25-Hydroxyvitamin D Deficiency : Impacting Deep-Wound Infection and Poor Healing Outcomes in Patients With Diabetes

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Abstract

BACKGROUND: The Kingdom of Bahrain has a high incidence of diabetes and associated foot complications. Simultaneously, low 25-hydroxyvitamin D (25[OH]D) levels are common in this population and may be associated with the traditional clothing used in desert climates.

METHODS: This investigation compared 25(OH)D levels and glycemic control with quantifiable wound healing parameters in a prospective, analytic, nonexperimental, cross-sectional pilot study. Consecutive consenting adult patients (N = 80) who presented to the regional wound care unit in January 2016 with either an existing or new wound were included. Collected data included three-dimensional wound photography, NERDS and STONEES criteria, and an X-ray with a positive probe-to-bone test. Blood values for 25(OH)D and hemoglobin A1c (HbA1c) were collected simultaneously.

RESULTS: Diabetes mellitus (types 1 and 2) was present in 90% of the sample patients. No patient had sufficient 25(OH)D levels; 15% had insufficient levels (30–50 ng/mL), and deficiency (levels <#20 ng/mL) was found in 85% of the sample. Males were slightly less affected by 25(OH)D deficiency compared with females (82.4% vs 91.3%). Poor glycemic control (HbA1c levels >#6.8%) was found in 69.4% (n = 50) of the persons with diabetes included in the sample. Those with both diabetes mellitus and a 25(OH)D deficiency (76.3%; n = 61) were more likely to demonstrate healing difficulty (40.9%; n = 25) or present with a stalled or deteriorating wound (44.2%, n = 27). A 3° F or higher periwound surface temperature elevation over a mirror image site was present in 82.5% of all wounds. Exposed bone in the ulcer base was found in 50% of the cases. For persons with diabetes, general linear modeling statistical analysis (adjusted R2 value = 47.9%) linked poor wound healing with three studied variables: 25(OH)D deficiency, poor glycemic control, and an exposed bone in the wound bed.

CONCLUSIONS: Vitamin D may be an overlooked factor in the pathophysiology of diabetic foot ulcer development and subsequent delay in wound healing outcomes. The authors recommend adding 25(OH)D deficiency to the list of multifactorial aggravating factors providers should consider correcting in this subgroup of patients.

INTRODUCTION

The Kingdom of Bahrain is an island between Saudi Arabia and the United Arab Emirates; the population numbers 1,620,608,[1] comprising local Bahraini and a migrant/expatriate population. The estimated prevalence of diabetes in Bahrain ranges from 8.2%[2] to 20%.[2]

The authors' tertiary public wound and hyperbaric oxygen unit in Al Sayh, Bahrain, sees a high wound-related workload. The clinical burden includes diabetes-related wound complications such as diabetic foot ulcers (DFUs). Despite addressing glycemic control (high hemoglobin A1c [HbA1c]) with attention to correcting the underlying cause (inadequate vascular supply correction, deep and surrounding infection management, and pressure offloading), wound healing often remains suboptimal.

Objective

Because both 25-hydroxyvitamin D (25[OH]D) deficiency (<20 ng/mL [normal, ≥50 ng/mL]) and diabetes mellitus (HbA1c) impact the immune response of patients, it became a priority to study the general glycemic status of patients with wounds. This study investigated whether 25(OH)D deficiency could be associated with the negative wound bed status indicators and poor wound healing outcomes observed in persons with wounds and diabetes mellitus. The basic objectives were to

- determine baseline 25(OH)D levels in consecutive patients with an existing or newly developed wound attending the authors' wound care unit for dressing changes over a period of 31 days; and
- examine the relationships among 25(OH)D status, glycemic control, and local wound bed indicators (superficial or deep and surrounding infection) on healing outcomes.

BACKGROUND

Vitamin D Deficiency in Bahrain

Although western Asia has abundant sunlight, 25(OH)D deficiency is common and thus frequently studied in the region. Golbahar et al[3] found 25(OH)D concentrations below 20 ng/mL in 49.4% (9.16 ± 4.04 ng/mL) of a sample of 500 healthy Bahraini blood donors (250 males and 250 females aged 15–65 years). There was a higher prevalence of insufficiency and deficiency in females (67.6%) than in males (31.2%) that increased 1.6-fold during the summer months. This was attributed to the cultural dress worn by both sexes in summer months, with a head cover and full-body protection against the sun ($P < .0001$). [3]

Two additional cross-sectional studies evaluating 25(OH)D levels followed thereafter on mothers and newborns (n = 403 mothers and n = 403 newborns)[4] and the fathers of these families (n = 364).[5] The populations of both studies represent a younger age group than in the Golbahar study. In the first study, 33% of the mothers and 52.9% of the newborns[4] had deficient 25(OH)D values (<#20 ng/mL). Of the fathers in the second study, 64% had insufficient 25(OH)D (<#50 ng/mL).[5]

The Link to Diabetes

The countrywide newborn study[5] suggested a link between 25(OH)D deficiency and early-onset type 1 diabetes. [6] This hypothesis was supported by another study of Bahraini children with type 1 diabetes who were newly diagnosed (N = 18) [7] ; 22% had a 25(OH)D deficiency,

and 28% had insufficient levels. Mean participant age was 9 years (± 2 years), and girls were more affected than the boys, with a close to significant difference (P < .06) found in the 25(OH)D levels of males (23.2 ± 4 ng/mL) compared with levels found in females (16.52 ± 4 ng/mL).[7]

Al Saweer[8] studied 168 adult patients with diabetes to determine their nutrition profile and found that 65% had 25(OH)D levels lower than 20 ng/mL. A small randomized controlled study (RCT) in 2009 (n = 41) supported an inverse relationship between low 25(OH)D levels and higher HbA1c.[9] This inverse correlation was also present in the treatment group of 337 patients with diabetes studied in Kurdistan, compared with a nondiabetic control group of 146 persons who did not reveal the same inverse relationship.[10]

DFUs, Vitamin D Status, and Wound Infection

In a study completed by He et al,[11] 861 persons with type 2 diabetes were evaluated regarding 25(OH)D status and the presence of diabetic peripheral neuropathy. 25(OH)D deficiency was positively correlated with existing diabetic peripheral neuropathy in 80% of the cases (odds ratio, 2.59 [1.48–4.53]). After linear regression analysis, 25(OH)D deficiency was determined to be a statistically significant independent risk factor for diabetic peripheral neuropathy (R2 = 0.88).[11]

In an RCT from Tiwari et al[12] who studied patients with diabetes and an infected foot ulcer, an associated risk of severe 25(OH)D deficiency less than 25 nmol/L (10 ng/mL) was also detected. Those with a diabetic foot infection were significantly more 25(OH)D deficient than patients with diabetes without a foot infection (P < .0001).

In a follow-up study by the same team, the presence of inflammatory cytokines was compared with the 25(OH)D status of 112 persons with a diabetic foot infection and compared with 109 control participants with diabetes.[13] A 25(OH)D deficiency was observed in 48.2% of this sample versus 20.5% of the controls. They also found significantly higher concentrations of interleukin 6, interleukin 1β, and tumor necrosis factor α in the diabetic foot infection group compared with the control group. They associated the altered immune response of patients with a foot infection with severe 25(OH)D deficiency.[13]

When the effect of 25(OH)D deficiency was correlated to the risk of developing sepsis and subsequent mortality for patients admitted to the ICU,[14] researchers found that 54% of patients were 25(OH)D deficient. The all-cause 30-day mortality was significantly higher in patients deficient in 25(OH)D (37% vs 20%; P = .04) and remained higher at 90 days (51%, vs 25%, P = .005). In a multivariate analysis, 25(OH)D deficiency was independently associated (odds ratio 2.7; 95% CI, 1.39–18.8; P = .02) with an increased 30-day mortality from sepsis-related conditions.[14]

Vitamin D Supplementation

Razzaghi et al[15] conducted an RCT on 60 patients with diabetes and Wagner grade 3 DFUs to determine the impact of 25(OH)D supplementation on wound size reduction and other metabolic markers. After a 12-week intervention, the wound size reduction in the treatment arm was double compared with the placebo group, with a mean HbA1c reduction of 0.6% compared with the 0.1% achieved without supplementation. Serum C-reactive protein levels

(reference range, 0.8–3 µg/mL) showed a reduction of 0.4 (±2.5) µg/mL in the treatment arm compared with an increased level of 1.9 (±4.2) µg/mL in the placebo arm.[15] In Kempker and colleagues'[16] systematic review, 25(OH)D supplementation was determined to be a cost-effective measure to correct low 25(OH)D and combat innate immunity loss leading to sepsis, especially in patients who were critically ill. This immunity loss associated with low 25(OH)D may explain the higher susceptibility to the development of sudden-onset deep and surrounding wound infection observed in persons with diabetes.[12–14]

Wound Infection and Assessment

Chronic wound infection assessment differs from its acute counterpart in that chronic infection markers are more difficult to discern than in acute infection. Two sets of wound bed status indicators, NERDS (local infection/critical colonization) and STONEES (deep or surrounding wound infection),[17] have been developed to serve as a consistent means of measurement of chronic wound infection in clinical practice. The NERDS criteria are N, Nonhealing wound; E, Exudate increased; R, Red friable granulation tissue; D, Debris; and S, Smell. The STONEES criteria are S, Size increased; T, Temperature increase of 3° F or greater versus a contralateral site; O, Os (Latin for bone); N, New skin breakdown; E, Edema/Erythema; E, Exudate increased; and S, Smell.

According to the literature, the most significant marker in the STONEES criteria is an increased skin surface temperature of 3° F or more when compared with the contralateral mirror-image area[18] This marker is eight times more likely to accurately predict deep or surrounding wound infection when accompanied by two other STONEES criteria;[19] this has been further validated in studies that compared different noncontact infrared thermometry methods.[20]

METHODS

All consenting patients (existing or newly referred, in consecutive order) with any type of wound who presented to the study wound care unit during January 2016 were included (N = 80). Patients had to be 18 years or older, sign a written consent, and agree to have the required laboratory investigations. Ethical approval was obtained from the King Hamad University Hospital Education and Proficiency Ethical Committee (reference KHUH/Research/no. 147/2016).

Data Collection Methods, Instruments, and Measurements

Primary data collected were blood work results (25[OH]D and HbA1c levels). Other investigations included a random blood glucose test (to account for any undiagnosed diabetes mellitus in patients without a previous diagnosis), a set of vital signs, a surface thermometry measurement of the wound and a mirror-image area on the body (to detect surface temperature differences as seen in Figures 1 and 2), and three-dimensional photographs to determine wound healing duration and outcome. Patients without diabetes were excluded from having an HbA1c obtained if their postprandial random blood glucose test was lower than 7.5 mmol/dL. The Wagner scoring system was used to classify DFU severity.

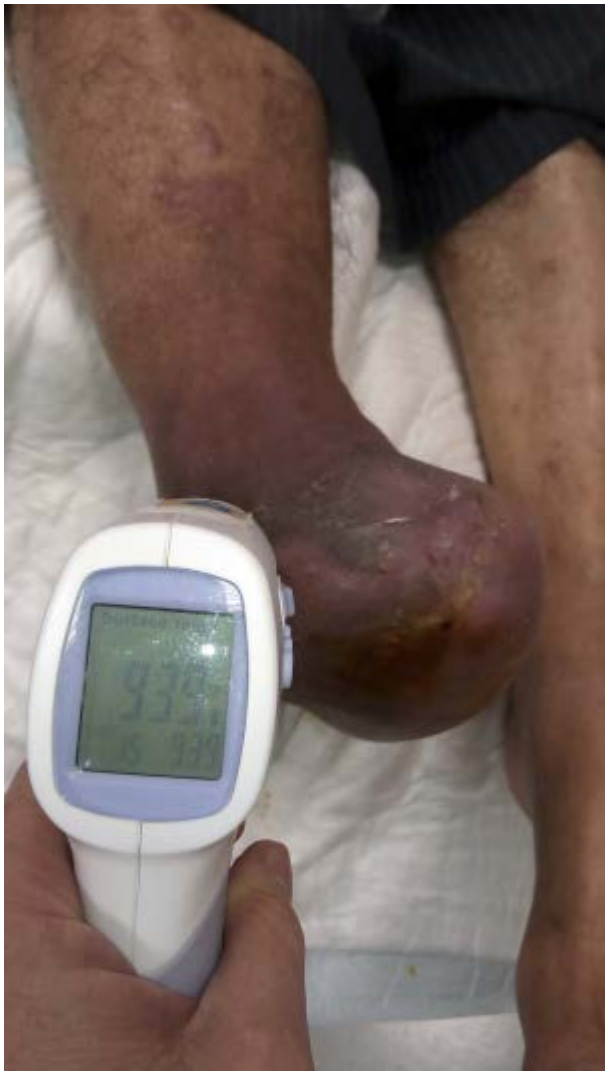

Figure 1. SURFACE SKIN TEMPERATURE ON AFFECTED LIMB (93.9° F). Positive STONEES criteria: temperature increase, os, erythema, and pain. Photograph used with patient permission.

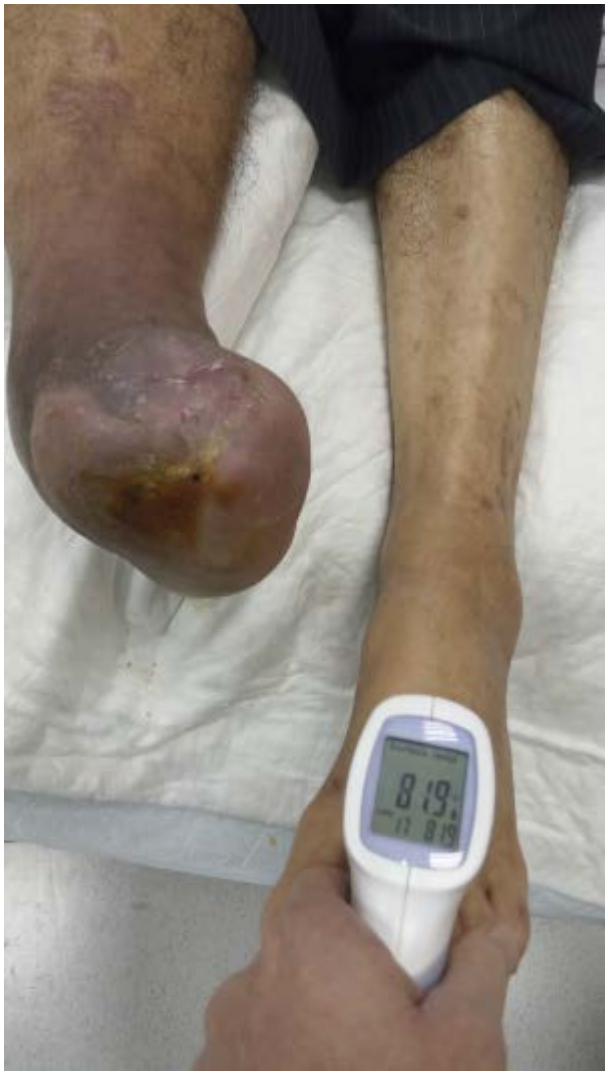

Figure 2. SURFACE SKIN TEMPERATURE ON CONTRALATERAL LIMB (81.9° F). Positive STONEES criteria: temperature increase, os, erythema, and pain. Photograph used with patient permission.

Wounds were assessed for STONEES criteria, including the probe-to-bone test (Os) and then added to determine a total number of criteria present; three or more indicated deep or surrounding wound infection. For a positive Os (exposed bone) criterion, an anterior-posterior and oblique view X-ray was requested to determine the presence of underlying osteomyelitis or untreated Charcot foot complications to expedite orthopedic intervention and antibiotic treatment as depicted in Figure 1 (see also Figures 2 and 3).

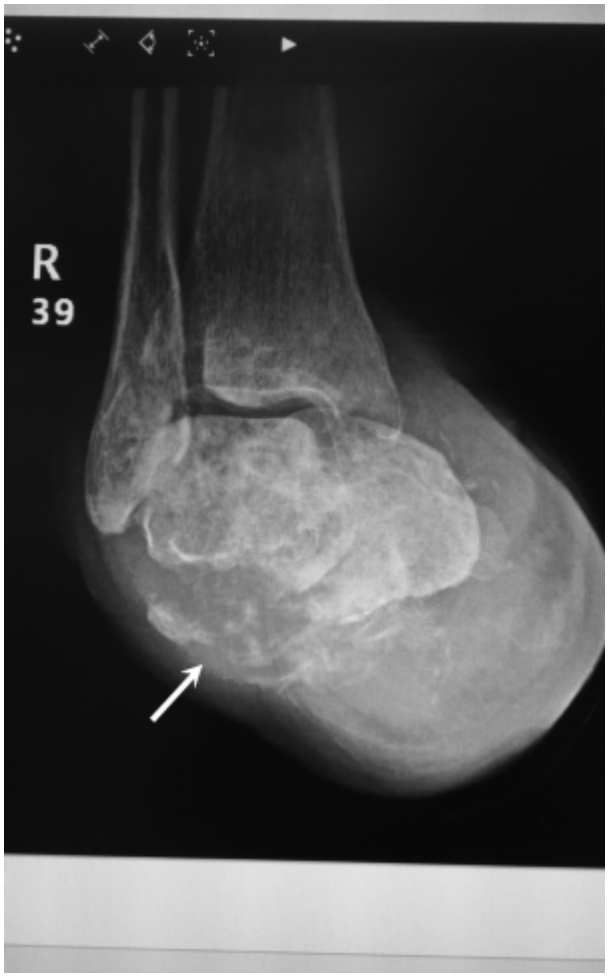

Figure 3. X-RAY OF AFFECTED LIMB. The affected limb is 12° warmer than the contralateral limb with bone destruction clearly visible at the arrow. X-ray used with patient permission.

Quantifiable wound status data using three-dimensional photography (Silhouette camera; ARANZ Medical, Christchurch, New Zealand) were used to calculate surface area/percentage of healing achieved and presented in a linear progress graph. Because all existing patients had this photographic data prospectively collected (it is a standard assessment modality used during visits to the authors' unit), it was a valid assessment set to analyze. All new patients were assessed in the same manner and followed up for the duration of the study.

Data Analysis

All data were entered into a spreadsheet by the investigators after verifying every finding with laboratory results, X-rays, and daily wound documentation sheets. The statistician who was involved in the analysis transferred that spreadsheet into SPSS 13.0 (IBM Corp, Armonk, New York) to perform one-way analysis of variance, Spearman correlation analysis, and $\chi 2$ tests.

In an attempt to model the relationship between the independent variable (variation of wound status) and some of the dependent variables (either in isolation or together) in this study, general linear models were created (with wound size as the dependent variable). One of the outcomes is known as the R2 value, depicting a statistical measure of how closely the data are connected to the established regression line. As additional measurement, an

adjusted R2 could be employed to support the initial R2 after adjustment for the number of predictors present in the linear model. The adjusted R2 increases only if statistical adjustment improves the model more than would be expected by chance and is more reliable than R2 alone.RESULTSOf the total sample (N = 80), 48% were older than 60 years (mean, 50 years), and 71.3% were male (Table 1). Diabetes mellitus was present in 90% of participants (n = 72), and an HbA1c greater than 6.8% was found in 62.5% (n = 45). An HbA1c in excess of 10% (indicating severe poor glycemic control; mean HbA1c, 8.15 was present in 13 patients with diabetes. Of the total sample, 76.3% (n = 61) had both diabetes mellitus and a 25(OH)D deficiency.

Table 1.

FREQUENCY DISTRIBUTION OF SAMPLE (N = 80)

Marker	Measure	Frequency	Percentage	High Risk, %
Age, y	<40	13	16.25	
	40–59	28	35.0	
	60–69	24	30.0	
	>70	15	18.75	48.75
Sex	Female	23	28.8	
	Male	57	71.3	
25(OH)D status	Deficiency <20 ng/mL	68	85.0	
	Insufficiency <50 ng/mL	12	15.0	100
	Sufficient >50 ng/mL	0	0.0	
HbA_{1c}	Nondiabetic	8	10.0	
	≤6.8	22	27.5	
	6.9 to 9.9	37	46.3	
	10 or higher	13	16.3	62.6
Wound status	Progressing; >30% healed in 4 wk	17	21.3	
	Slow healing; <30% healed in 4 wk	31	38.8	
	Stalled healing	12	15.0	
	Deterioration	20	25.0	78.8
STONEES criteria met	<3	34	42.5	
	>3	46	57.5	57.5
Surface temperature differential	<3° F	14	17.5	
	>3° F	66	82.5	82.5

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; HbA_{1c}, hemoglobin A_{1c}.

Because of wound complexity, prolonged wound duration (ie, wounds slow to heal, stalled, or deteriorated; mean, 138 days; range, 0–490 days) was found in 78.8% (n = 63) of the sample (Table 1). Wound parameter such as an increased surface temperature 3° F or more (mean, 4.3° F) was present in 82.5% of the sample (n = 66). Three or more STONEES criteria (with or without exposed bone) were found in 57.5%, (n = 46) with an overall mean of 2.5 STONEES criteria per person (Table 2).

Table 2.

FREQUENCY DISTRIBUTION OF QUANTIFIABLE MARKERS

Marker	n	Mean	Median	Mode	SD	Range	Minimum	Maximum
Age, y	80	55.8	59	63	15.9	71	18	89
25(OH)D level, ng/mL	80	12.4	11.5	4.2	7.8	44.8	4.2	49.02
HbA_{1c} (patients with diabetes)	72	8.15	8	8.7	2.2	10	4.3	14.30
Ulcer, d	80	138.8	88.5	9	143.8	490	0	490
% Healing	80	25.1	39.5	0	77.1	500	–400	100
% Healing per wk	80	1.48	2.1	0	21.39	181.90	–100	81.90
Temperature >3° F difference	80	4.3	4	3	2.81	10	0	10
Total STONEES criteria met	80	2.5	3	3	1.55	7	0	6

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; HbA_{1c}, hemoglobin A_{1c}.

The mean achieved 25(OH)D level was 12.4 (SD, 7.8) ng/mL (range, 4.2–49.02 ng/mL), indicative of severe 25(OH)D deficiency. Cross-tabulated findings revealed that 25(OH)D deficiency (<#20 ng/mL) was present in 91.3% of females and 82.4% of males (Table 3). When compared with the subgroup of participants with diabetes with an elevated HbA1c (>#6.8%; n = 50), 88% (n = 44) demonstrated a 25(OH)D deficiency of less than 20 ng/mL (Table 3).

Table 3.

COMPARISON OF VITAMIN D STATUS AND OTHER VARIABLES

		Vitamin D Status			
Variable		Deficient (<20 ng/mL)	Insufficient (≥20 ng/mL and <50 ng/mL)	Sufficient (≥50 ng/mL)	Total
Sex	Female	21	2	0	23
	Male	47	10	0	57
Metabolic control	Nondiabetic	7	1	0	8
	HbA_{1c} ≤6.8%	17	5	0	22
	HbA_{1c} 6.8%–9.9%	33	4	0	37
	HbA_{1c} ≥10%	11	2	0	13
Wound healing	Progressing (>30%/4 wk)	16	1	0	17
	Slow healing (<30%/4 wk)	25	6	0	31
	Stalled healing (0%/4 wk)	8	4	0	12
	Deteriorating (<0%/4 wk)	19	1	0	20
Surface temperature	<3° F difference	12	2	0	14
	≥3° F difference	56	10	0	66
Os criterion	No bone involvement	35	5	0	40
	Positive probe-to-bone test	33	7	0	40
STONEES criteria	Negative	28	6	0	34
	Positive	40	6	0	46
Total patients		68	12	0	80

Abbreviation: HbA_{1c}, hemoglobin A_{1c}.

Mean wound healing achieved per week was 1.48%, or 5.9% per 30 days, much lower than the 30% per 4 weeks' progress expected of healable wounds.[21] A slow healing rate was present in 38.8% (n = 31) of the total sample (Table 1), but of the subgroup of patients with diabetes (n = 72), 41.6% (n = 30) showed slow healing, and 25% had deteriorating wounds (n = 18).

An increased surface temperature of more than 3° F was recorded over a contralateral mirror-image comparator in 82.5% (n = 66) of the patients (Tables 1 and 3). An exposed bone in the wound bed (positive Os criterion, as seen in Figures 2 and 3) was present in 33 persons with 25(OH)D deficiency (41.3%; Table 3) and 35 persons with diabetes (48.6%; Table 4).

Table 4.

COMPARISON OF HBA_{1C} AND OTHER VARIABLES

Variables		HbA_{1c} Nondiabetic	HbA_{1c} ≤6.8%	HbA_{1c} 6.81%–9.9%	HbA_{1c} ≥10%	Total
Sex	Female	5	4	9	5	23
	Male	3	18	28	8	57
Vitamin D status	Deficient (<20 ng/mL)	7	17	33	11	68
	Insufficient (≥20–<50 ng/mL)	1	5	4	2	12
	Sufficient (≥50 ng/mL)	0	0	0	0	0
Wound healing	Progressing (>30%/4 wk)	3	5	4	5	17
	Slow (<30%/4 wk)	1	9	18	3	31
	Stalled (0%/4 wk)	2	3	7	0	12
	Deteriorating (<0%/4 wk)	2	5	8	5	20
Surface temperature	≤3° F difference	2	2	8	2	14
	>3° F difference	6	20	29	11	66
Os exposed	No bone involvement	3	12	18	7	40
	Positive probe-to-bone test	5	10	19	6	40
STONEES criteria	Negative for infection	3	7	19	5	34
	Positive for infection	5	15	18	8	46
Total		8	22	37	13	80

Abbreviation: HbA_{1c}, hemoglobin A_{1c}.
Gray box depicts subgroup of patients with diabetes with poor glycemic control. Brown box depicts the extent of poor wound healing in the subgroup of persons with diabetes regardless of glycemic control.

Statistically Significant Findings

Poor wound healing was statistically associated with both older age and higher HbA1c levels ($P < .0001$) on the one-way analysis of variance test. A further link was present between poor wound healing where three or more STONEES criteria, an exposed bone in the wound bed, or a 3° F temperature difference was present in the surrounding skin ($P < .006$).

The Spearman two-tailed test using a 1% level of significance correlated poor wound healing outcomes with older age as well as lower 25(OH)D levels. Correlations at this same level of significance were also present between older age and

- a 3° F or greater local versus contralateral mirror-image temperature increase,
- patients with three or more STONEES criteria (including the aforementioned temperature increase); and
- a wound with exposed bone (Os criterion).

Further correlations between length of wound duration and male sex and wound deterioration over time with either STONEES' Os or Temperature criteria were also present ($P = .05$).

General Linear Modeling

Using adjusted R2 values (Table 5), the combination of 25(OH)D and the presence of three or more STONEES criteria could only explain 8.9% of the variation in achieved wound healing status. When considering 25(OH)D and glycemic control, this value dropped to 3.2%. However, with the addition of a third factor (three or more positive STONEES criteria), 31.3% of the achieved wound healing status could be explained. When two metabolic markers (25[OH]D and HbA1c) were compared with a separate wound-related criterion from the STONEES set, it clearly revealed that an exposed bone in the wound bed (positive Os criterion) could explain 49.4% of the variation in achieved wound healing status.

Table 5.

GENERAL LINEAR MODELING: PATIENTS WITH AND WITHOUT DIABETES (N = 80)

Equation No.	Equation[a]	Adjusted R^2
1	Wound status = $\alpha + \beta_1 \times$ vitamin D level + $\beta_2 \times$ metabolic control + ε	0.032
2	Wound status = $\alpha + \beta_1 \times$ vitamin D level + $\beta_2 \times$ positive STONEES + ε	0.089
3	Wound status = $\alpha + \beta_1 \times$ vitamin D level + $\beta_2 \times$ metabolic control + $\beta_3 \times$ positive STONEES + ε	0.313
4	Wound status = $\alpha + \beta_1 \times$ vitamin D level + $\beta_2 \times$ metabolic control + $\beta_3 \times$ Os + ε	0.494

[a]Where α represents the intercept; β_1, β_2, and β_3 represent the coefficient of the respective variables; and ε represents the error term.

General Linear Modeling of Patients with Diabetes

The data of all persons with diabetes (n = 72) were analyzed separately to eliminate any confounding effects that the patients without diabetes may have had on the first round of general linear modeling (Table 6). 25(OH)D and the presence of three or more STONEES criteria increased the adjusted R2 score from 8.9% in the total sample to 17.1% in the diabetes-only group. The adjusted R2 value for 25(OH)D, glycemic control, and the presence of three or more STONEES criteria increased from 31.3% to 42.1%. These three factors therefore played a larger role in the achieved wound healing status of a patient with diabetes as compared with participants overall. Exposed bone remained an important criterion together with low 25(OH)D levels and poor glycemic control, explaining 47.9% of the wound outcomes.

Table 6.

GENERAL LINEAR MODELING: PATIENTS WITH DIABETES (N = 72)

Equation No.	Equation[a]	Adjusted R^2
5	Wound status = $\alpha + \beta_1 \times$ vitamin D level + $\beta_2 \times$ metabolic control + $\beta_3 \times$ positive STONEES + ε	0.421
6	Wound status = $\alpha + \beta_1 \times$ vitamin D level + $\beta_2 \times$ metabolic control + $\beta_3 \times$ Os + ε	0.479
7	Wound status = $\alpha + \beta_1 \times$ vitamin D level + $\beta_2 \times$ positive STONEES + ε	0.171

[a]Where α represents the intercept; β_1, β_2, and β_3 represent the coefficient of the respective variables; ε represents the error term.

DISCUSSION

In a study of 500 healthy Bahraini blood donors[3] without diabetes, 49.4% had 25(OH)D concentrations of less than 20 ng/mL; clearly, the Bahraini population is at general risk of 25(OH)D deficiency. This is further supported by research such as the mother and newborn study[4] and in the fathers of those newborns.[5]

In this study, 72 patients with diabetes and wound-related complications were documented as part of the sample. 25(OH)D deficiency (<#20 ng/mL) was present in 61 of those patients (84.7%). This finding supports previous research in that patients who are diabetic with poor glycemic control are prone to 25(OH)D deficiency.[7–10] This study also identified that this finding is more likely with a diabetes-related open wound present on the foot. Further, these findings support the correlation between older age coupled with both 25(OH)D deficiency and poor glycemic control.[22,23]

It is accepted in literature that males are more likely to have diabetes-related complications, [24–26] which may also include foot-related wounds. The results found in the males of this sample confirm this observation. However, the high presence of 25(OH)D deficiency found in the male population (82.4%) compared with 91.3% of the female population was an unexpected finding. In this study, the male sex was not protective against 25(OH)D deficiency when diabetes and a wound-related complication were comorbidities.

The overall severity of 25(OH)D deficiency found in this study (85%) is suggestive that the presence of a diabetes-related wound may be a positive indicator of a potential low 25(OH)D level. When 25(OH)D deficiency was compared with wound infection markers, half of the sample had either a positive Temperature criterion, Os criterion, or STONEES set of three or more criteria present. When those markers were compared with the maintenance of glycemic control, half of the sample again had an exposed bone, along with two or more other STONEES clinical signs present.

Of note, more than two-thirds of patients with a 25(OH)D deficiency presented with a positive increase in surface temperature over a mirror-image site, indicating a high likelihood of the presence of deep or surrounding wound infection.[17–19] A 3° F temperature increase on a foot of an individual with diabetes, even without additional STONEES criteria, should not be ignored. It may be indicative of sustained tissue trauma that could lead to ulcer formation. High-quality self-monitoring studies of patients with diabetes[27–29] have confirmed that a 3° to 4° F temperature increase on any area of the foot should be followed by plantar pressure redistribution and rest until the temperature subsides to prevent subsequent skin breakdown.

In this study, the inability of a wound to heal could not conclusively be attributed to a 25(OH)D deficiency, poor glycemic control, or even the presence of local infection markers individually, although it does support the studied 25(OH)D deficiency trend already identified in the Bahraini population[4–6] and also supports that 25(OH)D deficiency is associated with diabetes mellitus.[8–10,22–26] However, the simultaneous identification of local wound bed status indicators was important. Surface temperature differentials and a positive STONEES set of three or more clinical signs positively correlated to poor wound outcomes in the presence of either 25(OH)D deficiency or poor glycemic control.

Limitations

The study facility is located in a tertiary care hospital with hyperbaric oxygen therapy chambers. Most patients referred here are those with DFU (Wagner grade 3 or higher) complications and live within a confined island population. The study was designed to incorporate a small consecutive sample (N = 80) over a short study period to remain within reasonable clinical expenditure. These results should therefore be contextualized by the fact that this is a cross-sectional pilot study designed to support the premise that 25(OH)D deficiency should be considered when wound healing difficulty in persons with diabetes-related wound complications is encountered.

By designing an RCT as a follow-up to this cross-sectional study, the causal link supported by these results could be scientifically validated, defining 25(OH)D levels as an important cofactor that delays or prevents DFU healing. Prospective scientific studies (ideally RCTs) are required to demonstrate that patients with diabetes receiving 25(OH)D supplementation can obtain sufficient serum levels to support wound healing. These sufficient levels need to be linked to improved HbA1c levels and accelerated ulcer healing along with the management of the signs of infection.

CONCLUSIONS

In this study, a correlation was found between poor wound healing outcomes and the presence of poorly controlled diabetes mellitus and 25(OH)D deficiency. These factors were detrimental to the ability of wounds to avoid deep and surrounding wound infection (especially with increased surface temperature or an exposed bone present in the base of the wound bed). It also added to a delay in achieving the expected 12-week wound healing trajectory.

Vitamin D status may be an overlooked factor in the pathophysiology of DFU development and subsequent delay in wound healing outcomes. The strongest statistical associations (adjusted R2 = 49.4%) linked delayed DFU healing in participants with diabetes to 25(OH)D deficiency, poor glycemic control, and exposed bone in the wound bed.

As a result of this study, the initial wound assessment protocol at the study facility has changed; providers now obtain 25(OH)D and HbA1c levels simultaneously with the standard wound assessment procedures. This approach aids providers in considering multifactorial aggravating factors in this subgroup of patients as part of a holistic care plan.[21]

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