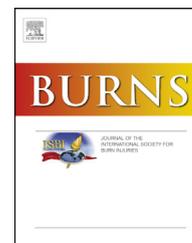


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Review

Vitamin D in burn-injured patients



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ABSTRACT

Recently, many studies have demonstrated pleotropic effects of vitamin D, including immune modulation and cardiovascular system activity. Sufficient vitamin D concentrations and supplementation of vitamin D may be of benefit in burn-injured patients. Low 25 (OH)D has been observed in nearly all pediatric and most adult burn patients. Vitamin D has primarily been studied in pediatric burn patients, focusing on bone marker measurements and the incidence of fractures. The preferred vitamin D dose, formulation, and route of administration remain unknown, and there is limited data on the impact of vitamin D status on clinical outcomes. Further research should focus on determining optimal monitoring strategies, supplementation regimens and clinical outcomes like mortality, length of stay and incidence of sepsis.

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1. Introduction

Vitamin D is an important hormone traditionally associated with bone mineralization and calcium homeostasis. In recent years, many studies have demonstrated its pleiotropic effects, including immune modulation and cardiovascular system activity. Sufficient vitamin D concentrations and supplementation of vitamin D may be of benefit in burn-injured patients. The focus of this review is to summarize literature surrounding vitamin D as it relates to burn-injured patients, including vitamin D homeostasis, serum concentrations and literature evaluating supplementation in both adult and pediatric patient population.

2. Vitamin D homeostasis

Vitamin D₃, or cholecalciferol, is synthesized in the skin under the influence of ultraviolet light from the sun, while vitamin D₂ (ergocalciferol) is obtained primarily through diet (see Fig. 1). Both undergo hydroxylation in the liver to form 25-dihydroxyvitamin D (25(OH)D) [1,2]. This form of vitamin D is found circulating in the serum and is measurable [3]. It is further converted, primarily in the kidneys, to activated 1,25-dihydroxyvitamin D (1,25(OH)₂D), which can bind to vitamin D receptors (VDRs) throughout the body [1,2]. Once in its active form, vitamin D increases the absorption of calcium in the small intestine. Bone resorption, osteopenia, immobilization, and disorders of vitamin D metabolism all affect circulating vitamin D levels [1-3].

Aside from its traditional role in bone and calcium homeostasis, vitamin D has many pleiotropic effects [1]. VDRs are expressed on the surface of many types of cells such as

keratinocytes, macrophages, B and T lymphocytes, neutrophils, renal tubule cells, parathyroid cells and pancreatic cells, among others [4-6]. Some of the subdomains of the receptors, such as the DNA-binding domain, hormone bindings, and transactivation, are conserved throughout all vertebrate species, which speaks to the important role of this molecule [7]. Within the immune system, monocytes express VDRs and 1,25(OH)₂D promotes differentiation in macrophages, which represent one of the first lines of immune defense [8]. It is thought that 1,25(OH)₂D can increase lysosomal enzyme production leading to increased phagocytosis [8]. In addition, 1,25(OH)₂D has been found to increase skin synthesis of an antimicrobial protein called cathelicidin [9]. Within the cardiovascular system, 1,25(OH)₂D serves as a negative modulator of the renin-angiotensin-aldosterone system. In animal studies, mice that under-express the VDRs have high serum levels of renin and angiotensin II, leading to higher blood pressure, water intake, and cardiac hypertrophy [10-12]. Finally, vitamin D has also been associated in regulation of cell proliferation of normal and cancerous cells, as well as in apoptosis [13]. Given these effects, as well as other pleiotropic effects of vitamin D, assessment of vitamin D status and supplementation may be warranted in patients with severe burn injury.

3. Burn pathogenesis

Significant burn injury results in several severe and unique physiologic derangements. Cardiovascular function is profoundly affected, leading to burn shock, in which tissue perfusion is inadequate to maintain delivery of oxygen and nutrients and removal of cellular waste products. This leads to significant fluid requirements and also creates a

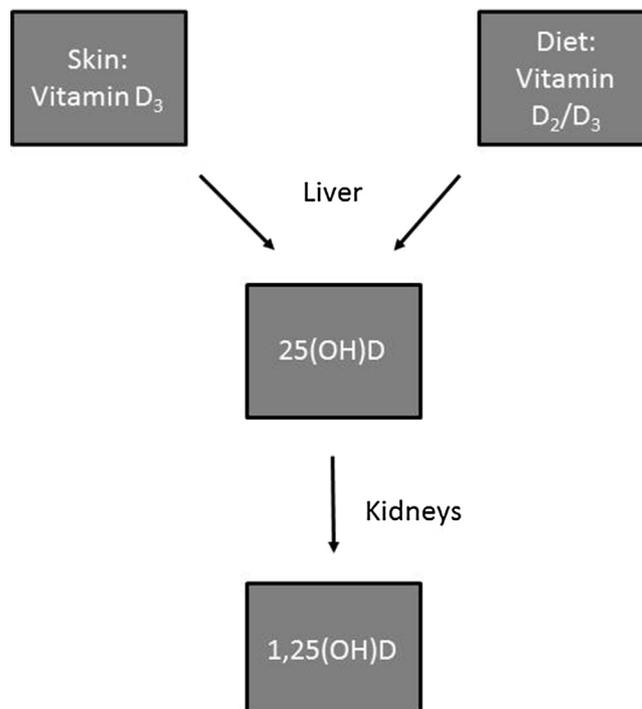


Fig. 1 – Vitamin D distribution [1,2].

hypermetabolic state with a profound increase in basal resting energy expenditure, greater than any other illness or injury. Despite aggressive fluid resuscitation, normal blood volume is not typically restored until 24–36h after injury [14,15]. Furthermore, extravasation of plasma into the burn wound and surrounding tissues results in significant edema from in the following derangements: changes in the permeability of the blood tissue barrier of the capillaries and venules, decreased capillary pressure due to arteriolar vasoconstriction, negative interstitial hydrostatic pressure, decreased plasma colloid osmotic pressure, and increased interstitial colloid osmotic pressure [16–18]. Finally, resultant profound hypoproteinemia leads to a sustained increase in water content and elevated lymph flow in non-burned tissue after the return of normal vascular permeability [17,18].

As most of vitamin D is protein-bound, these physiologic derangements may impact vitamin D status and needs. Additionally, while much emphasis is placed upon the caloric and protein requirements (which are substantial and the need for support is well established), the exact requirements for micronutrients remain unknown [19].

4. The immunologic response to burn injury

Significant burn injury creates a profound systemic inflammatory response syndrome. The initial intensity is dependent on the amount of tissue injury, the degree of burn shock, and the presence of host factors, such as age and comorbidities. Tissue damage occurs both directly as a result of thermal trauma, and indirectly through cellular injury induced by mediators such as oxygen free radicals and pro-inflammatory cytokines like tumor necrosis factor- α and interleukins IL-1, IL-6, and IL-8 [20,21]. This release is typically proportional to the extent of the burn and may be profound with significant injury. Furthermore, anti-inflammatory pathways increased production of IL-10 and transforming growth factor- β to combat production of inflammatory mediators [22,23]. However, this anti-inflammatory state may lead to immunosuppression that predisposes the host to infection. Vitamin D is an integral part of the immune system and its role in mitigating immunosuppression and infection has yet to be determined.

5. Vitamin D serum concentrations

Defining adequate, insufficient and deficient levels of vitamin D is still controversial. Based on the Institute of Medicine, patients with serum 25(OH)D <12ng/mL (<30nmol/L) have increased risk of developing rickets or osteomalacia [24]. Those

with levels between 12–20ng/mL (30–50nmol/L) have insufficient levels and >20ng/mL (>50nmol/L) are considered to have adequate levels [24] (Table 1). Moreover, guidelines by American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommended supplementation to maintain levels above 30ng/mL [25]. These set values are based on expert opinion and have not been subject to scientific evaluation, particularly in burn-injured patients. For most studies in critically ill patients, a cutoff <20ng/mL has been used to define deficiency [26]. “Normal” values range from 25–80ng/mL in medical literature [27]. Vitamin D deficiency or insufficiency is increasing in modern American society as many people work in indoor environments with a decline in sunlight and dietary exposure. Mobility restricted, house-bound elderly, and patients with chronic illnesses are especially vulnerable [28].

While a good predictor of vitamin D status in the general population, 25(OH)D has been found to be less accurate in critically ill patients, especially burn patients, due to variances between assays, acute fluid shifts, and alterations and polymorphisms in vitamin D binding protein (DBP) and albumin [29–32]. DBP tightly binds the majority (roughly 88%) of circulating 25(OH)D, while the remainder is bound to albumin. Only 0.03% of 25(OH)D is free in the serum [29]. Both albumin and DBP levels can fluctuate greatly with critical illness, particularly in burn injury, and are significantly impacted by fluid loading. In a study examining patients undergoing cardiopulmonary bypass, fluid loading led to a 35% reduction in 25(OH)D concentrations acutely, paralleling a 30% reduction in serum albumin concentration [33]. This can be even more dramatic with a severely burned patient, who may receive over 20L of fluid in the first 24–48h of burn resuscitation. Aside from fluctuant 25(OH)D serum concentrations in acute burn injury, vitamin D deficiency may arise from loss of transport proteins, including DBP and albumin. Lower DBP levels lead to renal 25(OH)D wasting. Albumin deficiency may persist for up to six months post-burn injury, making assessment of 25(OH)D an unreliable measure of vitamin D status in the acute phase of burn injury [34,35].

Vitamin D insufficiency can also arise from inadequate intake and vitamin D supplementation should be incorporated in the nutritional support of critically injured burn patients. Standard enteral nutrition formulas provide approximately 400–600 units of vitamin D per liter of formula; however, studies have shown that this amount is inadequate to normalize vitamin D status and that high dose regimens may be needed in critical illness [36].

Recently, measurement of bioavailable 25(OH)D, consisting of the free plus albumin-bound components, has become available and has been proposed as a better indicator of vitamin D status [32,37]. There is little data regarding bioavailable vitamin D in critically ill patients, and no data exploring its distribution in a burn-injured population [29,32].

Table 1 – Laboratory values^{31,65}.

Laboratory values	Normal value
25(OH)D	20–100ng/mL
1,25(OH) ₂ D	18–72pg/mL
PTH	10–65pg/mL or 10–65ng/L
FGF23	8–50ng/mL

6. Vitamin D in critical illness

Vitamin D status in critically ill patients has been the subject of much research over the last several years, and it is now widely recognized that vitamin D deficiency is common amongst

Table 2 – Vitamin D burn clinical trials.

Trial	Purpose	Study design	Interventions	Outcomes
Pediatrics				
Sobouti et al. [54]	Evaluate serum levels of 25 (OH)D in children with burn injuries	Prospective, cross-sectional study (N=118)	None	Mean vitamin D level 13.5 ng/dL. 96 patients (81.35%) had levels <20 ng/mL.
Gottschlich et al. [53]	Examine the effectiveness of vitamin D ₂ , D ₃ , or placebo supplementation on laboratory and clinical outcomes in children with extensive burn injury (TBSA >30%).	Prospective, randomized, double-blinded, placebo-controlled (N=50)	Control: 800IU D ₃ per L of tube feeds plus placebo Treatment: 800IU D ₃ per L of tube feeds plus 100IU/kg/day of either D ₂ or D ₃	25 (OH)D increased from admission to discharge in all 3 groups. No difference in 1-year BMDs. Trend towards reduced number of septic days in D ₃ group.
Mayes et al. [60]	Evaluate postintervention incidence of fractures in children during the rehabilitative phase postburn after participation in a randomized clinical trial of vitamin D supplementation.	Secondary analysis of previous prospective, randomized, double-blinded, placebo-controlled trial by Gottschlich et al. [53] (N=39).	Control: 800IU D ₃ per L of tube feeds plus placebo Treatment: 800IU D ₃ per L of tube feeds plus 100IU/kg/day of either D ₂ or D ₃	Long-bone fractures reported in 6 patients (15.4%); 4 in placebo group, 2 in D ₂ group, and none in D ₃ group (p=0.13). Patients with fractures had larger burn size, greater full-thickness burn, and increased incidence of inhalation injury.
Gottschlich et al. [67]	Examine vitamin D and endocrine status in acutely injured pediatric patients with burns >25% TBSA.	Prospective cohort (N=69)	Patients consumed vitamin D <i>ad lib</i> from oral diet, plus twice the RDA per L of tube feeds. Dose was doubled every 2 weeks (maximum 10 times RDA) if no improvement in 25(OH)D levels.	46% had adequate 25(OH)D levels (>15 ng/mL). 25(OH)D levels increased with time postburn.
Klein et al. [59]	Determine whether burn scar or adjacent healthy tissue can synthesize vitamin D ₃ from 7-dehydrocholesterol in pediatric patients with severe burns.	Prospective case-controlled study (N=12)	Control samples: skin samples from 5 male infant foreskins and 2 white female volunteers. Both control and burn patient samples were exposed to ultraviolet B light.	Conversion to D ₃ was reduced in burn scar and adjacent healthy tissue as compared to non-burn controls.
Mayes et al. [57]	Document the incidence of long bone fractures in children with burns >40% TBSA, and identify similar characteristics among these patients.	Retrospective cohort (N=104)	None	6 patients (5.8%) had 15 long bone fractures post-burn. All fractures occurred in patients <3 years of age. Four of six patients (66.7%) experienced fractures during the rehabilitative phase of their hospitalization.
Wray et al. [56]	Assess the effects of vitamin D deficiency on serum electrolytes in pediatric patients with burns >25% TBSA.	Retrospective cohort (N=41)	None	Increasingly negative relationship between burn severity and 25(OH)D. Hypovitaminosis D correlates with serum calcium and phosphorus abnormalities.
Klein et al. [55]	Test the hypothesis that burned children (>40% TBSA) develop vitamin D depletion after the burn injury has healed.	Prospective cohort (N=24)	None	Burned children have low 25 (OH)D levels, which correlate with BMD z scores.
Trial	Purpose	Study design	Interventions	Outcomes
Adults				
Blay et al. [61]	Determine the prevalence of vitamin D deficiency and insufficiency on admission	Retrospective cohort (N=318)	None	253 patients (79.6%) with low vitamin D (<30 ng/mL). Low vitamin D group with

(continued on next page)

Table 2 (continued)

Trial	Purpose	Study design	Interventions	Outcomes
Ding et al. [66]	in burned adults and correlate vitamin D status to clinical outcomes Investigate the role of vitamin D in dermal fibroblast-mediated wound healing and the interaction of vitamin D and TGFβ.	In vitro study (N=3)	4 treatments of cells from skin biopsies: 1. TGFβ1 2. 1,25(OH)2D 3. Both 1 and 2 in sterile phosphate buffered saline 4. Sterile phosphate buffered saline	longer ICU LOS, hospital LOS, and trend towards more ventilator days and complications. A synergistic effect of 1,25(OH)2D and TGFβ1 was found in fibroblast-mediated wound healing in vitro.
Terzi et al. [65]	Evaluate BMD, bone turnover markers, and 25(OH)D levels in male patients 1-year post burn. Evaluate relation between scar tissue characteristics and BMD and 25(OH)D levels.	Cross-sectional prospective study (N=45)	Burn group: adult males with >30% TBSA Control group: age-matched, healthy adult males	25(OH)D levels and femoral neck BMD z scores were lower in burn patients. Negative correlation between MVSS and 25(OH)D levels.
Rousseau et al. [63,64]	Assess effects of cholecalciferol bolus on vitamin D deficiency status in adult burn patients.	Prospective case-controlled study (N=49)	Control group: healthy adult Caucasian workers Burn group: adult Caucasian burn patients with TBSA >10% All subjects received 100,000 IU cholecalciferol via enteral administration.	Prevalence of vitamin D deficiency (<20ng/mL) was higher in burn patients. 7 days after bolus, 25(OH)D increased by 13.5%–260.3% in healthy controls, but changes ranged from –36.7% to 333.3% in burn patients.
Rousseau et al. [63,64]	Assess effects of D ₃ supplementation and an optimized calcium regimen on vitamin D status, bone and muscle health.	Randomized controlled trial (N=15)	Control: placebo IM injection quarterly Treatment: 200,000 IU cholecalciferol IM quarterly and daily oral calcium	Of all patients, 66% presented with vitamin D deficiency (<20ng/mL) and 20% with insufficiency (21–29ng/mL). No change in bone health between groups. Treatment group had improved quadriceps strength. 17% had vitamin D deficiency (<20ng/dL), 75% had vitamin D insufficiency (21–29ng/dL). 12 patients completed the study and no increase in 25(OH)D at 28 days was shown.
Rousseau et al. [62]	Describe vitamin D status at admission and 28 days with current protocol of D ₃ supplementation in adults with burns >10% TBSA.	Prospective cohort (N=24)	Enteral nutrition provides 600 IU D ₃ . Patients with TBSA <20% received additional 200 IU D ₃ via oral multivitamin, and patients with TBSA >21% received 220 IU D ₃ via IV preparation	

BMD=bone mineral density.

D₂=ergocalciferol.

D₃=cholecalciferol.

ICU=intensive care unit.

IM=intramuscular.

IU=international units.

IV=intravenous.

L=liter.

LOS=length of stay.

MVSS=Modified Vancouver Scar Scale Score.

N=number.

RDA=recommended dietary allowance.

TBSA=total body surface area.

TGFβ=transforming growth factor beta.

patients admitted to an intensive care unit (ICU) [38–44]. Several studies have demonstrated a relationship between low 25(OH)D and adverse outcomes in critically ill patients, including mortality, length of stay (LOS), sepsis, blood culture positivity and readmission rate [38,39,42,43,45]. Despite these findings, there is no consensus as to how often to monitor 25(OH)D levels or replete deficiency [46].

Several randomized controlled trials have evaluated vitamin D supplementation in a variety of critically ill populations, including those with sepsis, cystic fibrosis exacerbation, and acute respiratory failure requiring mechanical ventilation, surgical patients and a mixed medical population [36,41,47–50]. Most studies have supplemented enteral or intramuscular cholecalciferol at doses ranging from 200 international units (IU) daily to loading doses as high as 540,000 IU [36,41,47–50]. The primary endpoints studied and resultant outcomes were heterogeneous amongst these studies, and only one trial included over one hundred subjects [47]. The VITdAL-ICU trial was a double-blind trial that included 475 patients who were randomized to a single oral loading dose (540,000 IU) and 5 monthly maintenance doses (90,000 IU) or placebo in critically ill patients who were found to be vitamin D deficient (25[OH]D <20ng/mL) [47]. The primary outcome LOS was similar between groups (20.1 days vitamin D vs. 19.3 days placebo; $p=0.98$). There was no difference in short long-term mortality; however, subgroup analysis of patients with severe deficiency (<12ng/mL; $n=200$), revealed decreased hospital mortality in the experimental group (28.6% vs. 46.1%, HR 0.56 $p=0.04$) [47].

A recent meta-analysis summarized these data [51]. Five trials were found to be of low risk of bias [41,47,48,50,52]. Among them, administration of vitamin D in critically ill patients was associated with a significant reduction in mortality at the longest follow-up available, which ranged from 7 days to 6 months, depending on the study (31.6% vitamin D group [$n=320$] vs. 40.1% placebo-control group [$n=307$]; OR 0.70 [95% CI, 0.50–0.98]) [51]. The data were homogenous (p for heterogeneity=0.68; $I^2=0\%$). However, the overall quality of evidence for mortality was low. Thus, at this time it appears there may be a role for supplementation of vitamin D in critically ill patients, though more research is needed as to the type, dose, and route of supplementation, as well as which patient population(s) benefit most from therapy. Additionally, little is known as to if all critically ill patients, including those with burn injury, would benefit from supplementation, or just those with vitamin D deficiency.

7. Vitamin D in pediatric burn patients

Vitamin D in burn patients has been studied primarily in the pediatric population, with low 25(OH)D levels observed in nearly all pediatric burn patients [53–55]. In the acute setting, the correlation between 25(OH)D and bone marker measurements, such as calcium and parathyroid hormone (PTH) has been the primary focus, and there is limited data on clinical outcomes, such as mortality, LOS or incidence of sepsis [53,54,56]. See Table 2 for a summary of pediatric burn literature.

One study including 118 pediatric burn-injured patients with a mean age of 4 years found that only 4 patients (3.39%)

had sufficient 25(OH)D concentrations [54]. There was a positive correlation found between 25(OH)D and total serum protein ($r=0.35$), albumin ($r=0.42$), total calcium ($r=0.40$), and ionized calcium ($r=0.39$, $p<0.001$), and a negative correlation was found between total body surface area burn (TBSA) and 25(OH)D ($r=-0.29$, $p=0.001$) [54]. These correlations may be explained by anticipated loss of transport proteins and increased fluid shifts in burn patients, so the significance of these findings is unclear.

There are several studies that assess the impact of 25(OH)D on the bone health of pediatric burn patients after hospital discharge. The first is a retrospective cohort of 104 patients with a mean age of 6.7 years which documented the incidence of long bone fractures in children with TBSA >40% [57]. Fractures occurred in six patients between 73 and 283 days post-burn. Of these, 67% had low levels of both 25(OH)D and 1,25(OH)₂D. A similar study included 24 pediatric patients with burns >40% TBSA; 12 were seen in clinic 2 years post-burn and 12 were seen in clinic 7 years post-burn. Vitamin D levels remained low in most patients from both groups and correlated with low bone mineral density (BMD) z-scores ($r=0.53$, $p<0.05$) [55]. Another study found in those who were deficient in vitamin D, supplementation for at least three months improved bone mineral composition and lumbar spine bone mineral density (2.6%, 1.7%) [58]. These studies may support the use of vitamin D supplementation in order to reduce the risk of fractures in the future [59].

In a recent study of 50 pediatric burn patients ranging in age from 0.7 to 18.4 years with a mean TBSA 55.7%, subjects received 800 IU cholecalciferol (vitamin D3) per liter of tube feeding and were randomized to receive an additional 100 IU/kg/day of cholecalciferol, ergocalciferol (vitamin D2) or placebo [53]. No differences were found in 25(OH)D levels between groups. Overall, 25(OH)D levels were higher at discharge than at baseline, midpoint, and 1 year follow up ($p<0.01$). A trend towards a favorable effect of cholecalciferol supplementation on number of septic days was observed (3.6 ± 1.4 ergocalciferol vs. 1.1 ± 1.1 cholecalciferol vs. 6.2 ± 5.0 placebo days, $p=0.19$) [53]. Vitamin D levels improved at discharge in all three groups, and there was a trend towards reduced number of septic days with supplementation. The true clinical impact of vitamin D supplementation remains unknown. A secondary analysis of 39 of the 50 pediatric patients enrolled in the aforementioned study evaluated the post-intervention incidence of fractures. Long bone fractures were reported in 6 of the 39 patients: 4 (31%) in the placebo group, 2 (15%) in the ergocalciferol group, and none in the cholecalciferol group ($p=0.13$) [60]. Patients who experienced fracture had larger TBSA (84% vs. 53%, $p<0.0001$), more extensive full thickness injury (70% vs. 39.4%, $p=0.02$), increased incidence of inhalation injury (33% vs. 6%, $p=0.04$), and later post-burn day of admission (3.3 days vs. 1.1 days, $p=0.04$). BMD z-score was lower in the fracture group both at discharge ($p=0.06$) and at the 1-year time point ($p=0.09$), with those who received the placebo reaching statistical significance ($p<0.05$) compared with patients who received placebo and did not experience a fracture [60]. Patients who received vitamin D supplementation trended towards having fewer fractures, and supplementation should be considered, especially in patients with larger TBSA involvement, more extensive full thickness injury, inhalation injury, and delayed admission.

Finally, a small prospective cohort of 12 pediatric burn patients was used to determine if the skin from severely burned children can synthesize vitamin D₃ from 7-dehydrocholesterol. Subjects ranged from 4 to 14 years, had an average burn of 52% TBSA, and were studied at a mean of 14 months after their burn injury [59]. Skin biopsy samples were taken from burn scar and healthy-appearing skin adjacent to the scar. Skin 7-dehydrocholesterol was significantly lower in the burn scar than in unburned controls in both burn scar and skin adjacent to the scar. The conversion of 7-dehydrocholesterol to vitamin D₃ was significantly reduced compared with unburned control in both burn scar and adjacent healthy-appearing skin ($p=0.004$). Controls were not age-matched to burn patients and included adult volunteers, which is a limitation of this study, since the skin's capacity to produce vitamin D declines with age. Based on this study, burn patients may benefit from receiving vitamin D supplementation [59].

Although vitamin D studies in burn patients have primarily been amongst the pediatric population, the benefit of vitamin D supplementation is based upon the correlation between vitamin D levels and bone marker measurements, with the goal of preventing future bone fractures. The optimal Vitamin D dose, formulation, and route of administration is unknown, and there are few studies regarding the impact of hypovitaminosis D on clinical outcomes.

8. Vitamin D in adult burn patients

Limited data evaluates the incidence of vitamin D deficiency in adult patients with burn injuries. In a recent study of 318 adult burn patients, 253 patients (79.6%) had vitamin D insufficiency (10–29 ng/mL) or deficiency (<10 ng/mL) at admission, based on the study definitions [61]. Several smaller studies report incidences of low vitamin D in adult burn patients ranging from 66 to 92% [62–64]. This reported incidence may not reflect true vitamin D levels since 25(OH)D assessment may be impacted by fluid loading and protein shifts that occur after burn injury.

Limited data assesses vitamin D supplementation in burn-injured adults. One study examined the effect of a bolus dose of 100,000 IU cholecalciferol between 29 healthy patients and 20 burn patients with mean TBSA burn of 23% [64]. Serum 25(OH)D at days zero and seven were lower than healthy controls, but improved after supplementation from 11 to 19.3 ng/mL ($p<0.05$). PTH, which plays a role in vitamin D metabolism and may be suppressed due to the inflammatory response to burn injury, was found to be higher in burn patients at day zero than controls (37 vs. 16.5 ng/mL, $p<0.05$), and was reduced after supplementation to 16 ng/mL at day seven ($p<0.05$). Fibroblast growth factor 23 (FGF23), which is produced by osteocytes and is a regulator of vitamin D metabolism, was higher than healthy controls at days 0 (109.9 vs. 50 RU/mL, $p<0.05$) and seven (100.3 vs. 54.3 RU/mL, $p<0.05$), and was reduced after supplementation ($p<0.05$) [64]. This study supports the safe use of high-dose cholecalciferol in burn patients, and calls for further exploration of the role of PTH and FGF23 as it relates to vitamin D in burn patients. Another study of 12 adults with mean TBSA of 15% supplemented cholecalciferol either by oral route (TBSA $\leq 20\%$) or intravenously (TBSA $>20\%$) for 28 days [62]. Over this time, corrected total calcium increased from 2.22 mmol/L to

2.46 mmol/L ($p=0.02$), and there were no changes in 25(OH)D (13–12.5 ng/mL, $p=0.78$) or 1,25(OH)₂D (41–34.5 pg/mL, $p=0.12$). There was no change in PTH, albumin, or FGF23. This study found that supplementation of cholecalciferol was insufficient to increase vitamin D levels, and suggests that higher doses may be needed in burn-injured patients [62].

There is limited data in adults exploring clinical outcomes pertaining to vitamin D serum concentrations. A retrospective cohort of 318 burn-injured patients were categorized as vitamin D deficient (25(OH)D <10 ng/mL), insufficient (10–29 ng/mL), or sufficient (30–100 ng/mL) based on admission measurements [61]. Insufficient or deficient vitamin D were grouped in the “low” vitamin D group, and compared to those with sufficient vitamin D levels at admission. There was no difference in median TBSA between groups, although overall patients had small burns (4% in the normal vitamin D group, 5% in the low vitamin D group; $p=0.137$) [61]. Patients with low vitamin D levels had longer hospital LOS compared to those with normal 25(OH)D levels (3 vs. 2 days, $p=0.046$). Of the 97 patients admitted to the ICU, low vitamin D was associated with significantly longer ICU LOS (8.5 [2–23] vs. 2 [1–8.5] days, $p=0.013$). Additionally, patients in this study with low 25(OH)D tended to spend more time on the ventilator and had higher rates of complications, such as infection and graft loss [61].

Small studies compared intramuscular cholecalciferol 200,000 IU every three months and a daily oral dose of calcium carbonate ($n=8$; TBSA 32.5%) with patients who received placebo ($n=7$; TBSA 30%) [63]. No change in bone health was observed in either group, but the treatment group had significantly improved quadriceps strength when tested at high velocity. Serum 25(OH)D levels increased and PTH levels decreased over the course of one year between groups ($p=0.009$ and $p=0.003$, respectively). There were no differences found between groups with regards to calcium, FGF23, and phosphorus levels [63]. Another outpatient study of adult burn patients evaluated the relation between the characteristics of scar tissue, BMD, and vitamin D levels in 25 male patients with burn injuries $>30\%$ TBSA and at least one year post-burn compared to 20 age-matched, healthy male controls [65]. The burn patient group had lower 25(OH)D levels at baseline (13.4 vs. 21.1 ng/mL, $p=0.03$). There was no difference between groups in lumbar BMD, but femoral BMD and femoral neck z-scores were lower in the burn patient group (1.01 vs. 1.17, $p=0.04$, and 0.10 vs. 0.77, $p=0.04$, respectively). The Modified Vancouver Scar Scale Score (MVS.SS) was used for the assessment of scar tissues. A negative correlation between MVS.SS and 25(OH)D level was found ($r=-0.831$, $p=0.008$), but no correlation was found between MVS.SS and either lumbar or femoral BMD or z scores [65]. These studies support the use of vitamin D supplementation to raise vitamin D levels, improve muscle strength, potentially prevent BMD loss, and improve scarring.

Finally, vitamin D may also function directly on dermal cells to improve wound healing. In a recent *in vitro* study, skin biopsies from three female adults undergoing abdominoplasty surgery were treated with 1,25(OH)₂D, TGF- β 1, both, or vehicle, and the wound healing function of the dermal fibroblasts was measured [66]. The TGF- β family plays a major role in many aspects of cell growth and development, as well as in wound healing and scar formation. The authors found a synergistic effect of vitamin D and TGF- β 1, which resulted in increased

gene expression of TGF- β 1, connective tissue growth factor, and fibronectin 1, and enhanced fibroblast migration, myofibroblast formation, and collagen production. The results of this study suggest that supplementation of vitamin D in burn patients may help improve wound healing [66].

Most vitamin D studies in burn injury include a limited number of patients and are retrospective in nature; few studies have been conducted in adult burn patients. Several areas of future research remain, including the optimal dosing regimen and route of vitamin D supplementation, as no standard has been used throughout the burn literature [53,60,62–64]. It is still unclear as to the optimal method by which to measure vitamin D (such as using bioavailable measurement or the more routine 25[OH]D), as well as the timing of when to measure, since burn patients are subject to changes in serum proteins and fluid volume that may persist for some time, which makes assessment of vitamin D less accurate. Many studies in burn patients focus on the metabolic effects of vitamin D on electrolytes or bone marker measurements, but only recently have begun to look at clinical outcomes, such as LOS, ventilator days, time to wound healing, and incidence of sepsis [53,56,60,61]. Additionally, long-term follow up examining the effect of vitamin D on fractures and scar tissue have been conducted, but have been limited by study size [57,59,60,65].

9. Conclusion

Vitamin D is a hormone with many effects that may be of benefit to burn-injured patients, including immune regulation and promotion of wound healing. The accurate measurement of 25(OH)D may be affected by the fluid shifts and loss of transport proteins that burn patients experience, and optimal timing and method of measurement is yet to be determined. Though limited data exists in pediatric and adult burn patients, sufficient vitamin D concentrations and supplementation of vitamin D are a low-cost, low-risk intervention that may be of benefit, particularly in preventing fractures and impacting clinical outcomes such as reduced length of stay. Further research should focus on determining optimal monitoring strategies, supplementation regimens and clinical outcomes like mortality, LOS and incidence of sepsis.

Conflicts of interest and funding

None of the authors have any conflicts of interest to disclose.

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