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Increased risk for Covid-19 in patients with Vitamin D deficiency.

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Highlights

* Vitamin D deficiency is strongly associated with increased risk for Covid-19
* The odds ratio for Covid-19 increases with vitamin deficiency in the African American race
* Diabetes, obesity, and periodontal disease are associated with an increased risk for both Covid-19 and Vitamin D deficiency

Increased risk for Covid-19 in patients with Vitamin D deficiency.

Running title: Vitamin D deficiency and risk for Covid-19

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Abstract

Background: The new Covid-19 pandemic has disproportionally affected a variety of patients with underlying risk factors such as respiratory and cardiovascular diseases, diabetes, obesity, and African American race. Vitamin D deficiency that can result in compromised immune response has also been linked with increased risk and increased morbidities associated with Covid-19.

In the absence of large scale longitudinal studies that can determine the strength of association between vitamin deficiency and Covid-19, cross sectional studies of large cohorts of patients can be used.

Material and methods: We have used the *i2b2* patient's registry platform at the University of Florida Health center to generate a count of patients using the ICD 10 diagnoses codes for the period of **10/1/2015 – 6/30/2020**. Logistic regression of the aggregates was used for the analysis.

Results: Patients with vitamin D deficiency were 4.6 times more likely to be Covid-19 positive, as indicated by a COV19 ICD 10 diagnostic code, than patients with no deficiency (P-value<0.001). The association decreased slightly after adjusting for gender (with OR=4.58, p<0.001) and for malabsorption (with OR=4.46, p<0.001) respectively. The association decreased significantly but remained robust with P-value<0.001 after adjusting for race (with OR=3.76, p<0.001), periodontal disease status (with OR=3.64, p<0.001), diabetes (with OR=3.28, p<0.001) and obesity (with 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).

Conclusion: 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 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 and also dental caries (DC) (2) and periodontal disease (PD) (3, 4). In most people, more than 80% of vitamin D is formed in the skin following exposure to sunlight (2). Hypovitaminosis D status usually reflects deficient sunlight exposure and/or deficient dietary intake (2).

Recently vitamin deficiency was reported to be linked with susceptibility to Covid-19 and severity of outcomes for patients with Covid-19 (5). A few studies have presented conflicting results on association between vitamin D deficiency and viral respiratory infection, partially because of the heterogeneity of the population studied and failure to adjust for co morbidities (6, 7). Many retrospective studies have found an association between vitamin D levels with Covid-19 severity and mortality (8, 9). Studies in pediatric population demonstrated that patients with Covid-19 had significantly lower vitamin D levels compared to controls (10). In addition, fever was significantly higher in patients who had deficient vitamin D levels compared to patients who had sufficient levels (10, 11), on the other spectrum, older adults with vitamin D deficiency and Covid-19 had worse morbidity outcomes compared to 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 stay of patients infected with Covid-19 (13).

Few studies have also reported on a significant association between sun exposure, vitamin D and susceptibility and recovery from Covid-19 (14,15). Overall there is a significant controversy in the literature on the role of vitamin D deficiency on prevention, severity of symptoms and treatment of Covid -19 patients (16.17).

In the present study, we aimed to investigate in a large health center patients' registry, the strength of the association between vitamin D deficiency and Covid-19, after adjusting for likely covariates, such as demographics and inflammation-associated comorbidities.

Materials and methods

The study was exempted by the University of Florida (UF) institutional Review board (IRB) as the study didn't include personal health information (PHI).

The University of Florida patients' registry *i2b2* platform which provides data aggregates from patients visits from various UF health centers was used for the study, we have searched the ICD 10 diagnoses codes that occurred **in the period 10/1/2015 – 6/30/2020,** for vitamin D deficiency E 55.9, Diabetes E08- E13, obesity E65-E68, malabsorption K90, caries K02, periodontal disease K05, and periapical abscesses K04 and Covid-19 U07.1 that occurred during 2020 prior to 6/30/2020. 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: With the assumption of 24% population having vitamin D deficiency (18) and incidence of Covid-19 at 0.4% (19) . A total sample of 16540 (4135 in vitamin D deficiency group and 12405 in no vitamin D deficiency group) 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 987849 patients, 887 were diagnosed with positive Covid-19, 31950 had a 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% African Americans or other non-whites (Table 1). Patients with vitamin D deficiency were 4.6 times more likely to have 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 gender with OR=4.58, 95% CI 3.668 - 5.726, (P<0.001) and for malabsorption with (OR=4.46), 95% CI 3.554-5.599,(P<0.001) respectively, PA and DC with (OR =3.92) , 95% CI 3.157- 4.862, P<0.001 and 3.764, 95% CI 3.025- 4.685,(P<0.001) respectively. The association decreased significantly but the association remain robust with P-value<0.001 after adjusting for race (with OR=3.76), 95% CI 2.982-4.734, P<0.001), PD status (with OR=3.64) 95% CI , 2.911-4.55, (P<0.001), Diabetes (with OR=3.28), 95% CI 2.591- 4.151, (P<0.001) and obesity (with 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 (95% CI 3.554-5.599) times more likely to have positive Covid-19 status than patients with no deficiency . The association decreased significantly but the association remain robust with P-value<0.001 after adjusting for race (with OR=3.76) (95% CI

2.982-4.734), PD status (with OR=3.92) (95% CI , 2.911-4.55), Diabetes (with OR=3.28), 95% CI 2.591-4.151 and obesity (with OR=2.27), 95% CI 1.787 - 2.872 respectively (Figure 1).

In addition to adjusting for known risk factors for Covid -19 such as diabetes (17) obesity (21) and intestinal malabsorption that poses a risk for vitamin deficiency (22) we have adjusted for the presence of dental diseases DC, PD and PA that have recently been shown to be 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 (2,3,4,5).

Our data set included information on patients that were diagnosed with vitamin D deficiency over a period **10/1/2015 - 2019-06-30**, while the diagnosis of Covid-19 occurred in 2020. Using vitamin D levels obtained relatively recently (within the past 5 years) is a strength of this study. Research based upon the 2006 - 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 10-14 years prior to the pandemic (24-26). Rather than being stable, mean 25(OH)D levels were shown to increase significantly over 5 years, and the increase was driven by overall increases in vitamin D intake among the most vitamin D deficient study participants (24-26).

In this type of a cross sectional study e 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 African American patients are disproportionally affected by Covid-19, dental diseases and vitamin D deficiency compared to other races (27-28) primarily due to the fact that 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 that is down regulated by SARS-CoV-2 (32).

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 (33).This study may support the hypothesis that some of the protective effect of vitamin D against Covid 19 may be actually attributed to sun exposure (33).

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 (34). 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 due to lower sun exposure during the pandemic (35).

Nevertheless, recent systematic reviews and meta-analysis have concluded that vitamin D has potential in preventing respiratory infections, especially in those who have high levels of deficiency (36).

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 gender, 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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Conflict of interest statement: No conflicts

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Fig. 1.

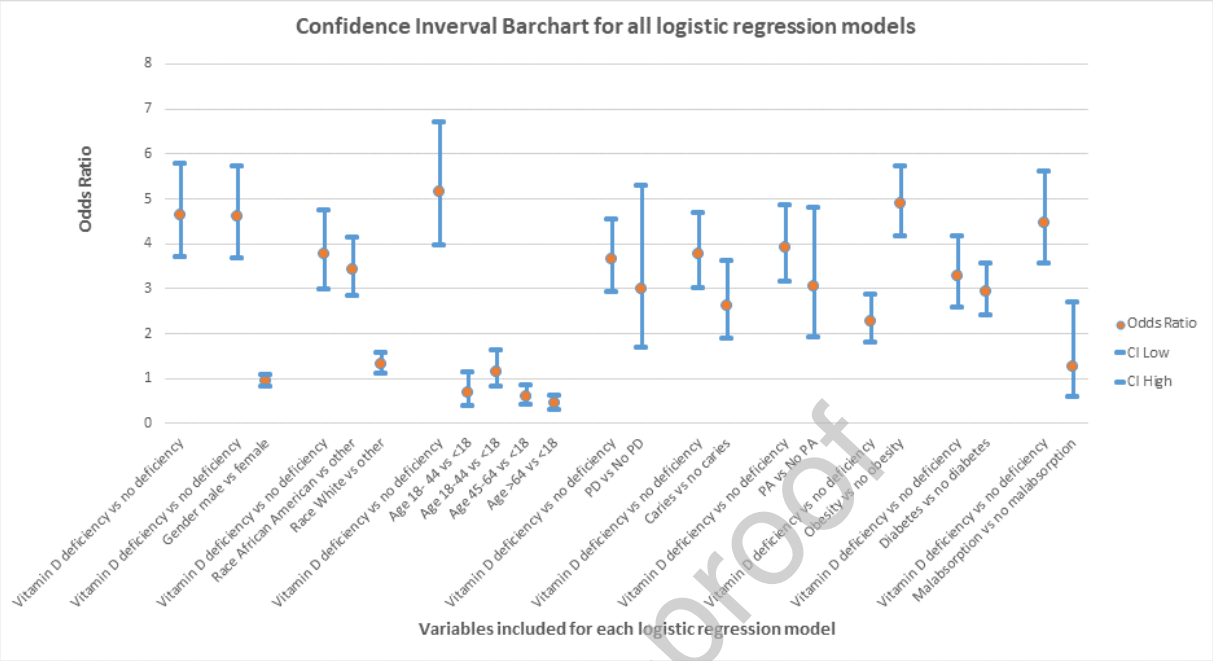

Table 1 Demographic information on patients with Covid-19, vitamin D deficiency, Covid-19 with vitamin D deficiency and Hospital population.

	Covid -19 (n=884)		Vitamin D Deficiency (n=31950)		Covid-19 and Vitamin D Deficiency (n=87)		Hospital (n=987849)	
	Count	%	Count	%	Count	%	Count	%
Gender								
male	499	56.4%	22281	69.7%	62	71.3%	455458	46.1%
female	385	43.6%	9669	30.3%	25	28.7%	532391	53.9%
Race								
African American	225	26.6%	6215	20.0%	33	40.2%	112083	11.34%

white	219	25.9%	2861	9.2%	9	11.0%	494158	50%
Other	401	47.5%	22073	70.9%	40	48.8%	381608	38.66%
Age								
Age <18	35	4.0%	1332	3.4%	2	2.0%	158488	16%
Age 18-44	31	3.5%	10346	26.5%	31	31.3%	307869	31.16%
Age 45-64	206	23.5%	12428	31.9%	37	37.4%	261618	26.48%
Age >64	173	19.7%	14882	38.2%	29	29.3%	259874	26.36%

Table 2: Odds Ratio for Covid- 19 with vitamin D deficiency before and after adjustments for comorbidities and demographic covariates.

	Odds Ratio	95% Wald Confidence Limits		P Value
Vitamin D deficiency vs no deficiency (Logistic regression model of Vitamin D deficiency without adjustment)	4.633	3.713	5.783	<0.001
Vitamin D deficiency vs no deficiency	4.583	3.668	5.726	<0.001
Gender male vs female (Logistic regression model of Vitamin D deficiency adjusted by gender)	0.935	0.818	1.069	0.3278
Vitamin D deficiency vs no deficiency	3.757	2.982	4.734	<0.001
Race African American vs other	3.424	2.837	4.134	<0.001
Race White vs other (Logistic regression model of Vitamin D deficiency adjusted by race)	1.325	1.122	1.565	<0.001
Vitamin D deficiency vs no deficiency	5.155	3.974	6.688	<0.001
Age 18- 44 vs <18	0.667	0.393	1.134	0.6514
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 (Logistic regression model of Vitamin D deficiency adjusted by age)	0.439	0.305	0.631	<0.001
Vitamin D deficiency vs no deficiency	3.64	2.911	4.55	<0.001
PD vs No PD (Logistic regression model of Vitamin D deficiency adjusted by PD status)	2.976	1.679	5.275	0.0002
Vitamin D deficiency vs no deficiency	3.764	3.025	4.685	<0.001
Caries vs no caries (Logistic regression model of Vitamin D deficiency adjusted by caries status)	2.612	1.892	3.605	<0.001
Vitamin D deficiency vs no deficiency	3.918	3.157	4.862	<0.001
PA vs No PA (Logistic regression model of Vitamin D deficiency adjusted by PA status)	3.044	1.928	4.805	<0.001
Vitamin D deficiency vs no deficiency	2.266	1.787	2.872	<0.001
Obesity vs no obesity (Logistic regression model of Vitamin D deficiency adjusted by obesity)	4.884	4.165	5.728	<0.001
Vitamin D deficiency vs no deficiency	3.28	2.591	4.151	<0.001
Diabetes vs no diabetes (Logistic regression model of Vitamin D deficiency adjusted by diabetes)	2.926	2.404	3.561	<0.001
Vitamin D deficiency vs no deficiency	4.461	3.554	5.599	<0.001
Malabsorption vs no malabsorption (Logistic regression model of Vitamin D deficiency adjusted by malabsorption)	1.267	0.595	2.7	0.5389