergocalciferol resulted in significant

reductions in ESA dose at 12 weeks compared to baseline [23]. More recently, Afsar *et al.* found that patients receiving paricalcitol had the lowest ESA resistance compared to those on calcitriol, cinacalcet, paricalcitol + cinacalcet, or no treatment, and that paricalcitol was significantly inversely associated with ESA resistance [24*]. Given these findings, vitamin D may support erythropoiesis, and shows promise as a potential adjunctive therapy for anemia.

Other calciotropic hormones and anemia

In addition to vitamin D, other hormones involved in the bone-mineral axis, including fibroblast growth factor 23 (FGF-23) and parathyroid hormone (PTH), have been shown to be involved in iron metabolism and erythropoiesis (Table 1).

Fibroblast Growth Factor-23 (FGF-23)

Coe *et al.* showed that FGF-23^{-/-} mice had significantly greater RBC counts, a higher percentage of pro-erythroblast cells and erythroid cells, and increased BFU-E cells and serum erythropoietin concentrations compared to wild type (WT) mice [25**]. The opposite was observed when WT mice were treated with a single dose of FGF-23 protein; serum erythropoietin and percentage of pro-erythroblast and erythroid cells in the blood and bone marrow decreased significantly. Interestingly, genetic ablation of Klotho, a necessary cofactor for FGF-23, in a mouse model resulted in increased RBC counts and hemoglobin concentrations along with increased pro-erythroid cells, erythroid cells, and BFU-E cells in the bone marrow compared to heterozygous and WT mice, though hematopoietic stem cells in the bone marrow were reduced [26*]. In humans, Scialla *et al.* found that among patients with stage 2–4 CKD, hemoglobin concentration decreased significantly as FGF-23 quartile increased [27]. These results suggest that unlike vitamin D, FGF-23 is a negative regulator of erythropoiesis and iron metabolism. Elevations in FGF-23, which often accompany cardiovascular disease and renal disease, therefore, have the potential to increase risk for anemia [28].

Parathyroid Hormone (PTH)

Previous studies have suggested that elevations in PTH may be associated with increased risk for anemia through alterations in erythropoiesis including reductions in erythroid progenitor formation and erythropoietin synthesis, and PTH-induced fibrosis of the bone marrow [29]. Indeed, Russo *et al.* found that PTH concentrations were significantly inversely associated with hemoglobin concentrations among non-dialysis CKD patients [30*]. Furthermore, a recent study assessing risk factors for hyporesponsiveness to ESAs found that elevated concentrations of PTH were associated with reduced odds of becoming responsive to ESAs [31]. While these findings suggest that elevations in PTH may impact iron metabolism and erythropoiesis, there remains uncertainty regarding the specific mechanism(s) and whether this association is independent of vitamin D.

Epidemiology of the vitamin D deficiency and anemia association

Vitamin D deficiency and anemia are important public health problems and are common in both acute and chronic illness. Past studies have demonstrated that low vitamin D status is

associated with anemia risk in children, elderly adults, those with CKD, and those with heart failure [2, 3, 5, 7]. Recent studies in patients scheduled for cardiac surgery and community-dwelling elderly men have also shown vitamin D status to be inversely associated with odds of anemia and positively associated with hemoglobin concentrations, respectively [32, 33*]. New studies have also extended these findings to explore racial and ethnic differences in the association between vitamin D and anemia, and to further clarify the association with specific subtypes of anemia.

Association of vitamin D with subtypes of anemia and racial differences in the association

Previous population-based studies have indicated that the association between vitamin D and anemia may vary with respect to the etiology of anemia. Lee *et al.* found that among Korean children, the lowest quartile of 25(OH)D was associated with increased odds of anemia in females, but the effect was attenuated to non-significance after adjusting for iron deficiency [34]. Therefore, if iron deficiency is the primary contributor to anemia, improvements in vitamin D status may not confer added benefit.

These results are consistent with a study by Smith *et al.* of generally healthy adults in which serum 25(OH)D concentrations < 20 ng/mL were associated with increased odds of anemia in blacks but not whites. When the cohort was categorized by subtypes of anemia, vitamin D status was associated with anemia of inflammation but there was no association with anemia without inflammation [35*]. This is in line with the mechanism of action of vitamin D on pro-inflammatory cytokines and hepcidin described above, and would suggest that when other factors such as iron deficiency, are the predominant contributors of the anemia, the association between vitamin D and anemia may be attenuated.

These results also point to effect modification by race in the vitamin and anemia association. Vitamin D deficiency and anemia are more common in blacks than in whites [36, 37], though whether lower vitamin D levels commonly found in blacks contribute to the higher prevalence of anemia is not clear. Atkinson *et al.* explored these racial differences in children, and found that hemoglobin increased significantly with increasing quartile of 25(OH)D in the entire study population and among the sub-group of whites, but not in blacks [38*]. However, serum 25(OH)D concentrations were significantly lower among blacks compared to whites. When quartiles were determined based on 25(OH)D concentrations in black children only, hemoglobin increased significantly with increasing quartile of 25(OH)D.

Taken together, these epidemiologic studies provide strong evidence for the link between vitamin D deficiency and anemia, particularly anemia of inflammation, and indicate that the association may differ by race. However, several of these studies are limited by their cross-sectional nature. Additional longitudinal and interventional studies are required to determine whether the association between vitamin D deficiency and anemia is indeed causal.

Clinical trials

Data from clinical trials exploring the therapeutic effect of vitamin D on anemia are sparse, but early clinical trials have suggested that treatment with vitamin D may reduce ESA

requirements in patients with CKD and increase hemoglobin concentrations [39–41]. In a recent trial by Riccio *et al.*, patients with stage 3b-5 CKD and anemia were randomized to receive either paricalcitol (a vitamin D analogue) or calcitriol (the hormonally active form of vitamin D) over 6 months [42**]. Subjects who received paricalcitol experienced a significant increase in hemoglobin over time, but interestingly, hemoglobin decreased in the group that received calcitriol.

In a placebo-controlled trial, Sooragonda *et al.* tested the efficacy of high-dose vitamin D in improving hemoglobin concentrations in subjects with iron deficiency anemia [43]. All subjects received iron supplementation. Those randomized to the intervention arm received a one-time intramuscular injection of 600,000 IU of vitamin D₃. After 12 weeks, hemoglobin concentrations did not differ between the vitamin D and placebo group, further confirming that among subjects with iron deficiency anemia, vitamin D is unlikely to offer additional improvements in hemoglobin after correction of iron deficiency.

While these trials add to the vitamin D and anemia literature, addressing which forms of vitamin D may be effective in raising hemoglobin levels and which type of anemia vitamin D may (or may not) improve, there remains a paucity of clinical trials specifically addressing the efficacy of vitamin D in improving anemia.

Implications for clinical practice

Given the mechanistic and epidemiologic evidence for an association specifically with anemia of inflammation, vitamin D may be especially important in preventing anemia in groups with chronic elevations in inflammation status. Patients with CKD represent an especially vulnerable group given the characteristic reductions in erythropoietin production, erythropoietin resistance, and reduced ability to convert 25(OH)D to the active hormonal form due to reductions in functional renal mass, along with increased FGF-23 concentrations, and elevations in inflammatory cytokines that promote hepcidin release. In decreasing pro-inflammatory cytokines and directly suppressing hepcidin expression, vitamin D may be effective in mobilizing iron stores and promoting erythropoiesis and hemoglobin synthesis.

Hepcidin concentrations have been shown to be inversely associated with hemoglobin concentrations and positively associated with anemia risk, and therefore represent a potential therapeutic target for addressing anemia [44]. Furthermore, hepcidin concentrations have been used to distinguish iron deficiency anemia from anemia of inflammation, and this distinction may be important in targeting therapies to people with different types of anemia [45**]. However, hepcidin is not yet available commercially to be measured in routine clinical practice. In the future, given its regulatory role on hepcidin mRNA expression, vitamin D may provide a promising therapy either alone or in conjunction with other pharmacotherapies; however, it is not currently FDA approved for this use.

Despite the recent advances in our understanding of the role of vitamin D in iron homeostasis, further clinical trials are needed confirm causality in the vitamin D and anemia association as well as determine optimal vitamin D dosing, the ideal population for therapy, and the preferred form of vitamin D to give.

Conclusions

Vitamin D is associated with anemia in various study populations and recent evidence suggests that the association may differ by race and is likely specific to anemia of inflammation. The link to anemia of inflammation is supported by recent investigations showing that vitamin D can reduce hepcidin-stimulatory pro-inflammatory cytokines, thereby reducing hepcidin, as well as act on hepcidin directly by down-regulating HAMP mRNA transcription. Recent studies have also suggested that vitamin D may support erythropoiesis, possibly through reduction of pro-inflammatory cytokines and increased erythroid progenitor cell proliferation. Other factors on the bone-mineral axis, including FGF-23 and PTH, may have regulatory roles in iron homeostasis and erythropoiesis, and there is some evidence suggesting that the actions of FGF-23 may be independent of vitamin D [25**]. The interplay between all three hormones in regulating iron metabolism will be an interesting area of future study.

In summary, there is strong evidence both epidemiologically and mechanistically to support a role for vitamin D in iron metabolism, but further clinical trials are needed to clarify the therapeutic efficacy of vitamin D in improving anemia.

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Key points

- Vitamin D status has been positively associated with hemoglobin concentrations and inversely associated with risk for anemia, particularly anemia of inflammation.
- The mechanism underlying this association involves the reduction of pro-inflammatory cytokines and the direct suppression of hepcidin mRNA transcription by vitamin D.
- Treatment with vitamin D or its analogues has been shown to reduce ESA requirements and increase hemoglobin concentrations in patients with chronic kidney disease.
- Other calciotropic hormones, FGF-23 and PTH, may also be involved in the regulation of iron metabolism and erythropoiesis
- Vitamin D could be a future treatment option for anemia of inflammation, but additional trials are needed to further define its therapeutic efficacy and the interplay between vitamin D, FGF-23 and PTH.

Figure 1. Alterations in Iron Recycling in Anemia of Inflammation and Proposed Role of Vitamin D

A. Alterations in Iron Recycling in Anemia of Inflammation: Iron recycling, under non-pathologic conditions, involves transferrin-bound iron in circulation traveling to the bone marrow to support erythropoiesis. Upon senescence, red blood cells (RBCs) are engulfed by macrophages and iron is recycled back into circulation to support further erythropoiesis. Dietary iron may also enter the circulating pool from absorption in the duodenum based on the body's needs. In anemia of inflammation, elevations in pro-inflammatory cytokines suppress erythropoiesis in the bone marrow and shorten RBC lifespan due to increased macrophage activation and erythrophagocytosis. Cytokines IL-6 and IL-1 β stimulate the liver to up-regulate expression of hepcidin antimicrobial peptide (HAMP). Hepcidin inhibits iron egress from cells of the reticuloendothelial system, including enterocytes and macrophages, by binding and eventual degradation of the cellular iron exporter, ferroportin, resulting in decreased iron absorption and increased iron sequestration in the macrophage. Collectively, depressed erythropoiesis, shortened RBC lifespan, iron sequestration in the macrophage, and reduced iron absorption impairs iron recycling and results in insufficient iron available for erythropoiesis and hemoglobin synthesis, ultimately leading to anemia.

B. Proposed Role of Vitamin D in Counteracting Anemia of Inflammation: Vitamin D has been shown to promote erythropoiesis by increasing erythroid progenitor proliferation and decreasing pro-inflammatory cytokines. Additionally, by decreasing hepcidin-stimulatory pro-inflammatory cytokines, and through direct transcriptional regulation of the HAMP gene, vitamin D may suppress hepcidin expression. Decreases in pro-inflammatory cytokines and hepcidin may increase iron bioavailability for erythropoiesis and hemoglobin synthesis by restoring iron recycling, preventing iron sequestration in macrophages, and removing impairments on iron absorption, thus protecting against anemia.

Table 1

Associations of biomarkers in anemia pathophysiology with calciotropic hormones

Vitamin D	FGF-23	PTH
↓ Pro-inflammatory cytokines	↓ Hemoglobin	↓ Hemoglobin
↓ Hepcidin	↓ Erythropoietin	↓ Erythropoietin
↑ Serum iron	↓ % pro-erythroblasts	↓ Erythroid progenitor formation
↑ Hemoglobin	↓ Erythroid cells	↑ Fibrosis of bone marrow
↑ Erythroid progenitor proliferation	↓ RBC count	↑ Erythropoietin resistance
↑ RBC count		
↑ Erythropoietin		
↓ Erythropoietin resistance		