Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Increased risk for COVID-19 in patients with vitamin D deficiency

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ABSTRACT

Objective: The 2019 coronavirus disease (COVID-19) pandemic has disproportionally affected a variety of patients with underlying risk factors such as respiratory and cardiovascular diseases, diabetes, obesity, and black race. Vitamin D deficiency, which can result in a compromised immune response, has been also linked to increased risk and increased morbidities associated with COVID-19. In the absence of large-scale longitudinal studies to determine the strength of association between vitamin deficiency and COVID-19, cross-sectional studies of large patient cohorts can be used.

Methods: We used the *i2b2* patient's registry platform at the University of Florida Health Center to generate a count of patients using the international classification of diseases (ICD)-10 diagnosis codes for the period of October 1, 2015, through June 30, 2020. Logistic regression of the aggregates was used for the analysis.

Results: Patients with vitamin D deficiency were 4.6 times more likely to be positive for COVID-19 (indicated by the ICD-10 diagnostic code COVID19) than patients with no deficiency ($P < 0.001$). The association decreased slightly after adjusting for sex (odds ratio [OR] = 4.58; $P < 0.001$) and malabsorption (OR = 4.46; $P < 0.001$), respectively. The association decreased significantly but remained robust ($P < 0.001$) after adjusting for race (OR = 3.76; $P < 0.001$), periodontal disease status (OR = 3.64; $P < 0.001$), diabetes (OR = 3.28; $P < 0.001$), and obesity (OR = 2.27; $P < 0.001$), respectively. In addition, patients with vitamin D deficiency were 5 times more likely to be infected with COVID-19 than patients with no deficiency after adjusting for age groups (OR = 5.155; $P < 0.001$).

Conclusions: Vitamin D deficiency is significantly associated with increased risk for COVID-19.

Introduction

Vitamin D is not a vitamin in the traditional sense. Rather, it is a group of fat-soluble compounds responsible for intestinal absorption of calcium, magnesium, and phosphate, and for a variety of additional biological effects [1]. Low levels of vitamin D can increase the likelihood of developing multiple acute and chronic ailments including cardiovascular and autoimmune diseases, diabetes, cancer, infectious diseases, dental caries (DC) [2], and periodontal disease (PD) [3,4]. In most people, more than 80% of vitamin D is formed in the skin after exposure to sunlight [2]. Hypovitaminosis D status usually reflects deficient sunlight exposure, deficient dietary intake, or both [2].

Recently, vitamin deficiency was linked with susceptibility to COVID-19 and severity of outcomes for patients with COVID-19 [5]. A few studies have presented conflicting results on the association between vitamin D deficiency and viral respiratory infection, partially because of the heterogeneity of the population studied and failure to adjust for comorbidities [6,7]. Many retrospective studies have found an association between vitamin D levels and COVID-19 severity and mortality [8,9]. Studies in the pediatric population demonstrated that patients with COVID-19 had significantly lower vitamin D levels compared with controls [10]. In addition, fever was significantly higher in patients who had deficient vitamin D levels compared with patients who had sufficient levels [10,11]; additionally, older adults with vitamin D deficiency and COVID-19 had worse morbidity outcomes compared with those who were not vitamin D deficient [12]. A prospective, interventional study found that a high dose of calcifediol reduced the need for intensive care stays in patients infected with COVID-19 [13].

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Table 1
Demographic information on patients with COVID-19, vitamin D deficiency, COVID-19 with vitamin D deficiency, and hospital population

	Odds ratio	95% Wald confidence limits		*P* value
Vitamin D deficiency vs. no deficiency	4.633	3.713	5.783	< 0.001
(logistic regression model of vitamin D deficiency without adjustment)				
Vitamin D deficiency vs. no deficiency	4.583	3.668	5.726	< 0.001
Sex male vs. female	0.935	0.818	1.069	0.3278
(logistic regression model of vitamin D deficiency adjusted by sex)				
Vitamin D deficiency vs. no deficiency	3.757	2.982	4.734	< 0.001
Race black vs. other	3.424	2.837	4.134	< 0.001
Race white vs. other	1.325	1.122	1.565	< 0.001
(logistic regression model of vitamin D deficiency adjusted by race)				
Vitamin D deficiency vs. no deficiency	5.155	3.974	6.688	< 0.001
Age 18–44 vs. <18	1.15	0.812	1.628	< 0.001
Age 45–64 vs. <18	0.585	0.409	0.838	0.0074
Age >64 vs. <18	0.439	0.305	0.631	< 0.001
(logistic regression model of vitamin D deficiency adjusted by age)				
Vitamin D deficiency vs. no deficiency	3.64	2.911	4.55	< 0.001
PD vs. no PD	2.976	1.679	5.275	0.0002
(Logistic regression model of vitamin D deficiency adjusted by PD status)				
Vitamin D deficiency vs. no deficiency	3.764	3.025	4.685	< 0.001
Caries vs. no caries	2.612	1.892	3.605	< 0.001
(logistic regression model of vitamin D deficiency adjusted by caries status)				
Vitamin D deficiency vs. no deficiency	3.918	3.157	4.862	< 0.001
PA vs. no PA	3.044	1.928	4.805	< 0.001
(logistic regression model of vitamin D deficiency adjusted by PA status)				
Vitamin D deficiency vs. no deficiency	2.266	1.787	2.872	< 0.001
Obesity vs. no obesity	4.884	4.165	5.728	< 0.001
(logistic regression model of vitamin D deficiency adjusted by obesity)				
Vitamin D deficiency vs. no deficiency	3.28	2.591	4.151	< 0.001
Diabetes vs. no diabetes	2.926	2.404	3.561	< 0.001
(logistic regression model of vitamin D deficiency adjusted by diabetes)				
Vitamin D deficiency vs. no deficiency	4.461	3.554	5.599	< 0.001
Malabsorption vs. no malabsorption	1.267	0.595	2.7	0.5389
(logistic regression model of vitamin D deficiency adjusted by malabsorption)				
COVID-19, coronavirus disease 2019; PD, periodontal disease. PA periapical abscesses				

A few studies have also reported on a significant association between sun exposure, vitamin D, and susceptibility to and recovery from COVID-19 [14,15]. Overall, significant controversy exists in the literature on the role of vitamin D deficiency in the prevention and treatment of COVID-19 and its effects on the severity of COVID-19 symptoms [16,17].

The present study investigated the patient registry of a large health center, examining the strength of the association between vitamin D deficiency and COVID-19 after adjusting for likely covariates, such as demographic characteristics and inflammation-associated comorbidities.

Materials and methods

The study was exempted by the University of Florida (UF) Institutional Review Board as the study did not include personal health information. The UF *i2b2* patient registry platform, which provides data aggregates from patient visits from various UF health centers, was used for the study. We searched the linternational classification of diseases (ICD)-10 diagnosis codes that occurred during the period of October 1, 2015, through June, 30, 2020, for vitamin D deficiency E 55.9, diabetes E08–E13, obesity E65–E68, malabsorption K90, caries K02, periodontal disease K05, and periapical abscesses (PA) K04 and COVID-19 U07.1 that occurred during 2020 before June 30, 2020. The demographic data was provided by the platform. The odds ratio (OR) for the associations were calculated by logistic regression of the aggregates using SAS statistical software. The 95% confidence interval (CI) and *P* value for each OR were tabulated. $P < 0.05$ was deemed significant.

Power analysis was completed with the assumption that 24% of the population has vitamin D deficiency [18] with the incidence of COVID-19 at 0.4% [19]. A total sample of 16 540 (4135 in the vitamin D deficiency group and 12 405 in the group with no vitamin D deficiency) achieve 80.001% power to detect a difference between the group COVID-19 incidence of 0.4%. The test statistic used is the two-sided *t* test. The significance level of the test is 0.0500 [20].

Results

From a total population of 98 7849 patients, 887 were positively diagnosed with COVID-19, 31 950 were diagnosis of vitamin D deficiency, and 87 patients had both vitamin D deficiency and COVID-19. This subgroup of 87 patients was composed of 98% adults, 71.3% males, and 88% black or other non-white individuals (Table 1). Patients with vitamin D deficiency were 4.6 times more likely to have a positive COVID-19 status than patients with no deficiency (95% CI, 3.713–5.783; $P < 0.001$). The association decreased slightly after adjusting for sex (OR = 4.58; 95% CI, 3.668–5.726; $P < 0.001$) and malabsorption (OR = 4.46; 95% CI, 3.554–5.599; $P < 0.001$), respectively, and for PA and DC (OR = 3.92; 95% CI, 3.157–4.862; $P < 0.001$; and OR = 3.764; 95% CI, 3.025–4.685; $P < 0.001$, respectively). The association decreased significantly but remained robust, with $P < 0.001$ after adjusting for race (OR = 3.76; 95% CI, 2.982–4.734; $P < 0.001$), PD status (OR = 3.64; 95% CI, 2.911–4.55; $P < 0.001$), diabetes (OR = 3.28; 95% CI, 2.591–4.151; $P < 0.001$), and obesity (OR = 2.27; 95% CI, 1.787–2.872; $P < 0.001$), respectively. In addition, patients with vitamin D deficiency were 5 times more likely to be infected with COVID-19 than patients with no deficiency after adjusting for age groups (OR = 5.155; 95% CI, 3.974–6.688; $P < 0.001$) (Table 2).

Discussion

In the present study, patients with vitamin D deficiency were 4.6 times (95% CI, 3.554–5.599) more likely to have a positive

Table 2
Odds ratio for COVID-19 with vitamin D deficiency before and after adjustments for comorbidities and demographic covariates

	COVID-19 (n = 884)		Vitamin D deficiency (n = 31 950)		COVID-19 and vitamin D deficiency (n = 87)		Hospital (n = 987 849)	
	Count	%	Count	%	Count	%	Count	%
Sex								
Male	499	56.4	22 281	69.7	62	71.3	455 458	46.1
Female	385	43.6	9669	30.3	25	28.7	532 391	53.9
Race								
Black	225	26.6	6215	20.0	33	40.2	112 083	11.34
White	219	25.9	2861	9.2	9	11.0	494 158	50
Other	401	47.5	2 2073	70.9	40	48.8	381 608	38.66
Age								
Age <18	35	4.0	1332	3.4	2	2.0	158 488	16
Age 18–44	31	3.5	10 346	26.5	31	31.3	307 869	31.16
Age 45–64	206	23.5	12 428	31.9	37	37.4	261 618	26.48
Age >64	173	19.7	14 882	38.2	29	29.3	259 874	26.36

COVID-19, coronavirus disease 2019.

COVID-19 status than patients with no deficiency. The association decreased significantly but remained robust, with P value < 0.001 after adjusting for race (OR = 3.76; 95% CI, 2.982–4.734), PD status (OR = 3.92; 95% CI, 2.911–4.55), diabetes (OR = 3.28; 95% CI, 2.591–4.151), and obesity (OR = 2.27; 95% CI, 1.787–2.872), respectively (Fig. 1).

In addition to adjusting for known risk factors for COVID-19 such as diabetes [17], obesity [21], and intestinal malabsorption, which poses a risk for vitamin deficiency [22], we have adjusted for the presence of dental diseases DC, PD, and PA, which have recently been associated with COVID-19 [23]. The adjustments for dental diseases did not decrease the OR for COVID-19 dramatically, which supports the theory that dental disease and COVID-19 are both increased by vitamin D deficiency, as suggested by previous researchers [2–5].

Our data set included information on patients who were diagnosed with vitamin D deficiency over the period between October 1, 2015, and June 30, 2020, while the diagnosis of COVID-19 occurred in 2020. Using vitamin D levels obtained relatively recently (within the past 5 y) is a strength of this study. Research based on the 2006 to 2010 UK Biobank data for vitamin D levels only weakly supported the link between vitamin D deficiency and COVID-19 [9,24]. Researchers have challenged the claim that vitamin D levels are stable over time where the levels were assessed 10 to 14 y before the pandemic [24–26]. Rather than being stable, mean 25(OH)D levels were shown to increase significantly over 5 y, and the increase was driven by overall increases in vitamin D intake in the most vitamin D–deficient study participants [24–26].

This type of cross-sectional study cannot address the question of causality. Dental diseases, vitamin D deficiency, and COVID-19 share common confounding variables such as socioeconomic status and racial predisposition that may affect this association. It is noteworthy to mention that black patients are disproportionally affected by COVID-19, dental diseases, and vitamin D deficiency compared with other races [27,28], primarily because pigmentation reduces vitamin D production in the skin [29,30].Vitamin D triggers the production of the antimicrobial proteins cathelicidins and defensins that can inhibit viral replication rates and reduce levels of cytokines that generate the inflammation responsible for the damage to the lining of the lungs, leading to acute respiratory disease [31]. Vitamin D also promotes the gene responsible for the expression of ACE2, which is down-regulated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [32].

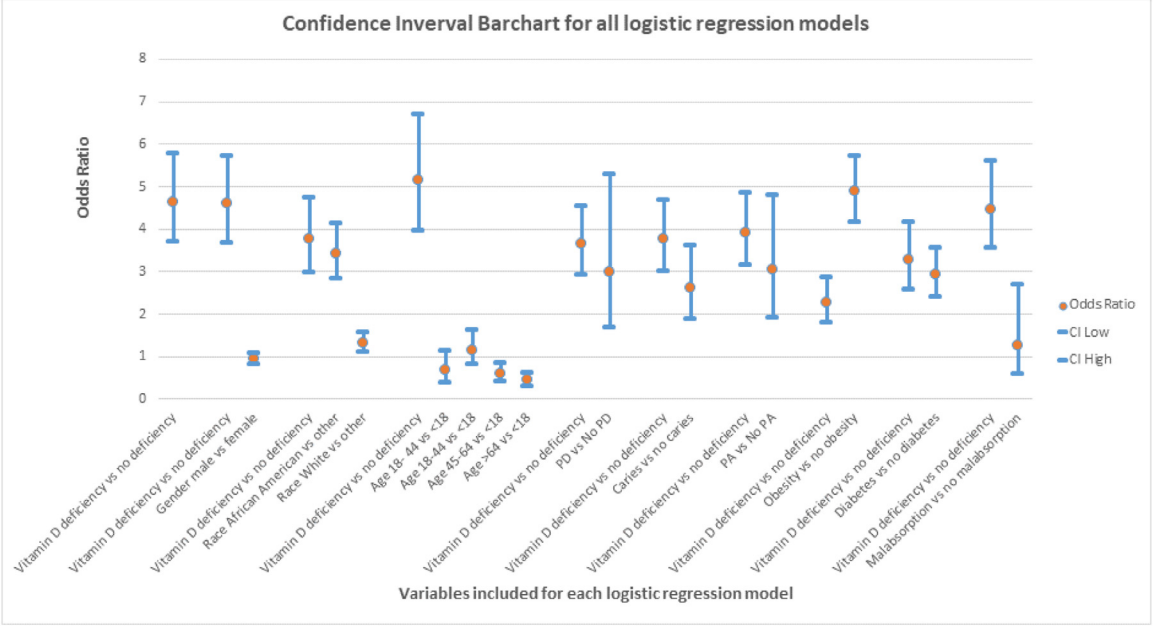

Fig 1. Confidence interval Barchart for logistic regression models.

In addition to the well-documented effect of vitamin D on the immune system, a recent study has demonstrated that sunlight may rapidly inactivate SARS-CoV-2 on surfaces, suggesting that there may be an environmental benefit associated with vitamin D as a result of sun exposure and that natural sunlight may be effective as a disinfectant for contaminated surfaces [15].This study may support the hypothesis that some of the protective effect of vitamin D against COVID-19 may actually be attributed to sun exposure [15].

Because vitamin D deficiency has been shown to potentially increase the risk of severe respiratory infections, some investigators have suggested vitamin D supplements for prevention and treatment of COVID-19 complications, especially acute respiratory disease [33]. However, the National Institutes of Health found insufficient evidence to recommend for or against using vitamin D supplementation specifically to prevent or treat COVID-19, and recommended to continue the previous established recommendations on vitamin D supplementation for other reasons, such as bone and muscle health, because people may require supplementation because of lower sun exposure during the pandemic [34]. Nevertheless, recent systematic reviews and meta-analyses have concluded that vitamin D has potential in preventing respiratory infections, especially in those who have high levels of deficiency [35].

In our cross-sectional, retrospective study of patients' registry, we did not have access to the individual medical information that seems to be of importance for observational study. Data on the initial infection severity status, the COVID-19 treatments, and the length of vitamin D deficiency are therefore missing. Nevertheless, the main comorbidities and demographic covariates were retrieved and have been adjusted so that the strength of the association between vitamin D deficiency and COVID-19 could be established.

In conclusion, the present study has demonstrated that vitamin D deficiency is strongly associated with COVID-19 infection ($P < 0.001$), even after controlling for sex, malabsorption, dental diseases, race, diabetes, and obesity. Perhaps the most important finding was that vitamin D deficiency increased the risk of developing COVID-19 by a factor of 5 after adjusting for age. Prospective interventional studies are required to validate the hypothesis that vitamin D supplementation can be helpful for the prevention and treatment of COVID-19.

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