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A prospective investigational study of vitamin D status in patients with hospital-acquired pneumonia

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Abstract

Introduction Hospital-acquired pneumonia (HAP) is the most common healthcare-associated infection (HCAI) contributing to death. Rising antimicrobial resistance has resulted in few effective antibiotics for HAP. Stimulation of human immunity and immunomodulation have been reported as a role of vitamin D.

Objectives The objectives of this study were to investigate vitamin D status of HAP patients and to examine if vitamin D status was related to the severity of HAP.

Method Patients with a diagnosis were recruited for a 3-month period from two acute hospitals. Vitamin D levels of participants were obtained.

Key findings Sixty-one participants were recruited with a mean age 72 years, with 77% of the participants over 65 years of age. Severe HAP was diagnosed in 92% of the participants, 5% had moderate and 3% had mild HAP. Vitamin D deficiency (<50 nmol/L) was found in 80% of the participants and 41% of the participants were found to be suffering from severe vitamin D deficiency (<15 nmol/L). Participants that had adequate vitamin D levels (12/61) (20%) were all taking prophylactic vitamin D on admission. Overall, 26/61 (43%) of the participants were taking prescribed prophylactic vitamin D supplementation on admission and despite this supplementation,14/26 (54%) were found to be vitamin D deficient.

Conclusion Vitamin D deficiency was highly prevalent in the HAP participants. Vitamin D deficiency was also present in some participants, despite prescribed prophylactic supplementation. Vitamin D stimulates immunity and hence vitamin D deficiency would have potentially increased the susceptibility of acquiring HAP.

Keywords: hospital-acquired pneumonia; vitamin D; severity of infection

Introduction

Healthcare-associated infections (HCAIs) are a common and a serious issue within healthcare systems, with over 300,000 patients a year in England experiencing a HCAI.[1] Hospital-acquired respiratory infections affect 1.5% of inpatients in England at any time, with more than half of these being cases of hospital-acquired pneumonia (HAP).[2] HAP is the most common HCAI contributing to death in the UK, with an estimated attributable mortality of 10%.[3]

HAP occurs 2 days or more after hospital admission and is defined as pneumonia that was not incubating at admission.[4, 5] Many bacteria that cause HAP, particularly the Enterobacterales *Escherichia coli* and *Klebsiella pneumoniae*, have become multi-drug resistant, including resistance to carbapenems.[6] Mortality rates associated with carbapenem-resistant Enterobacterales infections range from 29% to 52%.[7] Carbapenem-resistant HAP often requires the use of older nephrotoxic agents such as intravenous colistimethate. Resistance to colistimethate, has been reported in many countries including the UK,[8] limiting its utility. Vitamin D's role in infection defence, particularly in respiratory-tract infections, has become more of interest,[9, 10] with associations with tuberculosis infections,[11, 12] and a higher predisposition to severe infections and mortality in critically ill patients.[13] Observational studies suggest that correction of vitamin D deficiency may lead to a reduction in antibiotic consumption.[14, 15]

Intracrine synthesis of 1,25-dihydroxyvitamin D takes place when 25-hydroxyvitamin D is present, that is, in people who have adequate vitamin D levels. The locally synthesised 1,25-dihydroxyvitamin D has antibacterial, antiproliferative and anti-inflammatory properties.[10] Intracrine formation of 1,25-dihydroxyvitamin D occurs in many tissues such as lungs, placenta, skin and the gastrointestinal-tract and hence vitamin D deficiency may lower immunity to many infections. Additionally, vitamin D deficiency can lead to hypocalcaemia which in turn causes impairment of neutrophil and lymphocyte activity.[16] Low vitamin D levels will therefore cause an impairment of immunity; increase susceptibility to infections; and worsen patient outcomes.[16]

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Aim/Objectives

This research aimed to investigate the vitamin D status of HAP patients and to examine if this was related to the severity of HAP. We hypothesised that HAP patients would be deficient in vitamin D (<50 nmol/L) and that the severity of HAP may be related to vitamin D status.

Ethics Approval

The study was approved by the London - Chelsea Research Ethics committee (16/LO/0171) on 21 January 2016 and the Trust Research and Development department on 7 February 2016.

Method

This prospective study recruited HAP patients from the Sandwell and West Birmingham Hospitals (SWBH) *NHS* Trust across two sites between 1 March 2016 and 31 May 2016. Inclusion criteria were patients who were 18 years and above; could provide written informed consent and diagnosed with HAP during the study period on any medical ward, surgical ward and critical-care unit on either site. Exclusion criteria were paediatric patients; obstetric patients; patients diagnosed with community-acquired pneumonia (CAP), ventilator-associated pneumonia and other respiratory infections.

After obtaining consent, routine blood samples were measured using an LL-MS assay (liquid chromatography and mass spectrometry) to screen the serum vitamin D level. Vitamin D deficiency was defined as serum 25-hydroxyvitamin D_3 < 50 nmol/L and <15 nmol/L as severe deficiency as per SWBH biochemistry laboratory interpretation. The participant demographics, speciality admitted under, medications taken, severity of HAP and vitamin D status were collated and analysed using SPSS version 22.

Results

Sixty-one participants were eligible and recruited to the study during the 3-month period. The mean age was 72 years and ranged from 21 to 95 years. Most of the participants were over 65 years (Table 1) and the majority of the participants were white 48 (79%) (Table 2).

A third of the participants (34%) were recruited from Elderly care wards and 15% of the HAP participants required critical-care admission (Table 3).

Fifty-six participants (92%) were suffering from severe HAP, three (5%) had moderately severe HAP and two participants (3%) had mild HAP.

Table 1. Participants' demographics

	Frequency $N = 61$	%	Over 65 years	% over 65 years
Male	35	57	27/35	77
Female	26	43	20/26	77
Total participants that were over 65 years of age			47/61	77

Table 2. Participants' ethnicity, age, and sex

	Frequency $N = 61$	%	Over 65 years	% over 65 years
Black Asian and Minority Ethnic (BAME)	13	21	7/13	54
BAME and female	4	7	2/4	50
BAME and male	9	15	5/9	56
White	48	79	40/48	83
White and female	22	36	18/22	82
White and male	26	43	22/26	87

Table 3. Clinical specialty of participants

Specialty	Frequency $N = 61$	%
Elderly care	21	34
Critical care	9	15
Respiratory	7	11
Surgical	7	11
Gastroenterology	4	7
Oncology	3	5
Cardiology	3	5
Urology	2	3
General Medicine	2	3
ENT	1	2
Haematology	1	2
Neurology	1	2

Table 4. Vitamin D status of participants

Vitamin D level range and interpretation	Participants $N = 61$	White $N = 48$	BAME $N = 13$
Severe deficiency (<15 nmol/L)	25 (41%)	19 (40%)	6 (46%)
Deficiency (15–30 nmol/L)	15 (24%)	13 (27%)	2 (15%)
Deficiency/Insufficiency (30.1–50 nmol/L)	9 (15%)	7 (15%)	2 (15%)
Adequate/ normal range (>50–220 nmol/L)	12 (20%)	9 (19%)	3 (23%)
Toxic (>220 nmol/L)	0 (0%)	0 (0%)	0 (0%)

The majority participants in this study, that is, 49/61 (80%) were vitamin D deficient, that is, vitamin D levels of < 50 nmol/L. Twenty-five participants (41%) were suffering from severe vitamin D deficiency, that is, vitamin D levels < 15 nmol/L (Table 4). Vitamin D levels ranged from 10.3 nmol/L to 116.8 nmol/L, with an average of 31.6 nmol/L. Vitamin D status was similar in the white and BAME participants.

The participants that had adequate vitamin D levels 12/61 (20%) were all taking prophylactic vitamin D supplementation in the form of Adcal-D_3 tablets on admission.

Twenty-six participants (43%) were on prophylactic Adcal-D_3 supplementation on admission, with 14 of these participants vitamin D deficient despite supplementation.

Data did not follow a normal distribution and hence the Kruskal–Wallis test, was used for analysing the relationship between vitamin D levels (continuous-variable) and the severity of HAP (categorical variable with three categories). There was no statistical difference in the vitamin D levels of participants in the three HAP severity groups (mild, moderate and severe) Kruskal–Wallis test ($H(2) = 5.643$, $P = 0.06$).

Discussion

Vitamin D deficiency was prevalent in (80%) in the HAP participants with more than a third suffering from severe vitamin D deficiency (41%). Studies in CAP have found similar levels of vitamin D deficiency. A German study[17] found 82% of CAP patients ($n = 300$) were vitamin D deficient. In a Finnish study[18] of 1412 CAP patients, 65% were found to be vitamin D deficient. In a Dutch study[19] of 272 CAP patients, 53% were found vitamin D deficient. It is not surprising to find our results match with these findings.

The prevalence of vitamin D deficiency in the general population is 23% in those aged 19–64 years and 21% in those over 65 years of age.[20] Forty-five of the participants in this study (77%) were aged over 65 years and with a prevalence of vitamin D deficiency (80%) roughly four times higher. The majority of the participants were white and vitamin D status in this study was similar in the white and BAME participants.

Although vitamin D supplementation was regular prophylactic medication for nearly half of our study participants (43%), only one in two of those on prophylaxis had adequate vitamin D levels. This may point to insufficient initial therapeutic doses of vitamin D or non-adherence to therapy.

An association between the severity of HAP and vitamin D levels was not established in this study. However, since most of the participants were suffering from severe HAP (92%), this made it hard to reach this conclusion.

The agreed consent process was time-consuming, limiting the recruitment of potential HAP participants, leading to a small sample size. Potential participants suffering from mild to moderate HAP on oral antibiotics may have been discharged before being recruited to the study, leading to a higher proportion of severe HAP participants. As patients suffering from severe HAP were prescribed intravenous antibiotics and had longer hospital-stay this may have led to a selection bias. This study did not have a matched control group of non-HAP participants to compare the vitamin D of non-infected individuals; however, the high proportion of vitamin D deficiency compared to the general population suggests vitamin D deficiency may be a risk factor in HAP.

Future research should be supported by translators as the language barrier and the need to ensure informed consent is obtained, meant that potential participants who did not understand English were not invited to participate in the research.

However, there are no studies to our knowledge that have specifically researched vitamin D levels in HAP patients in general medical and surgical wards. This study was the first study that involved screening of serum vitamin D levels of HAP participants on general wards and included critical-care participants.

The prevalence of 80% vitamin D deficiency in this study, highlights the need to check vitamin D levels of HAP patients, especially for patients who are >65 years of age. NICE has recommended testing vitamin D levels of all individuals aged 65 years and above as they are deemed high risk.[21] In this study, 77% of the participants were >65 years of age. The findings of this study also support the growing body of literature[22] that recommends fortification of common foods such as cereals, bread and yoghurt as measures to prevent vitamin D deficiency in the general population. Setting up online education campaigns to increase public knowledge on the role of adequate vitamin D in maintaining immunity may prove beneficial.

Future studies should also include a control group of healthy non-HAP participants and should be designed to explore whether correction of vitamin D levels prevents further episodes of HAP or lowers antibiotic consumption in adults aged 65 years and above.

Conclusion

This study has found a high prevalence of vitamin D deficiency in HAP patients (80%), which is a likely risk factor. Despite the use of prophylactic vitamin D treatments in some HAP patients, some patients still had vitamin D deficiency suggesting under-dosing or poor adherence. No association was seen between HAP severity and vitamin D levels.

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Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Munira Ratansi. The first draft of the manuscript was written by Munira Ratansi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

Data Availability

Data for the study are available from the author Munira Ratansi.

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