


Vitamin D status in patients with chronic obstructive pulmonary disease at Chris Hani Baragwanath Hospital, Johannesburg, South Africa

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Background. There has been a growing interest in nutritional/lifestyle factors, including vitamin D, that may affect chronic obstructive pulmonary disease (COPD). Most data are from Caucasian populations and temperate climates, with minimal African data.

Objectives. The primary objective was to determine the prevalence of vitamin D deficiency (25-hydroxyvitamin D (25(OH)D) ≤ 20 ng/mL) and insufficiency (25(OH)D 21 - 29 ng/mL) among patients with COPD. Secondary objectives were to investigate the association between vitamin D and demographic/lifestyle factors, lung function parameters, markers of COPD severity and corticosteroid use.

Methods. A prospective, cross-sectional study of 76 patients with COPD was conducted at a tertiary hospital in Johannesburg, South Africa. Patients were interviewed regarding demographic/lifestyle factors, COPD severity markers and corticosteroid therapy. The most recent spirometry result was recorded. Blood samples were taken for measurement of calcium, alkaline phosphatase and vitamin D levels. Patients were stratified according to vitamin D status (deficiency and non-deficiency (25(OH)D > 20 ng/mL, i.e. combined insufficiency and adequate levels)), and statistical analysis was performed to assess for associations.

Results. The sample included 72% males and 63% black African patients. The prevalences of vitamin D deficiency and insufficiency were 48% (95% confidence interval (CI) 42 - 54) and 35% (95% CI 30 - 41), respectively. A Modified Medical Research Council (mMRC) dyspnoea score ≥ 2 was associated with a relative risk of 1.34 (95% CI 1.05 - 1.7) for vitamin D deficiency in univariate analysis. In multivariate regression analysis, only sunlight exposure (< 1 hour/day) was an independent predictor of vitamin D deficiency (odds ratio 2.4; 95% CI 1.3 - 4.5).

Conclusion. There was a high prevalence of suboptimal vitamin D levels in this COPD sample population. A higher mMRC score was associated with an increased risk of vitamin D deficiency, while low sunlight exposure was the only independent predictor of vitamin D deficiency.

Keywords. Vitamin D, vitamin D deficiency, vitamin D deficiency prevalence, 25(OH)D, COPD, chronic obstructive pulmonary disease.

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Study synopsis

What the study adds. This is the first study to provide prevalence data regarding vitamin D status in COPD patients in sub-Saharan Africa. The study highlights a relationship between vitamin D status and both symptom severity and sunlight exposure.

Implications of the findings. Owing to the high prevalence of suboptimal vitamin D status among COPD patients, it may be useful to screen patients for vitamin D deficiency, especially those with a more severe phenotype. There may be scope for further studies to evaluate whether vitamin D supplementation corrects the deficiency and provides any clinical outcome benefit.

Globally, > 170 million people are affected by chronic obstructive pulmonary disease (COPD), and COPD accounted for ~ 3.2 million deaths in 2015.^[1] Low- and middle-income countries bear a significant burden of COPD mortality. There has been a growing interest in

nutritional and lifestyle factors that may affect COPD. Globally, numerous studies have demonstrated a high prevalence of vitamin D deficiency in patients with COPD.^[2-10] Notably, most data are from Caucasian populations in countries with developed economies and

temperate climates. There is a paucity of data on the prevalence of COPD and vitamin D deficiency in Africa and among non-Caucasians.

Vitamin D₃ is predominantly synthesised in the skin. Ultraviolet (UVB) radiation converts pre-vitamin D₃ to vitamin D₃ (cholecalciferol). This step is influenced by the melanin content in the skin and sunlight exposure. The other less significant source of vitamin D is dietary intake. Vitamin D₃ is hydroxylated in the liver to 25-hydroxyvitamin D (25(OH)D). 25(OH)D is the major storage form and is used to ascertain vitamin D status in populations.^[11,12] Vitamin D is predominantly hydroxylated in the kidney to 1,25-dihydroxyvitamin D. This represents the active form of vitamin D, which enhances gastrointestinal absorption of calcium and phosphate and has a positive effect on bone turnover and bone mineral density.^[13]

There has been a growing interest in the non-calcaemic effects of vitamin D, which include immunomodulation.^[14] Vitamin D has been shown to combat mycobacterial and other respiratory infections through the production of cathelicidin (antimicrobial peptide).^[14] This interaction between vitamin D and cathelicidin may be relevant, because infectious exacerbations are linked to COPD disease progression. In addition, vitamin D deficiency has been associated with other respiratory conditions including tuberculosis,^[15] sarcoidosis,^[16] childhood asthma, cystic fibrosis^[13] and recently COVID-19.^[17]

Spirometric correlates concerning the association between the forced expiratory volume in the 1st second (FEV₁) and vitamin D have been conflicting in COPD patients.^[2,3,5,7,8] Most studies demonstrated a correlation between vitamin D levels and symptom scores,^[6,8,9,18] as well as ethnicity and sunlight exposure,^[5-7,9,18] among COPD patients.

Objectives

We therefore studied the prevalence of vitamin D deficiency and insufficiency (25(OH)D \leq 20 ng/mL and 21 - 29 ng/mL, respectively) in COPD patients in South Africa (SA). Secondary objectives were to look for an association between vitamin D and demographic/lifestyle factors, lung function parameters, markers of COPD severity, and corticosteroid type and dosage.

Methods

Study design

This was a prospective, cross-sectional study of COPD patients.

Study population

Patients with spirometry-confirmed COPD were included, as per the Global Initiative for Obstructive Lung Disease (GOLD) 2019 guideline.^[19] For inclusion, participants had to have a post-bronchodilator FEV₁/forced vital capacity (FVC) ratio $<$ 70% together with at least one of the classic symptoms of COPD – chronic cough, dyspnoea or chronic sputum production. The spirometry result was the most recent in the patient's file, or spirometry was repeated on the date of the interview if no result could be traced in the records. Patients had to be $>$ 18 years of age. Patients were excluded if they had reversible airflow limitation, current active pulmonary tuberculosis, a concomitant diagnosis of asthma, active malignancy, malabsorption or a history of pancreatic insufficiency, or if they were already on vitamin D supplementation.

Study setting

The study was conducted at a tertiary academic hospital in Johannesburg,

SA. Patients were recruited from the outpatient clinic and inpatient wards. Johannesburg is at a latitude of 26.2° south of the Equator.

Sample size

Based on previous studies, \geq 7% of COPD patients have normal vitamin D levels. Using an estimate of 7%, a precision of 5% and a confidence level of 95%, a sample size of 100 was initially aimed for. Unfortunately, owing to COVID-19 spirometry limitations and COVID-19 elective patient number curtailments, a sample size of only 76 patients was reached. Consecutive patients were recruited between November 2020 and July 2022.

Data collection

Data were collected by the investigators using a data sheet. Spirometry was performed if no result was available in the records. Pulmonary function tests were performed using a JAEGER Vyntus SPIRO PC spirometer (Vyaire Medical, USA) with a calculation of the percentage of the predicted FVC and FEV₁ values according to American Thoracic Society/European Respiratory Society recommendations. A 400 μ g dose of salbutamol was administered for post-bronchodilator spirometry. Patient demographic/lifestyle factors, clinical and COPD severity markers, spirometry results, laboratory data and treatment information were collected.

A 3 - 5 mL cuffed venous blood sample was taken in an acid citrate dextrose tube from participants. Samples were transported to the laboratory under cold-chain conditions.

Definitions

Ethnicity. Ethnicity was self-reported by the participants.

Season of sample collection. Dates of blood sample collections/interviews were categorised into seasons. Seasons were defined as follows: summer (December - February), autumn (March - May), winter (June - August), and spring (September - November).

Sunlight exposure. Sunlight exposure was self-reported by the participant and based on recall of the week preceding the interview. Categories were 1 - 4 hours/week, 5 - 6 hours/week, 1 - 2 hours/day, 3 - 5 hours/day and \geq 6 hours/day.

Exacerbation. An exacerbation was based on patient reports/file notes and included episodes requiring oral/intravenous (IV) corticosteroids, antibiotics, a casualty visit, medical practitioner consultation or hospital admission, or worsening of cough, dyspnoea or sputum production ($>$ 2 days).

Smoking status. A patient was regarded as an ex-smoker if they had not smoked for $>$ 3 months. Never-smoker was defined as $<$ 100 cigarettes consumed during the course of the patient's life.

Systemic corticosteroids. This was defined as use of IV/oral corticosteroids during the year preceding the interview.

Low-dose inhaled corticosteroids. This was defined as low- and medium-dose inhaled corticosteroids (fluticasone \leq 250 μ g/day, budesonide 160 μ g/day, and beclomethasone 200 - 400 μ g/day).

High-dose inhaled corticosteroids. This was defined as fluticasone \geq 500 μ g/day, budesonide 320 μ g/day, and beclomethasone \geq 400 μ g/day.

Vitamin D testing and definition

25(OH)D was measured with a double-sandwich immunoassay using a chemiluminescent label at a South African National Accreditation

System (ISO15189)-approved laboratory. The instrument used was the ARCHITECT i2000 (Abbott, USA). This method is traceable to the reference method, namely liquid chromatography-mass spectrometry, and meets the required standards for clinical testing.^[20] There is some variation in levels quoted for vitamin D deficiency and insufficiency in the literature. Definitions used for 25(OH)D in the present study were deficiency ≤ 20 ng/mL, insufficiency 21 - 29 ng/mL, and adequate ≥ 30 ng/mL.^[21]

Statistical analysis

All data obtained were entered onto an Excel spreadsheet, Microsoft 365, version 2405 (Microsoft, USA), by the first author (IK), and then into Statistica v13.3 (StatSoft, USA, currently maintained by TIBCO Software Inc., USA). The prevalence data were provided as percentages with 95% confidence intervals (CIs). The distribution of data was determined from histograms, using the Shapiro-Wilk and Lilliefors tests. Categorical variables were presented as counts (n) and percentages, and comparisons were made in vitamin D-deficient and non-deficient (25(OH)D > 20 ng/mL, i.e. combined insufficiency and adequate levels) groups using the χ^2 test. Continuous variables were summarised as means with standard deviations (SDs) for normally distributed data and medians with interquartile ranges (IQRs) for non-normally distributed data. Independent variables were compared in deficient v. non-deficient groups using the Mann Whitney U -test for independent medians and Student's t -test for independent means.

For multivariate analysis, eight variables were used to predict the presence of vitamin D deficiency or insufficiency. The choice of these variables was based on pathophysiological plausibility and prominence in the literature review regarding their effect on vitamin D levels. There were six continuous variables: age in years, body mass index (BMI), waist circumference, smoking pack history in years, FEV₁ and the Modified Medical Research Council (mMRC) dyspnoea score, and two categorical variables: sunlight exposure (< 1 hour/day v. ≥ 1 hour/day) and ethnicity (black v. non-black). Six variables with a p -value < 0.2 on the univariate model were selected for the final multivariate model.

Ethical considerations

Ethics approval was obtained from the Human

Research Ethics Committee (Medical) at the University of the Witwatersrand (ref. no. M200112) before commencement of the study. Written informed consent was obtained from each participant before recruitment.

Results

We included all 76 patients in our analysis. The study patient characteristics are summarised in Table 1. There were 55 males (72%). The ethnicity profile was as follows: black African 48 patients (63%), coloured (mixed race) 17 (22%), Indian/Asian 8 (11%), and white 3 (4%). The mean (SD) corrected calcium level was 2.25 (0.15) mmol/L and the median (IQR) alkaline phosphatase level 92 (76 - 121) U/L. Fig. 1 shows the sunlight exposure of the study participants.

Primary objective

The prevalence of vitamin D deficiency and insufficiency (25(OH)D < 30 ng/mL) was 84% (95% CI 80 - 88). Table 2 summarises the prevalence and median vitamin D level in each status category. The median (IQR) 25(OH)D level in our sample was 21 (14.5 - 26.5) ng/mL.

Secondary objectives

Univariate analysis

The differences between the vitamin D-deficient and non-deficient groups are

provided in Table 3. There was a relative risk (RR) of vitamin D deficiency for patients with daily sunlight exposure of < 1 hour/day compared with ≥ 1 hour/day of 1.62 (95% CI 1.02 - 2.57) (Fig. 1). There was no difference in vitamin D deficiency between black African and non-black African ethnicity ($p=0.11$). Smoking status (never-, ex- or current smoker) was not compared in the deficiency v. non-deficiency analysis, as two groups with a similar number of participants to facilitate meaningful comparison could not be constituted. The majority of participants were ex- or current smokers ($n=68$; 89%), and only 8 (11%) had never smoked.

There were no significant differences in spirometry parameters (FEV₁ and FEV₁ percentage predicted, FVC and FVC percentage predicted, FEV₁/FVC ratio) between the vitamin D-deficient and non-deficient groups.

Table 3 summarises the severity features and therapeutic differences between the vitamin D-deficient and non-deficient groups. An mMRC dyspnoea score of ≥ 2 was associated with an RR of 1.34 (95% CI 1.05 - 1.7) for vitamin D deficiency compared with a score of < 2 . No significant difference in the deficiency v. non-deficiency groups was noted in number of exacerbations in the preceding year, GOLD grade, GOLD group, use of

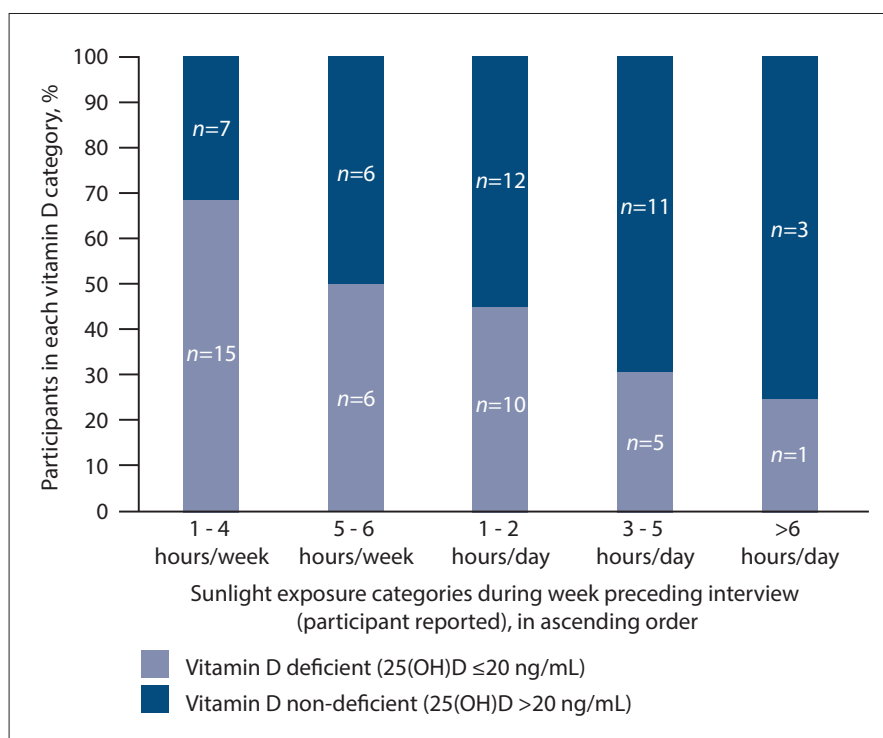


Fig. 1. Vitamin D status in relation to increasing sunlight exposure. (25(OH)D = 25-hydroxyvitamin D.)

inhaled or systemic corticosteroids during the preceding year, or inhaled corticosteroid dosage.

Multivariate analysis

Six variables with a *p*-value <0.2 on the univariate model were selected for the final

multivariate model (Table 4). Only sunlight exposure (<1 hour/day) was an independent predictor of vitamin D deficiency (odds ratio 2.4; 95% CI 1.3 - 4.5).

Table 1. Study patient characteristics (N=76)

Variable	n (%)*
25(OH)D (ng/mL), median (IQR)	21 (14.5 - 26.5)
Age (years), mean (SD)	62 (10)
BMI (kg/m ²), median (IQR)	21 (18 - 25)
Waist circumference (cm), median (IQR)	83 (73 - 92)
Smoking pack-years, median (IQR)	19 (5 - 37)
Season of blood collection	
Summer (December - February)	24 (32)
Autumn (March - May)	30 (39)
Winter (June - August)	12 (16)
Spring (September - November)	10 (13)
Lung function parameters, median (IQR)	
FEV ₁ (L)	1.1 (0.8 - 1.5)
FEV ₁ (% predicted)	41.9 (31.1 - 65.2)
FVC (L)	2.5 (1.9 - 3.1)
FVC (% predicted)	86.1 (59.9 - 99.9)
FEV ₁ /FVC (%)	44.6 (35.6 - 55.5)
Number of exacerbations in past year, median (IQR)	2 (2 - 3)
mMRC dyspnoea score	
0	1 (1)
1	16 (21)
2	15 (20)
3	39 (51)
4	5 (7)
GOLD [†] grade	
1	7 (9)
2	23 (30)
3	30 (39)
4	16 (21)
GOLD [†] group	
A	7 (9)
B	33 (43)
C	9 (12)
D	27 (36)

25(OH)D = 25-hydroxyvitamin D; IQR = interquartile range; SD = standard deviation; BMI = body mass index; FEV₁ = forced expiratory volume in the 1st second;

FVC = forced vital capacity; mMRC = Modified Medical Research Council; GOLD = Global Initiative for Obstructive Lung Disease 2019.

*Except where otherwise indicated. Mean (SD) for normally distributed data, median (IQR) for non-normally distributed data.

[†]Singh *et al.*^[19]

Discussion

The main finding from this study was the high prevalence of vitamin D deficiency (48%) and insufficiency (35%) in the study population. In an analysis of the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) cohort,^[5] with a large sample size of 1 609, 20.6% and 33.2% of participants were vitamin D deficient and insufficient, respectively. The same definitions for vitamin D levels were used in the present study. The proportion with deficiency was significantly lower in the SPIROMICS cohort than in the present study. Some reasons that may account for this discrepancy in findings are a higher proportion of patients with a milder COPD phenotype (majority GOLD grade 2) and a majority of Caucasians (lower skin melanin content) in the US study.

In another large US study, Kunisaki *et al.*^[6] found 40.4% of participants to be vitamin D deficient and 33.1% to be insufficient. This is not dissimilar to our study findings, as the population matched our cohort's COPD disease severity (majority GOLD grade 3 and with a high exacerbation risk). The marginally lower prevalence of deficiency may be accounted for by ethnicity (majority Caucasian participants).

Gawron *et al.*^[22] in a small Polish case-control study found the highest reviewed rates of vitamin D deficiency (90.2%) in COPD patients. Controls had similarly high vitamin D deficiency rates, and these findings may be accounted for by winter-only, nadir vitamin D sampling in a temperate location.

Holick^[14] in a review article quoted a vitamin D deficiency prevalence of 40 - 100% in elderly non-institutionalised healthy people in the USA, and stated that >50% of postmenopausal women with osteoporosis

Table 2. Prevalence of vitamin D deficiency and insufficiency in the study population (N=76)

Vitamin D status	Prevalence, % (95% CI)	n	25(OH)D (ng/mL), median (IQR)
Deficiency and insufficiency (<30 ng/mL)	84 (80 - 88)	64	18 (12.5 - 23.5)
Deficiency (≤20 ng/mL)	48 (42 - 54)	37	14 (11 - 17)
Insufficiency (21 - 29 ng/mL)	35 (30 - 41)	27	25 (22 - 27)
Adequate levels (≥30 ng/mL)	16 (12 - 20)	12	37.5 (31.5 - 38.5)

CI = confidence interval; 25(OH)D = 25-hydroxyvitamin D; IQR = interquartile range.

Table 3. Differences between vitamin D-deficient and non-deficient (insufficient and adequate) groups

Variable	Vitamin D deficiency (25(OH)D ≤20 ng/mL) (n=37), n (%) [*]	Vitamin D non-deficiency (25(OH)D >20 ng/ml) (n=39), n (%) [*]	p-value/RR (95% CI) [†]
Demographic and lifestyle factors			
Age (years), mean (SD)	64 (11)	61 (8)	0.10
Gender male	27/37 (73)	28/39 (72)	0.91
Weight (kg), median (IQR)	58 (53 - 72)	58 (47 - 68)	0.44
Height (m), mean (SD)	1.66 (0.08)	1.66 (0.09)	0.90
BMI (kg/m ²), median (IQR)	20 (19 - 26)	21 (17 - 23)	0.56
Waist circumference (cm), median (IQR)	83 (76 - 94)	83 (72 - 90)	0.44
Smoking pack-years, median (IQR)	24 (7.5 - 40)	17 (5 - 27)	0.13
Lung function parameters, median (IQR)			
FEV ₁ (L)	0.94 (0.69 - 1.49)	1.11 (0.77 - 1.75)	0.18
FEV ₁ (% predicted)	41.20 (28.50 - 53)	42.90 (32.20 - 70)	0.22
FVC (L)	2.39 (1.71 - 3.01)	2.56 (1.95 - 3.32)	0.22
FVC (% predicted)	82 (57.10 - 97.30)	89 (66.14 - 100.40)	0.22
FEV ₁ /FVC (%)	42 (36.27 - 55.50)	47.98 (34.14 - 55.56)	0.72
COPD severity markers			
mMRC dyspnoea score			
<2	4/37 (11)	13/39 (33)	RR of deficiency: 1.34 (1.05 - 1.7)
≥2	33/37 (89)	26/39 (66)	
Number of exacerbations in past year			
≤1	21/37 (57)	27/39 (69)	0.26
>1	16/37 (43)	12/39 (31)	
GOLD [‡] grade			
1	3/37 (8)	4/39 (10)	GOLD 1 and 2 v. 3 and 4: 0.45
2	10/37 (27)	13/39 (33)	
3	14/37 (38)	16/39 (41)	
4	10/37 (27)	6/39 (15)	
GOLD [‡] group			
A	2/37 (5)	5/39 (13)	GOLD A and B v. C and D: 0.80
B	18/37 (49)	15/39 (38)	
C	1/37 (3)	8/39 (21)	
D	16/37 (43)	11/39 (28)	
Therapy			
Use of inhaled corticosteroids in past year			
Yes	33/37 (89)	32/39 (82)	0.38
No	4/37 (11)	7/39 (18)	
Use of systemic corticosteroids in past year			
Yes	21/37 (57)	21/39 (54)	0.80
No	16/37 (43)	18/39 (46)	
Inhaled corticosteroid dose			
Low [§]	8/37 (22)	5/39 (13)	0.39
High [¶]	25/37 (68)	27/39 (69)	

25(OH)D = 25-hydroxyvitamin D; n = number in category; RR = relative risk; CI = confidence interval; SD = standard deviation; IQR = interquartile range; BMI = body mass index, FEV₁ = forced expiratory volume in the 1st second; FVC = forced vital capacity; mMRC = Modified Medical Research Council; GOLD = Global Initiative for Obstructive Lung Disease 2019.

^{*}Except where otherwise indicated. Mean (SD) for normally distributed data, median (IQR) for non-normally distributed data.

[†]All values are p-values except mMRC score, which is RR (95% CI).

[‡]Singh *et al.*¹⁹

[§]Includes low- and medium-dose inhaled corticosteroids (fluticasone ≤250 µg/day, budesonide 160 µg/day, beclomethasone 200 - 400 µg/day).

[¶]Fluticasone ≥500 µg/day, budesonide 320 µg/day, beclomethasone ≥400 µg/day.

Table 4. Binomial logistic regression for vitamin D deficiency (six variables)

Variable	Beta value	SE	p-value
Intercept -1.97			
Age	0.03	0.03	0.29
Smoking pack-years	0.02	0.01	0.25
FEV ₁	-0.64	0.56	0.26
mMRC dyspnoea score	0.25	0.36	0.48
Ethnicity (black v. non-black)	-0.055	0.35	0.11
Sunlight exposure*	0.89	0.31	0.005

SE = standard error; FEV₁ = forced expiratory volume in 1 second; mMRC = Modified Medical Research Council.

*Sunlight exposure <1 hour/day v. ≥1 hour/day.

(without COPD) were reported as having suboptimal vitamin D (25(OH)D <30 ng/mL). A large African meta-analysis^[23] found a population prevalence of 59% for combined vitamin D deficiency and insufficiency, compared with 84% in our COPD study. Similar findings were noted in case-control studies.^[4,9,18] These general population vitamin D deficiency/insufficiency prevalence estimates appear lower than in the COPD population.

Some of the postulated mechanisms for a higher prevalence of vitamin D deficiency in COPD patients include a sicker phenotype, resulting in less sunlight exposure; a poorer diet; smoking resulting in pigmentary skin changes and decreased cutaneous pre-vitamin D₃ activation; possible increased vitamin D catabolism due to corticosteroid use; and lower BMI and hence lower fat/muscle stores of the vitamin.^[13]

Sunlight exposure was significantly associated with vitamin D deficiency in univariate analysis in the present study, and remained the only independent predictor in the multivariate model. This association is evident in many European studies. Jolliffe *et al.*,^[7] in a multicentre cross-sectional study in London with 278 participants, showed that the absence of a recent sunny holiday correlated with vitamin D deficiency in a COPD cohort. Kentson *et al.*^[9] in a Swedish case-control study with 38 COPD patients also found vitamin D deficiency to be associated with a lower ultraviolet score (UVS). The UVS was a composite measure of seasonality and sunlight (UV) exposure. The association between low sunlight exposure and vitamin D is attributable to the vitamin D pathway and UV-dependent skin activation, as mentioned previously.

The present study found a trend towards an association between vitamin D deficiency and a larger number of smoking pack-years, lower FEV₁ and older age. In an Italian cohort, Malinovski *et al.*^[3] found no association between vitamin D level and age or smoking history. A Belgian study^[4] also found no age or current smoking association with vitamin D. Burkes *et al.*^[5] found an inverse trend to our study, with younger age associated with vitamin D deficiency. This trend in our study may be explained physiologically, as age and disease severity may limit mobility, resulting in decreased outdoor sunlight exposure. Also, skin pigmentation can become darker with ageing, decreasing cutaneous vitamin D UV activation. Burkes *et al.*,^[5] and Persson *et al.*^[18] in a multivariate analysis, also showed an association between vitamin D levels and smoking status.

The majority of reviewed studies showed an association between a lower FEV₁ and vitamin D deficiency.^[2,5,7-9,18] Three studies showed no

vitamin D-FEV₁ association.^[3,22,24] The relationship between FEV₁ and vitamin D deficiency in our study may not have reached significance owing to disparate sampling times and a limited sample size.

Our data showed that an mMRC dyspnoea score ≥2 was associated with an increased risk of vitamin D deficiency. Kentson *et al.*^[9] also demonstrated an association between higher symptom scores (which include dyspnoea as a component) and vitamin D deficiency (COPD Assessment Test and mMRC dyspnoea score if not on vitamin D supplementation). Kunisaki *et al.*^[6] made a similar association, but with the St George's Respiratory Questionnaire (SGRQ). In their large Norwegian case-control study, Persson *et al.*^[18] found the same association between mMRC dyspnoea score and vitamin D status in univariate analysis, but not in multivariate analysis, similar to our data. Hyun *et al.*,^[8] in a South Korean study, also found high fibrinogen and low vitamin D to be associated with higher mMRC dyspnoea scores. The outlier in the literature^[7] found no correlation between vitamin D and the SGRQ (with dyspnoea as a component).

Strengths of the present study include an SA context (where data are sparse) and a wide variety of factors investigated. Additionally, a diverse sample of COPD severity was included. Vitamin D levels were measured over all seasons in the study population as a whole (on the date of interview for each patient), which may be more representative of the prevalence of vitamin D deficiency than vitamin D nadir (winter/spring)-only sampling. The majority of patients were recruited from an outpatient department (OPD) setting, reducing the confounding of acute illness. The same investigator conducted surveys and measured parameters, hence negating the effects of inter-investigator inconsistency/variability.

Limitations of this study include a smaller sample size due to COVID-19 clinic number curtailments and spirometry restrictions. It was a cross-sectional study, and vitamin D levels were only measured at a single time/season in each patient. There may be seasonal variations in vitamin D levels in individual patients. No inferences about causality can be made, as vitamin D-deficient participants were not followed up prospectively. No analysis of the comorbidities of participants was made, and these could have affected the results. A single-centre tertiary hospital study may limit the transferability of findings to other COPD populations.

Conclusion

There was a high prevalence of vitamin D deficiency and insufficiency in this COPD sample population. A higher mMRC score was associated

with an increased risk of vitamin D deficiency, while sunlight exposure was the only independent predictor of vitamin D deficiency.

Recommendations

There is scope for case-control studies to evaluate the prevalence of vitamin D deficiency among healthy/hospitalised African participants compared with their COPD counterparts. Given the high prevalence of vitamin D deficiency in COPD patients, routine testing in high-risk groups may be valuable. These findings need to be validated in a milder phenotype COPD population. Future studies should focus on the clinical impact of vitamin D replacement in deficient patients.

Declaration. The research for this study was done in partial fulfilment of the requirements for IK's MMed (Int Med) degree at the University of the Witwatersrand.

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Author contributions. IK wrote the proposal, obtained ethics clearance, collected data, and wrote the final article. SA vB contributed to the conceptualisation of the study, and supervised the protocol and article writing. SO contributed to the conceptualisation of the study, supervised the protocol, assisted in data interpretation, and supervised the article writing. MK assisted with data collection and editing the protocol and article. SK assisted with data collection.

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