Severe vitamin D deficiency is common in critically ill patients at a high northern latitude

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Background: Critically ill patients at southern latitudes have been shown to have low vitamin D levels that were associated with prolonged hospital stay. To our knowledge no studies have been conducted on vitamin D status amongst critically ill patients at high northern latitudes. Despite the Icelandic population traditionally taking vitamin D supplements, we hypothesized that the majority of critically ill patients in Reykjavik, Iceland have low vitamin D levels.
Methods: This was a prospective observational study on 122 patients admitted to Landspitali University Hospital intensive care unit. Serum vitamin D (25(OH)D) was measured in all patients on two occasions (first and second day). The prevalence of vitamin D deficiency and its effect on hospital stay was calculated.
Results: Only 9% of patients had vitamin D levels recommended for good health (>75 nmol/l) and 69% were deficient (25(OH)D < 50 nmol/l). The average difference between the first and second vitamin D samples was 2.8 nmol/l. Forty-three percentage of the severely vitamin D deficient stayed in the ICU for more than 4 days compared to 19% of patients with better status ($P = 0.196$).
Discussion: Vitamin D deficiency is very common in critically ill patients at high northern latitudes and patients with severely deficient vitamin D levels had trend towards longer intensive care unit stay. Furthermore, 43% of the patients had vitamin D levels under 25 nmol/l that is associated with osteomalacia. It appears that a single vitamin D measurement gives a reasonable clue about the vitamin D status in critically ill patients.

Editorial comment: what this article tells us
Vitamin D supplementation for various patient groups is a controversial issue. Beneficial effects from high dose supplementation to critically ill patients with very low plasma concentrations have been reported. This study characterizes vitamin D status in a Scandinavian critical care cohort from Iceland.

Vitamin D and its metabolites, the circulating 25-hydroxyvitamin D (25(OH)D) and the active 1-25-dihydroxyvitamin D (1,25(OH)2D), are fat soluble vitamins or pro-hormones. Their essential role in bone metabolism and musculoskeletal health has long been known. In later years

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their more complex role in many different metabolic pathways in the human body has been described.[1]

Despite increased public awareness of the importance of vitamin D the prevalence of vitamin D insufficiency has been increasing in the general population. Vitamin D deficiency is now highly prevalent worldwide and has been recognized as a pandemic.[2,3]

This pandemic combined with more understanding of the complex role of vitamin D has led to vitamin D deficiency being associated with many non-musculoskeletal chronic diseases like cancer, cardiovascular diseases, autoimmune diseases and diabetes mellitus.[1,3]

Although there is still some controversy concerning what serum 25(OH)D value should be considered sufficient, the Endocrine Society has defined vitamin D deficiency as a 25(OH)D value of 50 nmol/l or less, vitamin D insufficiency as 50–75 nmol/l and vitamin D sufficiency as 75 nmol/l or greater for children and adults.[4] Moreover, severe vitamin D deficiency is frequently described as 25(OH)D value below 25 nmol/l.[5]

Serum levels of 25(OH)D have been shown to be inversely associated with all-cause, cardiovascular, cancer and respiratory disease, however the role of vitamin D in acute critical illness is less well-studied and understood. Recent studies have suggested association between serum 25 (OH)D levels and acute respiratory infections and acute myocardial infarction.[6,7]

Two recent studies from countries at southern latitudes showed that low levels of vitamin D are common in intensive care patients and low levels were associated with prolonged hospital stay and increased mortality. In both studies only a single serum 25(OH)D level measurement was performed.[8,9]

In a recently published preliminary study on 14 intensive care patients it was shown that serum 25(OH)D levels vary when measured every hour over 24 h suggesting that a single random measurement not necessarily reflects the correct vitamin D status of critically ill patients. The variability was reduced when any two or three measurements were used within the 24 h.[10]

Landspitali University Hospital is located in Reykjavik, Iceland (64° North), a high latitude location where the winter season is long. For over 6 months of the year ultraviolet B photons are blocked by the atmosphere so they cannot influence the synthesis of vitamin D in the skin. Even in the summer the large solar zenith angle causes inhibition of ultraviolet B radiation so that hardly any vitamin D can be produced in the skin before 10:00 hours and after 15:00 hours. This contributes to vitamin D deficiency with seasonal variation at northern latitudes.[11] Despite good public awareness of vitamin D importance for health and the good availability of inexpensive vitamin D supplements, vitamin D deficiency is common.[12–15] No national vitamin D fortification programme exists in Iceland.

We hypothesized primarily that a significant proportion of the critically ill patients in Reykjavik had low vitamin D and secondarily that low vitamin D was associated with longer hospital stay. To this date vitamin D in critically ill patients has not been prospectively measured at similar high northern latitude.

Materials and methods

Participants

Approval for the study was obtained from the National Bioethics Committee (Hafnarhusid, Tryggvagata 17, 101 Reykjavik, Iceland; Protocol no. VSN 13-042-S1) and the Data Protection Authority (Raudararstig 10, 105 Reykjavik, Iceland; Protocol no. 2013020322VEL/-). A written informed consent was obtained from every participant or a close relative. Adult patients, 18 years or older, admitted to the ICU of Landspitali University Hospital for 12 hours or longer were prospectively included between February 2014 and September 2015. Patients admitted after elective major surgery were excluded from the study. The patients were evenly distributed over the different seasons of the year, but otherwise not selected.

The ICU serves both medical and surgical patients in the only tertiary care hospital in Iceland. The following clinical data were collected from patients' charts during hospital stay: Gender, age, height, weight, indication for ICU admission, major underlying diseases, ICU length of stay, readmission to the ICU, duration of mechanical ventilation, APACHE-II score,

hospital length of stay, vitamin D (25(OH)D) serum concentrations and routine blood tests (haemoglobin values, white blood cell count, sodium, potassium, creatinine, ionized calcium, C-reactive protein).

Patients' vital status was followed throughout the hospital stay or for 90 days from admission to the ICU, whichever was longer.

Patients' vitamin D status was classified according to the classification of the Endocrine Society and previous studies as sufficient (25(OH)D > 75 nmol/l), insufficient (25(OH)D 50–75 nmol/l), deficient (25(OH)D 25–50 nmol/l) and severely deficient (25(OH)D < 25 nmol/l).[4,5]

Laboratory

For measurement of 25(OH)D, blood samples were drawn from every patient within 24 h following admission to the ICU and then again during the following 48 h. The two consecutive measurements in every patient were done to reduce a possible inaccuracy due to variability of serum 25(OH)D in patients over time. Additionally a third sample was drawn from a subgroup of 20% of all patients within a time frame of three to 90 days following the first sample for comparison. The third samples were therefore drawn following the early acute phase of illness and were drawn in order to screen for a possible lack of correlation with the samples drawn in the early acute phase of illness. The third sample may reflect deviation from baseline 25(OH)D level possibly altered due to the acute illness. 25(OH)D was measured in the serum of every participating patient, using Elecsys® Vitamin D total assay by Roche Diagnostics, an electro-chemiluminescence binding assay, as previously described.[16]

Statistical analysis

The primary outcome parameter were serum vitamin D (25(OH)D) concentrations and secondary outcomes included serum vitamin D concentrations below 25 nmol/l, ICU length of stay and hospital length of stay. Based on pilot data 120 subjects were considered sufficient to describe the topic and answer the main question of the study. Data registration, analysis and preparation of graphical figures were performed using Microsoft® Office Excel® 2007 and R version 3.2.2 statistical software. Descriptive statistics were used to describe patients' baseline characteristics. Descriptive statistics were also used to describe the primary outcome, results of 25(OH)D measurements and classifications of vitamin D deficiency. Baseline characteristics and secondary outcomes were analysed separately for the severely vitamin D deficient patients and others. Difference in baseline characteristics between the two groups was evaluated with multiple *t*-tests, chi-square tests and Fisher's exact tests. Paired *t*-test was used to compare repeated measurements of 25(OH)D. In all analysis *P*-values less than 0.05 were considered statistically significant.

Results

During the study time 122 patients admitted to the ICU of Landspitali University Hospital were included in the study. Table 1 shows the baseline characteristics of the study population. The majority of the patients were males (64%), mean age 65 years and mean BMI of 27 kg/m^2. APACHE-II score ranged from 4 to 38 with a mean score of 20 which predicts hospital mortality of 35%.[17]

In Fig. 1 the primary outcome, 25(OH)D values of the study population, are shown. Nine percent of all included ICU patients had sufficient levels of vitamin D, 25(OH)D > 75 nmol/l. Sixty-nine percentage of the patients were classified as vitamin D deficient and 43% severely deficient. Mean 25(OH)D value in all three separate measurements were similar, ranged from 38 to 41 (Fig. 2).

The most common reason for ICU admission was severe sepsis in 20% of patients, followed by respiratory failure (18%) and severe bleedings (15%). Most patients had multiple comorbidities with hypertension, smoking and coronary heart disease being the most common (Table 1).

The secondary outcome variables are shown in Table 2, comparing severely vitamin D deficient patients to others but these groups did not significantly differ in baseline characteristics except that coronary heart disease was less common in severely vitamin D deficient patients than other patients (23% vs. 44%, $P = 0.026$).

Table 1 Baseline characteristics.

Characteristics	Total study group (n = 122)
Age, mean (SD), years	66.0 (14.4)
Gender, count (ratio), M/F	78/44 (1.8)
BMI, mean (SD), m^2/kg	26.7 (6.1)
APACHE II, mean (SD), count (%)	20 (8)
<15	37 (30)
15–23	44 (36)
>23	41 (34)
Reason for admission, count (%)	
Acute abdominal surgery	8 (7)
Bleeding	18 (15)
Cardiac arrest	16 (13)
Heart failure	4 (3)
Myocardial infarction	5 (4)
Renal failure	6 (5)
Respiratory failure	22 (18)
Sepsis	24 (20)
Other	19 (16)
Comorbidity, count (%)	
Coronary heart disease	43 (35)
Hypertension	73 (60)
Insulin dependant diabetes mellitus	9 (7)
Non-insulin dependant diabetes mellitus	13 (11)
Heart failure	31 (25)
Liver disease	8 (7)
Metastatic cancer	20 (16)
Lung disease	33 (27)
Renal disease	18 (15)
Peripheral vascular disease	8 (7)
Cerebrovascular disease	12 (10)
Smoking	62 (51)
Alcohol abuse	17 (14)

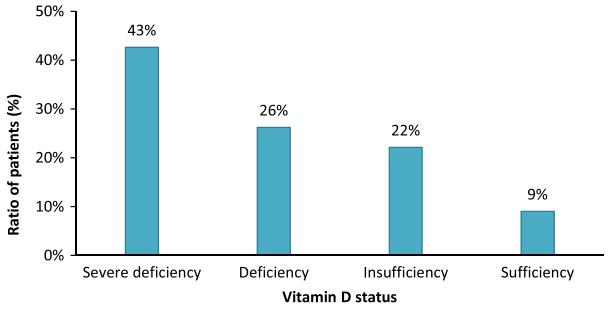

Fig. 1. Primary outcome. Classification of vitamin D status according to mean of two measurements of 25(OH)D in 122 ICU patients.

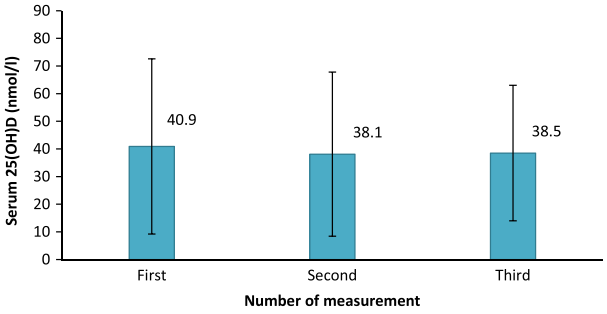

Fig. 2. Mean 25(OH)D values on three separate. One hundred and twenty-two patients were measured in the first and second measurement and a subgroup of 23 patients were measured in the third measurement. Error bars show the standard deviation.

Both 90-day and in hospital mortality for the study population were 25%. There was no difference in in-hospital, 30-, 60- or 90-day mortality between severely vitamin D deficient patients and others (13 vs. 17, P = 0.502, 12 vs. 16, P = 1.000, 14 vs. 17, P = 0.470 and 14 vs. 17 P = 0.639 respectively). The severely vitamin D deficient patients (25(OH)D > 25 nmol/l) had trend towards longer hospital stay, ICU stay and time on mechanical ventilation compared with other patients although these results were not statistically significant (Table 2).

Table 3 shows comparison of vitamin D levels between different subgroups of patients. Patients with coronary heart disease had significantly higher vitamin D than patients without and patients with metastatic cancer had significantly lower vitamin D than patients without the disease.

The first vitamin D measurements were slightly higher than the second (mean difference 2.8 nmol/l). A subgroup of 23 patients was measured three times. The third measurement was on average done 18 days (range 3–86) after the first measurement. Figure 3 shows comparison of classification of vitamin D status of these patients according to different measurements.

Discussion

The results of this study reveal that critically ill patients at high northern latitude are at very high risk for being vitamin D deficient and that the severely vitamin D deficient patients may have a longer hospital stay than other patients. In fact only about one in every ten patients had vitamin D levels recommended for maintaining

Table 2 Secondary outcomes.

Outcomes	25(OH)D < 25 nmol/l (n = 52)	25(OH)D ≥ 25 nmol/l (n = 70)	Study group (n = 122)	P-value
Mortality, count (%)				
In hospital	14 (27)	17 (24)	31 (25)	0.741
30-day	12 (23)	16 (23)	28 (23)	0.977
60-day	14 (27)	17 (24)	31 (25)	0.741
90-day	14 (27)	17 (24)	31 (25)	0.741
Hospital stay				
ICU stay, count (%), days				
<2	11 (22)	25 (35)	36 (30)	0.196
2–4	18 (36)	22 (31)	40 (33)	
>4	23 (46)	23 (19)	46 (38)	
Mechanical ventilation, count (%), days				
0	15 (29)	32 (46)	47 (39)	0.166
1–3	17 (33)	17 (24)	34 (28)	
>3	20 (38)	21 (30)	41 (34)	
Hospital stay, count (%), days				
<10	18 (35)	24 (34)	42 (34)	0.435
10–19	15 (30)	27 (39)	42 (34)	
>19	19 (37)	19 (27)	38 (31)	

Chi-square test comparison of severely vitamin D deficient and others. P-values < 0.05 considered statistically significant.

Table 3 Vitamin D values in different patient categories.

Binomial baseline variables	Yes (nmol/l)	No (nmol/l)	P-value
Male	39.3	39.8	0.931
Coronary heart disease	49.5	34.1	0.008*
Hypertension	43.5	33.6	0.060
Insulin dependant diabetes mellitus	36.6	39.7	0.717
Non-insulin dependant diabetes mellitus	49.1	38.4	0.408
Heart failure	48.9	36.3	0.091
Liver disease	26.2	40.4	0.053
Metastatic cancer	26.0	42.2	0.005*
Lung disease	44.0	37.8	0.374
Renal disease	38.7	39.6	0.924
Peripheral vascular disease	63.4	37.8	0.130
Cerebrovascular disease	45.1	38.9	0.536
Smoking	41.0	38.0	0.590
Alcohol abuse	44.9	38.6	0.453
Binomial secondary outcome variables			
Mortality			
In hospital	37.2	40.3	0.615
30-day	40.2	39.3	0.905
60-day	38.3	39.9	0.803
90-day	38.3	39.9	0.803

Mean serum values of 25(OH)D from two measurements according to binomial variables and t-test comparison. P-values < 0.05 considered statistically significant and are marked with *.

good health.[4] Furthermore, 43% of the patients had vitamin D levels under 25 nmol/l that is associated with osteomalacia. This in spite of the fact the level of education in the population studied is relatively high, the tradition to take vitamin D supplements is general and massmedia have in recent years repeatedly reported stories suggesting the importance of taking supplementary vitamin D, which is readily available and inexpensive. The results of the present study show that vitamin D deficiency was as common and even more common than previously reported among critically ill patients at more southern latitudes.[9,18–20]

The results of the current study also show that, although there is some intrapatient variability in vitamin D serum concentrations in repeated measurements over days, the absolute difference is rather small suggesting that vitamin D serum concentrations measured in critically ill patients are sufficiently accurate to guide clinical supplementation.

The current results may be viewed in light of a recent report that showed low levels of vitamin D in anaesthesia and intensive care staff at

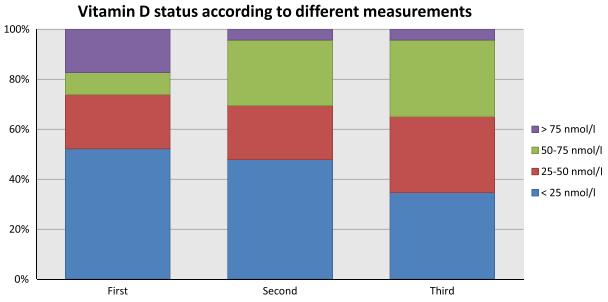

Fig. 3. Vitamin D (25(OH)D) values, for the subgroup of 23 patients who were measured three times, according to classification of vitamin D status. There was not a statistically significant difference in classification of vitamin D status between the measurements.

Landspitali despite high ratio of staff taking vitamin D supplements.[21] Thus, it seems plausible that vitamin D status of critically ill patients is similarly poor or worse.

The association of vitamin D deficiency with worse outcomes in multiple chronic diseases is

clear from several studies and according to a recent Cochrane meta-analysis vitamin D supplementation in the elderly might reduce mortality.[22–24] The results of this study shows a trend towards worse outcomes in acute critical illness for the vitamin D deficient.

The discovery of vitamin D receptors in immune cells has led to researchers revealing vitamins D role in the innate and adaptive immune system. 1,25(OH)2D stimulates the production of cathelicidin, an antimicrobial peptide, in innate immune cells and a study indicated impairment of bacteriocidality in vitamin D deficiency especially in septic critically ill patients.[25] On the other hand its role in the adaptive immune system is inhibitory. 1,25(OH)2D has a suppressive effect on cytokines and is considered to reduce the severity of systemic inflammatory response in the critically ill. Therefore, it is rational to further study effects of vitamin D in the critically ill. This is supported by recent review that demonstrated 38–100% prevalence of vitamin D insufficiency and deficiency in the critically ill.[18]

Several studies have shown that vitamin D deficiency is a predictor of acute kidney injury, sepsis and all-cause mortality in critically ill patients.[19,20,26] Recently Flynn et al. [27] studied the effects of vitamin D deficiency in critically ill surgical patients and showed that low vitamin D levels were associated with longer hospital stay, organ dysfunction and increased infection rates. Venkatram et al. [28] demonstrated an association between vitamin D insufficiency and hospital mortality in medical intensive care patients.

It has to be taken into consideration, when interpreting 25(OH)D in critical illness, that while vitamin D has been shown to reduce the systemic inflammatory response, the systemic inflammatory response has also been shown to reduce serum levels of 25(OH)D.[29,30] It is not clear how critical illness affects serum 25(OH)D levels but several other nutritional biomarkers have also been shown to be reduced during inflammatory state. 25(OH)D levels may be lowered in acute critical illness compared to normal state because of increased conversion to 1,25(OH)2D for stimulation of innate immunity. The illness leading to ICU admission may also have lowering effects on 25(OH)D by increasing immobility and decreasing sun exposure.[19] In addition, fluid resuscitation and haemodilution may dilute the 25(OH)D concentration. Patients admitted to ICU often undergo massive fluid resuscitation. This could lead to an overestimation of vitamin D insufficiency and deficiency when using measurements during the initiation of intensive care. This is a limitation to the current study. However, a study on patients undergoing cardiopulmonary bypass showed that 25(OH)D levels almost returned to baseline 24-h following bypass and had returned to baseline at 5 days following bypass. Taking into consideration these alterations in the serum concentration of 25(OH)D in critical illness, repeated measurements might be helpful in evaluating vitamin D status in the ICU.[31] Vitamin D is highly bound to vitamin D binding protein. The critically ill have been shown to have lower levels of vitamin D binding protein than healthy individuals and some assays for measuring 25(OH)D underestimate the circulating amount under these circumstances. However, the laboratory assay used in the current study has not shown such underestimation.[32]

Another strength of the current study is that serum 25(OH)D was measured twice for all patients reducing the effect of 24-h variability of serum 25(OH)D value and a subgroup of patients was measured three times for comparison.[10] According to the results of the study, a single measurement of 25(OH)D in acute illness gives a reasonably good clue about the patients vitamin D status and may be a useful guide in supplementation. On the other hand, one of the study weaknesses is that serum 25(OH)D measured in critical illness might not accurately reflect patients' baseline value although measured more than once as stated earlier.

This study adds to the growing literature on vitamin D status of the critically ill by providing new information on patients at high risk for vitamin D deficiency because of their high northern latitude residency. Vitamin D supplementation is widely available, relatively inexpensive and well-tolerated.[4,33] It is necessary to consider if vitamin D supplementation in acute critical illness might improve outcome. Some intervention studies have recently been published, however to this date the results of these have been inconclusive.[33] The VITdAL-ICU trial by Amrein et al.[34]

showed lower mortality with vitamin D supplementation only in patients with severe vitamin D deficiency. In conclusion, and considering the results of observational studies so far, there is a need for further study of this question, where a dose finding study would be important before going to a large multicentre randomized controlled interventional trial, assessing the effects of vitamin D supplementation on outcomes in acute critical illness.

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