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CLINICAL VIGNETTE

Evaluation of Vitamin D Levels in Patients With Coccidioidomycosis, a Case Control Study

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Introduction

Infection by *coccidioides spp*., a fungus, found only in the western hemisphere has been a growing concern in endemic areas of Southwest America[1,2]. Ethnicity, pregnancy, and cell-mediated immunodeficiency have shown to be risk factors for this disease[3,4]. Immune deficiency plays an important role by increasing the severity of this infection[3].

Studies have shown vitamin D deficiency is associated with more severe granulomatous diseases such as tuberculosis[5-7]. In a recent study, Vitamin D deficiency was associated with severity of liver disease in Human Immunodeficiency Virus (HIV) and Hepatitis C co-infected patients[8]. Vitamin D deficiency has also been linked to worsening oral candidiasis in HIV patients attributed to the down-regulation of calprotectin which influences neutrophil function[9].

Vitamin D is an important factor in the immune response and affects vitamin D receptors (VDRs) on macrophages, dendritic cells, and activated T and B lymphocytes. The VDRs promote the immune reaction as well as up regulation of the innate immune response such as stimulating defensin and cathelicidin-an antimicrobial peptide[10,11].

Vitamin D deficiency has been shown to also inhibit the adaptive immune reaction by inhibiting maturation of the dendritic cells antigen presentation and decreasing T-Cell proliferation[10,12]. When *coccidioides spp*. spores are inhaled, the natural immune response occurs in two phases. The first response involves neutrophils, monocytes, eosinophils, and natural killer cells. The second phase is composed of macrophages and dendritic cells[13].

Vitamin D binding protein, known as gc-globulin, is a protein related to the albumin family. This protein transports vitamin D to its target tissue and is found in plasma, ascitic fluid, cerebrospinal fluid, and on the surface of many proteins. Vitamin D binding protein binds 85-90% of the total 25-Hydroxyvitamin D in circulation. The non-vitamin D-binding protein fraction consists of albumin bound vitamin D, which is the bioavailable form for 10-15% of the total. Less than 1% of vitamin D is in the free form. From prior research, vitamin D-binding protein seems to inhibit actions of vitamin D, because the bound fraction may be unavailable to act on target cells. Genetic variation affects the affinity of the binding protein to vitamin D. The clinical assays measure total vitamin D and do not distinguish fractions bound to carrier proteins[14].

Even though vitamin D deficiency has shown to decrease immune response to tuberculosis and HIV, to our knowledge, no data have been published on vitamin D deficiency and its association with *coccidioidomycosis*.

We compare vitamin D levels in patients with and without coccidioidomycosis in a teaching county hospital population in the San Joaquin Valley.

Methods

Study design:
This is a retrospective, matched case-control study. The patients were older than 18 years and were selected from the Medicine Department clinic of Kern Medical Center from 1990 to 2010. A case was defined as positive for *coccidioidomycosis* either by serology (97%) or by pathology or cultures (31%) (N=118). Controls were patients without any clinical or laboratory findings suggestive of *coccidioidomycosis* (N=472). All cases and controls had vitamin D levels measured. Cases and controls were matched (ratio of 1 to 4) by age, race, and sex and evaluated for co-morbidities. All vitamin D

levels were measured using the Abbott AxSYM Immunoassay System.

Both cases and controls were gender matched with 63% male and 37% females. Both had 16.9% African Americans, 14.4% Caucasians, and 68.6% Hispanics. Among cases 35% of patients had pulmonary *coccidioidomycosis* and 65% with disseminated form with mean age of the cases at 42.8 years old (18-88).

Definition:
The definitions of vitamin D deficiency were similar to previous studies[15,16]. Vitamin D deficiency was vitamin D OH total <20 ng/ml and Vitamin D insufficiency was a value ≥ 20 and <30 ng/ml[15,16]. Diabetes Mellitus (DM) was defined as hemoglobin A1C greater than 6.5, previous history of diabetes, or two fasting glucose greater than 126 mg/dl[17]. Chronic kidney Disease (CKD) was defined as presence of kidney damage or decreased kidney function for three or more months, irrespective of cause according to the Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) guidelines[18].

Data analysis and statistical methods:
JMP (SAS) version 9 was used for data analysis. Two sample independent t-tests were used to test for significant differences. Odds ratios were used to compare prevalence between case and control groups. Descriptive statistics were also generated for groups of interest. All p-values < 0.05 were considered statistically significant.

Results

The average vitamin D level in cases was 25.9 ng/ml and in controls was 22.5 ng/ml, which was significantly lower than cases p<0.01 (Figure 1).

A numerical analysis of the values showed the vitamin D average for controls was statistically lower than the cases p<0.002. Although averages showed a statistical difference, the prevalence of vitamin D insufficiency (20< vitamin D <30) was not statistically higher among cases, OR = 1.52 {CI95 (0.92, 2.5)} p=0.0504.

The prevalence of vitamin D deficiency (<20) was statistically higher in controls OR = 1.88 {CI95(1.1054, 3.1922)} p=0.0099 (Figure 2).

When combining vitamin D deficiency and insufficiency (vitamin D < 30) there was no statistical difference between the cases and the controls with OR=0.89 {CI95 (0.57,1.39)} p=0.30 (Figure 3).
In terms of comorbidities, 46% of the cases had DM and 7% had CKD. In the control patients, 68% had DM , 23% had CKD, 30% had no co-morbidities, and 6% had other disease (Table 1).

Further analysis found a high prevalence of vitamin D insufficiency and deficiency combined (vitamin D <30) in subjects with DM with an OR=1.766 {CI95 (1.203, 2.593)} p=0.0037, as well as those subjects with CKD with an OR =1.83 {CI95 (1.106, 3.027)} p=0.0187 (Figures 4 and 5).

We also found the prevalence of DM and CKD were statistically higher in controls compared to cases respectively with an OR = 1.799 {CI95 (1.171, 2.763)} p=0.004 (Figure 6), and an OR=3.789{CI95(1.895, 7.723)} p=0.0001 (Figure 7).

After exclusion of DM and CKD from cases and controls, we found no statistical difference between cases and controls for prevalence of vitamin D deficiency and insufficiency combined, OR = 0.95 {CI95(0.60,1.51)} p=0.4241 (Figure 8,9).

For insufficiency (20<vitamin D<30) OR 1.54 {CI95(0.9238, 2.5770)} p=0.0487 the study found a higher prevalence among the cases. For deficiency (vitamin D <20) the study showed OR = 0.5771 {CI95 (0.3319,1.0038)} p=0.0258 indicating a higher prevalence among the controls.

Discussion

This study showed no correlation between vitamin D levels in patients with or without *coccidioidomycosis*. A recent abstract by University of California Davis investigators, presented at the Annual Infectious Diseases Society of America in 2011 showed similar results[19]. These findings are in contrast to the role of vitamin D in tuberculosis, severe liver disease, in coinfected HIV/HCV, and oral candidiasis in HIV patients.

Our patient population was mostly Hispanic which may not represent the general population.

Furthermore, this study does not explore the effects of free vitamin D verses the bound form. Glucocorticoid or stress hormones are known to decrease vitamin D receptors gene expression in most tissues, which in turn can down regulate metabolic pathways as well as the immune response. Genetic variation of affinity among races for binding protein

to vitamin D has not been studied and could affect result of this study with mostly Hispanic population.

Table 1: Demographics

	Cases (118)	Controls (472)
Age, Average years	42.8	44.5
18 to 39, % (n)	35.5% (42)	35.5% (168)
40 to 59, % (n)	55% (65)	55% (260)
≥60, % (n)	9.3% (11)	9.3% (44)
Gender, % male (n)	63% (75)	63% (300)
Race: , % (n)		
Caucasian	14.4% (17)	14.4% (68)
Hispanic	68.6% (81)	68.6% (324)
African American	16.9% (20)	16.9% (80)
Comorbidities, % (n)		
Chronic Kidney Diseases	7%(9)	23%(111)
Diabetes	46% (37)	68% (322)
HIV+	0%(0)	<0.1% (2)
Gastric Bypass	0%(0)	<0.1% (4)
Malignancy	1%(2)	5% (25)
End Stage Liver Disease	1%(2)	1%(8)
Coccidioidomycosis infection % (n)		
Pulmonary	35.5% (42)	0%
Disseminated	64.5% (76)	0%
Any positive culture for *C. immitis*	31% (37)	0%
Positive complement fixation titers	97.4% (115)	0%

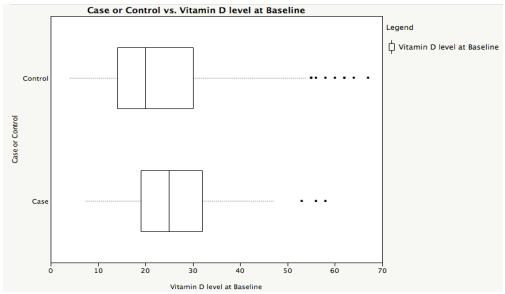

Figure 1: Case or Control verses Vitamin D levels at Baseline

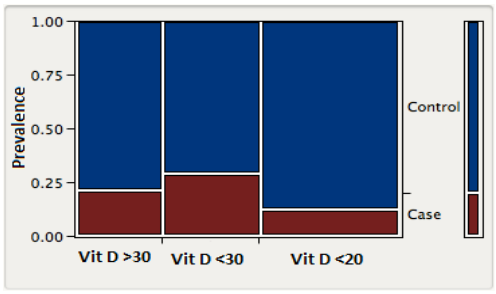

Figure 2: Case or Controls

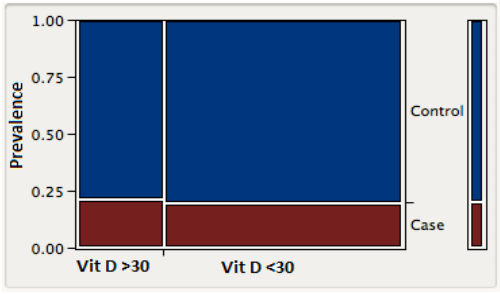

Figure 3: Case or Controls

In conclusion, this study does not support routine measurement of vitamin D levels in patients with *coccidioidomycosis*.

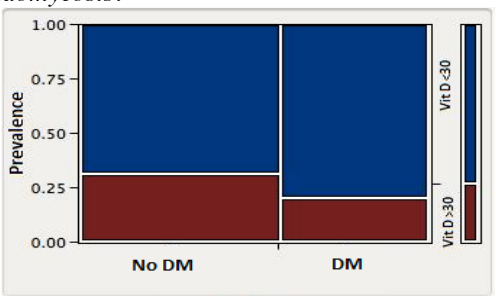

Figure 4: Comorbidities: DM (Diabetes Mellitus)

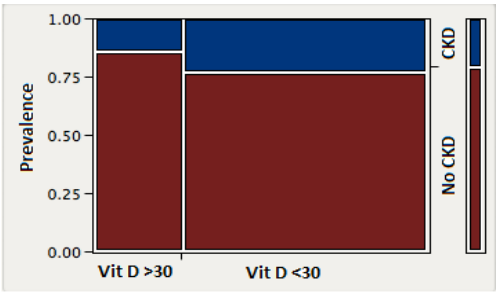

Figure 5: Comorbidities: CKD (Chronic Kidney Disease)

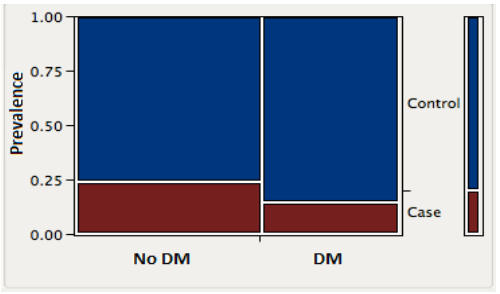

Figure 6: Comorbidities: DM (Diabetes Mellitus) in Case and Controls

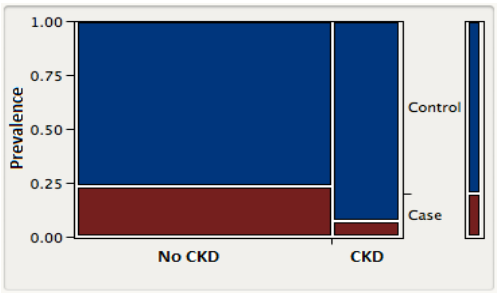

Figure 7: Comorbidities: CKD (Chronic Kidney Disease) in Case and Controls

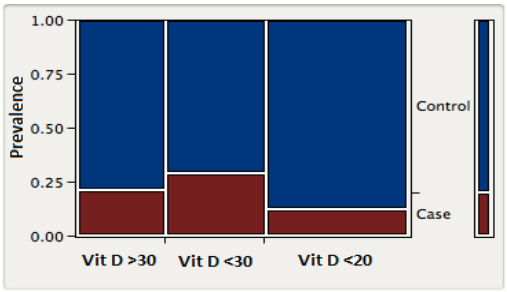

Figure 8: DM (Diabetes Mellitus) and CKD (Chronic Kidney Disease) Excluded

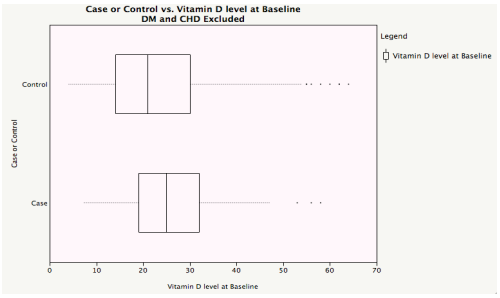

Figure 9

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