Low Vitamin D Level on Admission for Burn Injury Is Associated With Increased Length of Stay

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Currently, there have been few studies that have evaluated the incidence of vitamin D deficiency in adult burn patients or correlated vitamin D levels with burn-related outcomes. The primary objective of the study was to identify the incidence of vitamin D deficiency and insufficiency in an adult burn population. The secondary objective was to determine the impact of vitamin D deficiency and insufficiency on clinical outcomes in burn care. A single-center, retrospective, and observational cohort analysis of adult patients admitted for initial management of burn injury, who had a 25-hydroxyvitamin D (25D) level measured on admission, was performed. Patients were categorized as vitamin D deficient (25D <10 ng/ml), insufficient (10–29 ng/ml), or sufficient (30–100 ng/ml) based on admission measurements. Clinical outcomes including complications, intensive care unit (ICU) and hospital length of stay (LOS), and survival were compared between patients with vitamin D deficiency/insufficiency and patients with vitamin D sufficiency. Three-hundred and eighteen patients were eligible for evaluation. Admission 25D level correlated with deficiency in 46 patients (14.5%), insufficiency in 207 (65.1%), and normal in 65 (20.4%). Patients with vitamin D deficiency or insufficiency experienced higher rates of complications and longer ICU and hospital LOS compared with those with normal vitamin D levels. A large proportion of patients with burn injury presented with vitamin D insufficiency and deficiency which was associated with poor outcomes, including prolonged ICU and hospital LOS. Additional studies are needed to further describe the relationship between vitamin D status and clinical outcomes. (J Burn Care Res 2017;38:e8–e13)

Vitamin D is a group of fat soluble prohormones, which is known to decrease the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease.[1] It also plays various roles in skeletal and nonskeletal health, specifically bone strength. Vitamin D is obtained from sunlight exposure, food, and dietary supplements, with the majority being obtained from sunlight.[1] Vitamin D is biologically inactive and must undergo activation in the body. Vitamin D is metabolized in the liver to 25-hydroxyvitamin D (25D), which can be measured to determine a patient's vitamin D status (eg, deficiency).[2] The 25D is then metabolized in the kidneys by the enzyme 25D-1-alpha-hydroxylase to its active form, 1,25-dihydroxyvitamin D.[2] Vitamin D deficiency has been recognized as a medical condition characterized by muscle weakness, bone pain, and fragility fractures.[3] Vitamin D deficiency in adults can advance osteopenia and osteoporosis, cause osteomalacia, and increase the risk of fracture.[1] Even though vitamin D plays a vital physiologic role, the clinical implications of vitamin D deficiency and insufficiency are not entirely understood, and monitoring is often overlooked.

Various at-risk populations for vitamin D deficiency have been identified, but there is insufficient literature about such populations, including patients with burn injury. Patients with burn injury are especially at an increased risk for low vitamin D levels

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1559-047X/2016

DOI: 10.1097/BCR.0000000000000445

after discharge, as their burned skin may not be able to synthesize vitamin D in the presence of ultraviolet light.[4] Thus, patients who are vitamin D deficient on admission are predicted to have various problems in recovery from burn injury. Patients with large burns commonly experience symptoms that overlap with symptoms of vitamin D deficiency, including pruritus, muscle weakness, and peripheral neuropathy, making a clinical diagnosis of vitamin D deficiency difficult without laboratory measures.[2] Vitamin D deficiency in burn patients has also been associated with low bone mineral density, increased risk of falls and fractures, and impairment of the bacterial killing efficiency of monocytes and macrophages.[2] However, to date, there have been few studies that have specifically evaluated the incidence of vitamin D deficiency in adult burn patients or correlated vitamin D levels with burn-related outcomes. Therefore, this study was conducted to determine the prevalence of vitamin D deficiency and insufficiency on admission in patients with burn injury and to correlate vitamin D status with clinical outcomes related to burn care.

METHODS

Study Location and Design

This was a single-center, retrospective, and observational cohort analysis. The primary objective of this study was to identify the incidence of vitamin D deficiency and insufficiency in an adult burn population. The secondary objective was to determine whether deficiency and insufficiency influences complication rates and clinical outcomes in burn care. Complications evaluated included infections (bacteremia, urinary tract infection (UTI), pneumonia, and wound infection/cellulitis), cardiovascular complications, graft loss, and renal failure. Clinical outcomes included intensive care unit (ICU) and hospital length of stay (LOS), duration of mechanical ventilation, and survival. Patients aged 18 to 89 years who were admitted to the burn service at The Ohio State University Wexner Medical Center for initial management of burn injury between January 1, 2008 and February 15, 2014, with a 25D level measured on admission, were eligible for inclusion. Patients who were pregnant or incarcerated were excluded. Patients were categorized as vitamin D deficient (25D <10 ng/ml), insufficient (10–29 ng/ml), or sufficient (30–100 ng/ml) based on admission 25D measurement. Complications and clinical outcomes were compared between patients with vitamin D deficiency or insufficiency (low vitamin D) and patients with vitamin D sufficiency (normal vitamin D).

Data Collection and Definitions

Patients were identified electronically by admission to the burn service. Data were collected retrospectively from the electronic medical record and the institutional burn quality database. Pertinent demographic and burn-related data were collected including: age, sex, race, height, weight, body mass index (BMI), comorbidities, home medications, depth of burn injury (partial/full) and corresponding percent TBSA burned, and burn etiology. Home medications were assessed and categorized into five groups: 1) medications that increase vitamin D levels, 2) medications that decrease vitamin D levels, 3) calcium supplementation, 4) multivitamin, and 5) vitamin D supplementation. Admission laboratory data collected included calcium, albumin, ionized calcium, C-reactive protein (CRP), phosphate, and 25-dihydroxyvitamin D levels. Clinical outcomes including ICU and hospital LOS, number and types of complications, survival and duration of mechanical ventilation were recorded. Complications included bacteremia/septicemia, UTI, pneumonia, cardiac arrest or other cardiac complication, graft loss, renal failure, and wound infection/cellulitis. All complications were collected from the institutional burn quality database.

Currently, there are no universal guidelines for the cutoffs for vitamin D levels for the diagnosis of vitamin D deficiency or insufficiency. The institutional laboratory standards to define 25D levels are as follows: deficiency as less than 10 ng/ml, insufficiency as 10–29 ng/ml, and sufficiency as 30–100 ng/ml. Although there are differences of opinion regarding levels that define vitamin D insufficiency and deficiency, there is virtually unanimous agreement that a level less than or equal to 12 ng/ml defines vitamin D deficiency in the United States.[5]

Statistical Analysis

Patients with low vitamin D were compared with those with normal vitamin D levels on admission. Continuous variables are presented as mean ± SD or median (25–75% interquartile range) and were compared using Student's *t*-test or Mann-Whitney *U* test as appropriate based on assessment of normality using the Shapiro–Wilk test. Categorical variables are expressed as frequency (percent) and were compared using χ^2 or Fisher's exact test as appropriate. All tests were two-tailed, and a *P* value <.05 was determined to represent statistical significance. All analyses were performed using SPSS version 19.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Patients

Three-hundred and eighteen patients were included for evaluation with a median admission 25D measurement of 18.95 (12.6–26.5) ng/ml. Admission 25D measurements correlated with vitamin D deficiency in 46 (14.5%) patients, insufficiency in 207 (65.1%) patients, and sufficiency in 65 (20.4%) patients. Patients were categorized into two groups: patients with low vitamin D levels (deficiency/insufficiency; n = 253) and patients with normal vitamin D levels (sufficiency; n = 65).

Baseline characteristics were similar between patients with low vitamin D and those with normal vitamin D levels (Table 1). Patients in both groups were overweight (BMI 25–29.9 kg/m^2) based on a median admission BMI of 25.5 kg/m^2 in the normal vitamin D group and 27.3 kg/m^2 in the low vitamin D group. Patients were generally healthy with few comorbidities in both groups. Patients with normal vitamin D were more likely to have a prior diagnosis of diabetes compared with those with low vitamin D (Table 1).

The burn characteristics were also similar between both groups, with both groups presenting with smaller burn injuries as indicated by median TBSA of 4 and 5% in the normal and low vitamin D groups, respectively (Table 1). The majority of patients in both groups also presented with partial-thickness injury, with a lower proportion presenting with full-thickness injury.

Table 2 summarizes the admission laboratory data including 25D, calcium, ionized calcium, albumin, CRP, and phosphate levels. The baseline laboratory values were similar between the two groups and were within normal limits, with the exception of 25-hydroxyvitamin levels as expected. Measurements for both groups for calcium, ionized calcium, albumin, CRP, and phosphate were within normal range based on institutional laboratory reference ranges.

Few patients in both groups presented with home medications that could influence either vitamin D levels or the effectiveness of vitamin D. The normal group contained no patients that reported home medications that may increase vitamin D, 5 (7.8%) reported medications that may decrease vitamin D, 5 (7.8%) reported taking calcium, 6 (9.4%) a multivitamin, and 9 (14.1%) vitamin D supplementation. The low group had 8 (3.2%) patients reporting a home medication that may increase vitamin D, 36 (14.2%)

Table 1. Comparison of baseline characteristics between patients with low and normal vitamin D levels

	Normal Vitamin D, n = 65	Low Vitamin D, n = 253	*P*
Age (yr)	39.2 (26.4–54.9)	43.4 (33–55.7)	.086
Body mass index (kg/m^2)	25.5 (21.9–32.1)	27.3 (23.6–32.5)	.087
Comorbidities, n (%)			
Diabetes mellitus	5 (7.7)	3 (1.2)	.01
Obesity	2 (3.1)	9 (3.6)	>.999
Congestive heart failure	1 (1.5)	7 (2.8)	>.999
Hypertension	1 (1.5)	11 (4.3)	.471
Immunosuppressed or chronic steroid use	12 (18.5)	34 (13.4)	.304
Malignancy	8 (12.3)	15 (6)	.105
Burn severity			
TBSA burned (%)	4 (1.5–7)	5 (2–11)	.137
Partial-thickness injury, n (%)	58 (89.2)	218 (87.6)	.816
Full-thickness injury, n (%)	21 (32.3)	106 (42.6)	.137
Burn etiology, n (%)			
Flame	30 (46.2)	111 (43.9)	.316
Flash	14 (21.5)	31 (12.3)	.316
Scald	12 (18.5)	65 (25.7)	.316
Electrical	2 (3.1)	2 (2.4)	.316
Contact	6 (9.2)	26 (10.3)	.316
Chemical	0 (0)	10 (4)	.316
Steam	1 (1.5)	4 (1.6)	.316
Admission to the ICU, n (%)	19 (29.2)	78 (30.8)	.880
Mechanical ventilation, n (%)	13 (20)	61 (24.1)	.622

ICU, intensive care unit.

Table 2. Comparison of baseline laboratory values on admission between patients with low and normal vitamin D levels

	Normal Vitamin D, n = 65	Low Vitamin D, n = 253	*P*
25-hydroxyvitamin D (ng/ml)	34.2 (31.9–42.5)	16.6 (11.6–22)	<.001
Calcium (mg/dl)	8.6 (8.4–8.8)	8.5 (7.9–8.9)	.224
Ionized calcium (mg/dl)	4.53 ± 0.40	4.39 ± 0.28	.265
Albumin (g/dl)	3.55 (3.1–3.9)	3.4 (2.8–3.9)	.271
C-reactive peptide (mg/L)	7.01 (1.28–39.47)	6.9 (1.99–58.5)	.388
Phosphate (mg/dl)	3.55 (2.85–4)	3.4 (2.8–4)	.456

a home medication that may decrease vitamin D, 7 (2.8%) reported taking calcium, 34 (13.5%) a multivitamin, and 14 (5.6%) vitamin D supplementation. During hospitalization, the majority of patients did not receive supplementation with vitamin D with 6.2% of normal group and 42.7% of low vitamin D group receiving vitamin D supplementation.

Complications and Clinical Outcomes

When evaluating the incidence of complications between the two groups, a higher proportion of the low vitamin D group experienced each complication with the exception of renal failure and wound infection/cellulitis, which were similar in both groups (Figure 1). Despite the numerically higher number of complications in the low vitamin D group, these differences failed to reach statistical significance.

Patients with low vitamin D levels spent 1 day longer in the hospital compared with patients with normal vitamin D levels (Figure 2; 3[1–14] vs 2 [1–9] days, *P* = .046). Among patients admitted to the ICU, patients with low vitamin D levels also had a significantly longer median LOS than those with normal vitamin D levels (8.5 [2–23] vs 2 [1–8.5] days, *P* = .013). Patients with low vitamin D levels requiring mechanical ventilation had a trend toward longer duration of mechanical ventilation, although this did not reach statistical significance (8 [2–15] vs 1 [1–11] days, *P* = .146). As expected based on the small burn size, the survival rate was very high in both groups: low group, 96.4%, and normal group, 96.9%.

DISCUSSION

This study demonstrated a high incidence of vitamin D deficiency (14.5%) and insufficiency (65.1%) among adult patients presenting with burn injury.

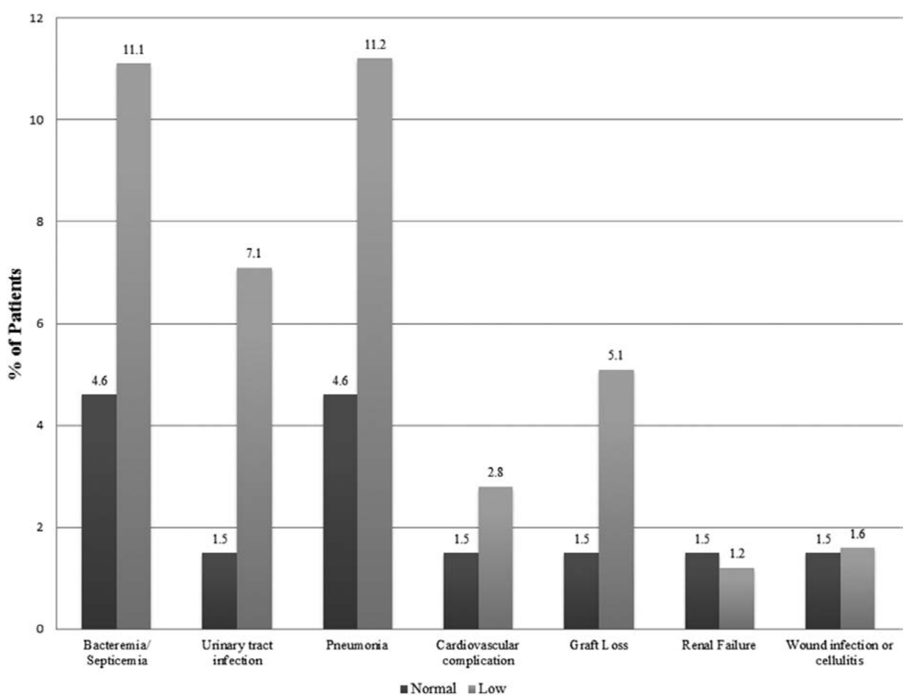

Figure 1. Comparison of complication rates between patients with low and normal vitamin D levels.

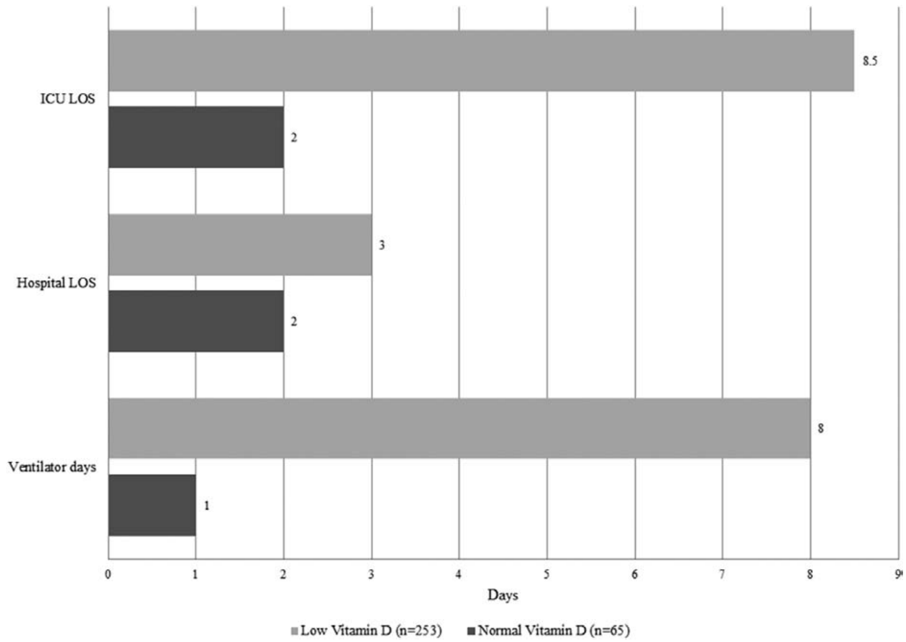

Figure 2. Comparison of clinical outcomes between patients with low and normal vitamin D levels on admission.

These rates are considerably higher compared with the general adult population, with about 26% of population being vitamin D insufficient and about 10% being vitamin D deficient in the United States according to the National Center for Health Statistics from 2011.[6] However, it is crucial to note that populations living at a latitude higher than 37° north of the equator in the Northern Hemisphere are at the greatest risk of developing vitamin D deficiency.[7] In the United States, this translates roughly to a line drawn between San Francisco, CA, and Richmond, VA.[7] This is because of the reduced sun exposure in the autumn and winter months, which leads to less vitamin D synthesis.[7] The results from this study demonstrated that the burn population within this region exhibits a higher incidence of vitamin D insufficiency/deficiency than the normal population across the United States. Furthermore, patients with vitamin D deficiency or insufficiency experienced higher rates of complications and longer ICU and hospital LOS compared with those with normal vitamin D levels despite similar baseline characteristics and severity of burn injury.

It is well known that vitamin D is involved in calcium homeostasis and bone development, but its role in immunology is less established, and existing data suggest a correlation with complications involving bacterial growth, wound healing, and infections.[8–10] There are various aspects of epithelial barrier function, innate immune function, and adaptive immunity that are vitamin D dependent. Vitamin D improves the physical epithelial barrier by stimulating gap junction genes (eg, connexion 43), adherens (eg, E-cadherin), and tight junction genes (eg, occluding) to strengthen the barrier and improve cell communication.[8,11–13] Vitamin D is also a stimulator of antimicrobial peptides (eg, β-defensins and cathelicidin LL-37) in innate immunity.[8,14] It has been determined that innate immunity and the production of antimicrobial peptides can defend humans against bacteria, viruses, and fungi.[8,14] Vitamin D also plays a role in adaptive immunity in which vitamin D can inhibit T cell proliferation and act as a suppressor of adaptive immunity.[15] As a result, vitamin D insufficiency/deficiency may lead to autoreactive cytotoxic T cell activation, which may result in acceleration of allograft rejection and induction of autoimmune disease.[15] It has also been demonstrated that vitamin D has a role in promoting wound healing and fighting infection.[8,16] As mentioned previously, vitamin D is required for the production of cathelicidin and defensins, which is needed for wound healing and closure. In burns, the lack of defensins has been suggested as a mechanism for increased susceptibility to infection and sepsis.[8,16] Thus, vitamin D deficiency may be the cause of increased susceptibility to infection and increase risk of autoimmune diseases. Together, these data and our results suggest that vitamin D levels play a significant role in infection-related burn complications. One possible explanation of why patients with low vitamin D levels experienced more complications such as bacteremia, septicemia, UTI, pneumonia, and graft loss could be due to the decreased ability to fight infection.

The trend toward higher incidence of complications among those with low vitamin D likely resulted in the increased ICU and hospital LOS observed in the current study. However, since this was a retrospective study, a causal relationship between vitamin D levels and outcomes cannot be directly established considering that other variables could potentially influence the outcomes that were observed. To minimize the interference of these confounding variables, data to depict general health status in our patients were reported including BMI, age, and comorbidities such as diabetes mellitus, hypertension, and heart failure. Based on similar baseline characteristics, with the exception of a higher incidence of diabetes in the normal vitamin D level group, it is unlikely that chronic comorbidities played a factor in the differences observed in clinical outcomes. The nonstatistically significant differences in age and BMI between patients with low vitamin D levels and normal vitamin D levels suggest that these variables may be correlated with vitamin D status. There is a consistent association in the published literature between increasing BMI and lower serum 25D concentrations.[17] Therefore, there is a possibility that BMI and other variables not evaluated could contribute to the observed clinical differences in the current study.

The limitations of this study include inherent limitations related to the retrospective study design and relatively small sample size. Based on the study period spanning more than 6 years, potential changes in practice during this time period could influence outcomes. The population included primarily relatively small burns and a predominance of partial-thickness injury, limiting application of the results to patients with severe burn injury. This study was also limited to a single burn center in Central Ohio, which limited the geographic representation within the population. The results from this study may not be applicable to areas with lower incidence of vitamin D insufficiency/deficiency based on more sun exposure, varying seasons, and time of sunrise/sunset. Finally, the role of vitamin D supplementation was not evaluated among our patients in this study because it was found that the majority of patients with low vitamin D levels were not treated with vitamin D on admission. This was attributed to relatively short hospital LOS leading to the potential for hospital discharge before the availability of the 25D laboratory result and subsequent assessment for potential vitamin D supplementation by the burn team.

A high proportion of patients presenting with burn injury were observed to have baseline vitamin D insufficiency and deficiency. Low vitamin D levels in patients presenting with burn injury were associated with a higher incidence of complications and with longer ICU and hospital LOS compared with normal vitamin D status, despite similar severity of burn injury. Additional studies are needed to further correlate vitamin D status and clinical outcomes among patients with burn injury. In addition, the role of vitamin D supplementation in this population warrants exploration.

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