Title page

Serum 25-hydroxyvitamin D Levels in Hospitalized Adults with Community-Acquired Pneumonia

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Running title

25-hydroxyvitamin D Levels in Community-Acquired Pneumonia

Acknowledgment

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Conflict of Interest

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Abstract

Introduction: Community-acquired pneumonia (CAP) is the infectious disease with the highest number of deaths worldwide. Several studies have shown an association between vitamin D deficiency and increases susceptibility to respiratory tract infections. Objective: The aim of this study was to evaluate the serum 25-hydroxyvitamin D (25OHD) levels in hospitalized adults in general room with CAP. Materials and methods: An observational study was carried out in 207 hospitalized adults of both sex with CAP over 18 years from Rosario city, Argentina (32º 52' 18''S) between July 2015 to June 2016. Results: 167 patients were included in the data analysis (59% women, 57.4±19.6 years, body mass index 27.2±7.8 kg/m^2). The 63% showed unilobar infiltrate and in 37% were multilobar. The CURB-65 index was 66.5% low risk, 16.0% intermediate risk and 17.5% high risk. According to Charlson comorbidity index (CCI) 53.5% had not comorbidity (CCI=0) and 46.5% showed CCI≥1. The 25OHD level was: 11.92±7.6 ng/ml (51.5%: <10 ng/ml, 33.5%: 10-20 ng/ml, 13.2%: 20-30 ng/ml, 1.8%: >30 ng/ml). Higher 25OHD were found in male (female: 10.8±6.7 ng/ml, male: 13.5±8.5 ng/ml, p=0.02) and 25OHD correlated with age (r= -0.17; p=0.02). 25OHD also correlated with CURB65 index (r= -0.13; p=0.049), CCI (r= -0.20, p=0.007) and with the 10 years life expectative (%) (r= 0.19; p=0.008). In addition, higher 25OHD were found with lower CCI (CCI 0= 13.0±8.2 ng/ml, CCI ≥1= 10.5±6.7 ng/ml; p=0.0093). Conclusion: hospitalized adults with CAP have lower 25OHD levels and would be associated with CAP severity.

Key words: 25-hydroxyvitamin D; community-acquired pneumonia; severity; comorbidity.

Introduction

Community-acquired pneumonia (CAP) is the infectious disease with the highest number of deaths worldwide.[1] However, the importance of this disease is often underestimated. CAP incidence varied by country, age and gender, and is higher in individuals aged ≥65 years and in men.[2] The annual incidence of CAP ranges from 2.7 and 10 per 1000 persons.[3] CAP is diagnosed in an estimated 4.5 million patients annually in the United States, and 1.1 million requires hospitalization.[4] Mortality varied from 1% to 48% and was associated with advanced age, co-morbid conditions and CAP severity.[5] In outpatients the mortality rate of pneumonia is low, close to 1-5%, but in patients requiring hospitalization the mortality rate is ~12% and increases in those who develop bacteremia and require intensive care unit reaches almost 40%.[6] In United States CAP cause 15.9 deaths per 100,000 populations.[7] In Argentina is the 6th cause of death in general and the 5th cause in people over 60 years.[8,9]

Several studies have shown an association between vitamin D deficiency and increases susceptibility to respiratory tract infections.[10,11] The importance of vitamin D on the regulation of immune cells has increased in the last decade with the discovery of the vitamin D receptor (VDR) in this cells. Despite demonstration of several immune-modulating effects of vitamin D/vitamin D receptor signaling, such as transcription of anti-microbial compounds and regulation of cytokine production and immune cell activity,[12,13] the mechanisms underlying these relationships are still not fully understood.[14]

The aim of this study was to evaluate the serum 25-hydroxyvitamin D (25OHD) levels in hospitalized adults with CAP and its relationship with CAP severity. In addition, the CAP clinical characteristics were analyzed.

Methods

Study design. An observational study in 207 hospitalized adults of both sex with CAP over 18 years from Rosario city, Argentina (32º52'18"S) were carried out from July 2015 to June 2016 in 13 internal medicine service. The inclusion criteria were patients with CAP hospitalized in general room greater than 18 years old who wants to participate of this study and gave written informed consent to participate. This study included patients fulfilling the following CAP criteria: (1) a new radiographic infiltrate and two or more of symptoms or signs (cough, sputum, dyspnea, fever, pleuritic chest pain, crackles or rhonchi); or (2) complicated parapneumonic effusion or empyema.

The exclusion criteria were: CAP that was not the primary cause of hospitalization, patients hospitalized in the last 14 days, or who had previous history of neoplasia, acquired immune deficiency syndrome, chronic renal or liver disease, autoimmune or connective diseases, or were treated with glucocorticoids, anticonvulsants or vitamin D in the last year.

The study was approved by the Ethics Committee of School of Medicine, Rosario National University, Argentina and was conducted in compliance with the Declaration of Helsinki.

Data collection. The baseline characteristics, biochemical determination and X-ray reports were obtained from medical records. The baseline characteristics recorded were: sex, age, body mass index (BMI), smoking status, alcohol intake, medical history, previous medication (antibiotics, glucocorticoid, vitamin D supplementation, immunosupresors) and CAP symptoms. Blood pressure, cardiac and respiratory rate, body temperature, hemoculture and sputum culture were considered. The clinical course was measured by days of hospitalization, severe complications and in-hospital mortality. In addition, the CURB-65 index (***C****onfusion,* ***U****rea,* ***R****espiratory rate,* ***B****lood preassure, age* ≥***65***) was evaluated as a CAP severity parameter and the Charlson comorbidity index (CCI) and the 10 years life expectative (%) calculated with age and CCI were considered as comorbidity index.[15,16]

Biochemical determination. General biochemical determinations were performed, including a full blood count, renal and liver function tests. The total 25OHD levels (D2 and D3) were determined by chemiluminescence assay (ADVIA Centaur Vitamin D Total Assay - Siemens®) in the first 48 hours of hospitalization and measure in a centralized laboratory. Vitamin D severe deficiency was defined as 25OHD levels <10 ng/ml, deficiency as 25OHD levels between 10-20 ng/ml, insufficiency as 25OHD levels between 20-30 ng/ml (50-75 nmol/liter) and 25OHD levels >30 ng/ml was considered as optimal.[17]

Statistical analyses. Categorical variables were expressed as number (percentages) and continuous variables as mean±standard deviation (SD) for normally distributed data or media (25th-75th percentiles) for sewed data as evaluated by the Kolmogorov-Smirnov test. Baseline characteristics were compared among the categories of serum 25OHD levels using χ^2, Fisher exact test, one-way ANOVA or Kruskal-Wallis test, where appropriate. Differences were considered significant if $p<0.05$. Statistical analyses were performed with GraphPad Prism 2.0 (GraphPad, San Diego, USA).

Results

A total of 207 patients with CAP were recruited, and 167 were finally included in this study. Forty patients were excluded because incomplete data collection or a radiographic infiltrate because other cause. The included patients were 59% women and 41% men. The mean age was 57.4±19.6 years (range: 18-96), the body mass index was 27.2±7.8 kg/m2.

The baseline characteristics and medical history of hospitalized adults with CAP in the whole group and according 25OHD levels is shown in Table 1. A significant differences in age was observed between the groups with 25OHD <10 ng/ml and 25OHD 10-20 ng/ml, but no differences was found between the groups with 25OHD <10 ng/ml and 25OHD >20 ng/ml. In addition, higher proportion of women in the group with 25OHD <10 ng/ml was found.

INSERT TABLE 1

No differences in symptoms and physical examination of hospitalized adults with CAP in the whole group and according 25OHD levels were observed (Table 2).

INSERT TABLE 2

Furthermore, no differences were observed in biochemical measurement of hospitalized adults with CAP in the whole group and according 25OHD levels (Table 3).

INSERT TABLE 3

X-ray, blood and sputum cultures characteristics and clinical follow-up

No differences according 25OHD levels were observed (data not shown).

In the X-ray, 63% of the patients showed unilobar infiltrate and in 37% a multilobar infiltrated was observed. Unilateral pleural effusion was found in 11% and only 4% was bilateral. Only one patient had atelectasis and in another a unilobar cavitation was observed.

Blood cultures were performed in 95% of the patients and only 14% were positive (67% Streptococcus pneumoniae, 15% Klebsiella pneumoniae, 12% Serratia, 6% Staphylococcus aureus).

The sputum culture was requested in 58% of the case -60% were representative- and the 49% were positive (37% Streptococcus pneumoniae, 16% Streptococcus viridans, 16% Pseudomonas aeuruginosa, 11% Staphylococcus aureus, 10% Haemophilus influenzae, 5% Klebsiella pneumoniae, 5% enterobacter).

Pleural effusion culture was performed in 4.6% of the patients, being positive in 14.3%.

Ampicillin-sulbactam (39%) and ampicillin-sulbactam associated with clarithromycin (35%) were the most frequently antibiotics used.

The clinical follow-up showed sepsis (n=7, 4.2%), sensory impairment (n=7, 4.2%), acute renal failure (n=5, 3%), respiratory failure (n=4, 2.4%) and death (n=3; 1.8%). No patient had deep venous thrombosis, pulmonary thromboembolism or extrapulmonary infection.

25OHD levels in hospitalized adults with CAP

The 25OHD level in the whole group was 11.9±7.6 ng/ml (51.5%: <10 ng/ml, 33.5%: 10-20 ng/ml, 13.2%: 20-30 ng/ml, 1.8%: >30 ng/ml). A significant correlation was found between 25OHD and age (r= -0.17; p=0.02). Furthermore, higher 25OHD were found in male (female: 10.8±6.7 ng/ml, male: 13.5±8.5 ng/ml, p=0.02). Due to the characteristics of the pathology under study, 54% of the determinations were in winter, 28% spring, 2% summer and 15% autumn. As expected 25OHD levels in winter-spring (11.0±6.4 ng/ml) were lower than summer-autumn (16.1±10.9 ng/ml, p=0.01).

We didn´t found correlation either C-reactive protein (CRP) and eritrosedimentation rate (ERS) in our study (data not showed)

25OHD levels according to severity and comorbilities scores

The CURB65 index was 66.5% low risk, 16.0% intermediate risk and 17.5% high risk. According to Charlson comorbidity index (CCI) 53.5% had not comorbidity (CCI=0) and 46.5% showed CCI≥1.

Despite a correlation between 25OHD and CURB-65 index (r= -0.13; p=0.049) was found, the CURB-65 showed no differences according to 25OHD levels and no differences in 25OHD levels was observed according to CURB-65 (low risk 0-1: 11.9±7.5 ng/ml; intermediate/high risk 2-5: 11.6±7.3 ng/ml).

A correlation between 25OHD and CCI (r= -0.20, p=0.007) and with the 10 years life expectative (%) (r= 0.19; p=0.008) were also observed. In addition a higher CCI according to 25OHD categories (<10, 10-20 and >20 ng/ml) levels (p=0.05) was observed and higher 25OHD levels according to lower CCI (CCI 0= 13.0±8.2, CCI ≥1= 10.5±6.7 ng/ml; p=0.0093) was also found.

Discussion

It´s known that there is a high prevalence of vitamin D insufficiency and deficiency in adults and adolescent around the world. This is accentuated in the winter months and in high altitude areas. Here, we found only 1.8% with 25OHD >30 ng/ml and a high prevalence of 25OHD deficiency (85%) among hospitalized adults with CAP. This could be explained in part by the CAP characteristics with a high prevalence in winter (54% in our study population). However, the CAP in summer-autumn also showed deficiency levels (16.1±10.9 ng/ml). Moreover, Lu et al investigate the correlation between the level of 25OHD and CAP in elderly hospitalized patients and they found that patients hospitalized by CAP had lower 25OHD levels respect non-pneumonia group.[18]

Serum 25OHD levels in women was lower than in men but no difference according BMI was observed our study. Moreover, no correlation between 25OHD levels and BMI was found. Others authors described higher 25OHD level with normal BMI than those with overweight and obesity.[19] We also found that vitamin D deficiency is negatively associated with age. These findings were observed even in children with CAP. These patients with vitamin D deficiency had a significantly higher neutrophil percentage, but significantly lower lymphocyte percentage so vitamin D deficiency could affect the immune response in children with CAP.[20] We did not find differences in the others biochemical determinations when the groups were stratified according to 25OHD levels.

In addition, no differences in X-ray and blood and sputum cultures characteristics were found according to 25OHD levels. The microbiological rescue obtained in the blood culture was similar to that described in the literature as the used therapy. [21,22]

Although in our study we had low number of complications, this may be due to the fact that high-risk patients were not included, since only hospitalized patients were considered in the general room.

When we analyzed the medical history we found that patients with COPD had lower 25OHD levels respect others pathologies. Despite the small number of patients with 25OHD >20 ng/ml, this was previously reported by others authors.[23,24]

Kim et al found 80.4% vitamin D deficiency (<20 ng/ml) in patients hospitalized with CAP and serum vitamin D level was negatively associated with risk of 28-day mortality.[25] Here we showed similar percentage of 25OHD deficiency but the design of our study did not allow us to estimate mortality. A meta-analysis published of fourteen observational reports published from January 2000 to March 2014 suggests that vitamin D deficiency increases susceptibility for severe infections and mortality of the critically ill. They found 25OHD levels less than 20 ng/ml were associated with increased rates of infection (RR 1.49), sepsis (RR 1.46), 30-day mortality (RR 1.42) and in-hospital mortality (RR 1.79). In a subgroup analysis of adjusted data including vitamin D deficiency as a risk factor for 30-day mortality the pooled RR was 1.76.[26]

The different cutoff levels used by different studies are based with different study endpoints as fracture or osteoporosis and were done in the general population. So the applicability of these cutoff levels in the critically ill is unclear because cutoff values perhaps are different in pleiotropic endpoints.[26] Serum 25OHD concentration has been linked to mortality from all causes, cardiovascular diseases and respiratory diseases in different studies, but appropriate cutoffs to define risk categories are under debate.[27]

The PSI (Pneumonia Severity Index) is used to classify in five risk class the severity of a patient with pneumonia.[28] Through this score it can establish if the patients should be treated as outpatients or as hospitalized patients. But this index considers as comorbidities neoplastic disease, liver disease, renal disease, congestive heart failure and cerebrovascular disease giving a score to each of them. In our study the three first comorbidities were consider as exclusion criteria because of their interference with vitamin D metabolism. For the reasons described, we didn´t used PSI in our study. Despite the knowledge that chronic kidney disease, chronic liver disease and neoplastic disease influence with the metabolism of vitamin D, many published studies did not exclude these important factors. Remmelts et al studied 272 hospitalized patients with CAP and they found vitamin D deficiency was associated with adverse outcome in CAP and that vitamin D status was an independent predictor of 30-day mortality and adds prognostic value to other biomarkers and prognostic scores in the PSI score.[29]

CURB-65 index is one of the most frequently tools used for evaluating CAP-associated risk of mortality and clinical severity.[15] As CCI is a method of classifying comorbidity and a valid method of estimating risk of death from comorbid disease.[16] In our study 25OHD levels correlated with CURB65 score and CCI and with the 10 years life expectative (%). Traditionally biomarkers of infection for diagnostic and prognostic purposes have widely been used such as white blood cell count, CRP and eritrosedimentation rate but their prediction of risk in CAP is limited. We didn´t found correlation either CRP and eritrosedimentation rate in our study.

Conclusion

It is concluded that hospitalized adults with CAP have a high percentage of severe deficiency of 25OHD levels and high Charlson comorbidity index which could lead to higher CAP severity.

The knowledge of the characteristics of our population with CAP diagnosis is important for a better therapeutic approach.

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Conflict of Interest

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Table 1. Baseline characteristics and medical history of hospitalized adults with CAP

	All patients (n=167)	25OHD <10 ng/ml (n=86)	25OHD 10-20 ng/ml (n=56)	25OHD >20 ng/ml (n=25)	p-value *
Baseline Characteristics					
Age (years)	57.4±19.6	61.3±17.9[a]	50.6±19.4[b]	59.2±22.0[a,b]	**0.0050**
Sex (n,%)					**0.0390**
Female	99 (59.3)	58 (68.6)	27 (48.2)	13 (52.0)	-
Male	68 (40.7)	27 (31.4)	29 (51.8)	12 (48.0)	-
BMI (kg/m^2)	27.2±7.8	27.0±6.9	28.4±9.7	25.3±5.5	ns
Smoking status (n,%)					ns
Non smoker	110 (65.9)	54 (62.8)	36 (64.3)	20 (80.0)	-
Current or ex-smoker	57 (34.1)	32 (37.2)	20 (35.7)	5 (20.0)	-
Alcohol intake (n,%)					ns
Non-drinker	154 (92.2)	81 (94.2)	50 (89.3)	23 (92.0)	-
Current (> 3 units /day)	13 (7.8)	5 (5.8)	6 (10.7)	2 (8.0)	-
Days of hospitalization	6.0 (3-8)	6.0 (4-8)	5.5 (3-9)	4.0 (2-8.5)	ns
Medical History					
Asthma [#]	20 (12.0)	8 (9.3)	9 (16.1)	3 (12.0)	ns
Bronchiectasis [#]	1 (0.6)	1 (1.2)	0 (0)	0 (0)	ns
COPD [#]	21 (12.9)	17 (20.2)	7 (7.3)	0 (0)	**0.0104**
Splenectomy [#]	0 (0)	0 (0)	0 (0)	0 (0)	ns
Hospitalization in the last year [#]	21 (12.9)	11 (12.9)	8 (14.5)	2 (8.7)	ns
Hospitalization for pneumonia [#]	11 (6.7)	5 (5.9)	4 (7.4)	2 (8.0)	ns

*Mean±standard deviation (SD) for normally distributed data or media (25th-75th percentiles) for sewed data. [#] Dichotomous variables (yes/no); only the n and percentage of the "yes" are shown. BMI: Body Mass Index; COPD: chronic obstructive pulmonary disease. Values bearing different letters between columns are significantly different (p<0.05). *Comparison between the three 25-hydroxyvitamin D categories.*

Table 2. Symptoms and physical examination in of hospitalized adults with CAP

	All patients (n=167)	25OHD <10 ng/ml (n=86)	25OHD 10-20 ng/ml (n=56)	25OHD >20 ng/ml (n=25)	p-value *
Symptoms					
Sputum [#]	125 (74.9)	65 (75.6)	43 (76.8)	17 (68.0)	ns
Dyspnea [#]	120 (71.9)	65 (75.6)	38 (67.9)	17 (68.0)	ns
Fever [#]	135 (80.8)	69 (80.2)	47 (83.9)	19 (76.0)	ns
Hypothermia [#]	3 (1.8)	2 (2.32)	1 (1.8)	0 (0)	ns
Chest pain [#]	61 (36.5)	29 (33.7)	24 (42.9)	8 (32.0)	ns
Abdominal pain [#]	9 (5.4)	4 (4.7)	4 (7.1)	1 (4.0)	ns
Days of clinical symptoms at admission	4 (2-7)	4 (2-7)	3 (1.25-5)	5 (2.5-6)	ns
Physical examination					
Systolic blood pressure (mmHg)	120 (100-130)	120 (100-130)	120 (110-130)	120 (100-130)	ns
Diastolic blood pressure (mmHg)	70 (60-80)	70 (60-80)	70 (60-80)	70 (60-80)	ns
Heart rate (beats per minute)	90 (80-100)	90 (82-100)	90 (80-100)	86 (72-104)	ns
Respiratory rate (cycles per minute)	23 (20-28)	24 (20-28)	22 (20-28)	20 (19-28)	ns
Mental Confusion [#]	21 (12.6)	13 (15.1)	4 (7.1)	4 (16.0)	ns
Arterial hypotension [#]	9 (5.4)	5 (5.8)	2 (3.6)	2 (8.0)	ns
Crackling [#]	135 (80.8)	71 (82.6)	44 (78.6)	20 (80.0)	ns

*Media (25th-75th percentiles). *Comparison between the three 25-hydroxyvitamin D categories. [#] Dichotomous variables (yes/no); only the n and percentage of the "yes" are shown.*

Table 3. Biochemical measurement in of hospitalized adults with CAP.

	All patients (n=167)	25OHD <10 ng/ml (n=86)	25OHD 10-20 ng/ml (n=56)	25OHD >20 ng/ml (n=25)	p-value *
Hematocrite (%)	37.8 (34.0-41.1)	37.2 (33.8-41.4)	38.0 (35.8-41.4)	36.9 (33.5-40.5)	ns
Haemoglobin (mg/dl)	12.5 (11.2-13.8)	12.4 (10.9-13.8)	12.9 (11.6-13.8)	12.1 (11.1-14.1)	ns
White blood cell count ($10^3/mm^3$)	14.1 (9.6-18.4)	14.1 (98.9-18.7)	14.0 (9.7-18.3)	14.5 (8.7-18.3)	ns
Neutrophils (%)	83 (75-88)	84 (75-88)	81 (74-87)	83 (77-87)	ns
Lymphocytes (%)	10 (6-15)	10 (6-15)	10 (8-14)	12 (6-16)	ns
Platelets (mil/mm^3)	241 (185-317)	239 (173-318)	237 (184-311)	268 (202-337)	ns
Uremia (mg/dl)	36.5 (24.5-53.5)	35.0 (26.0-55.0)	42.0 (23.5-53.0)	34.5 (24.0-66.5)	ns
Creatinine (mg/dl)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	0.9 (0.6-1.2)	0.8 (0.7-1)	ns
Blood glucose (mg/dl)	118 (102-151)	119 (102-158)	117 (101-151)	118 (103-139)	ns
Natremia (mEq/l)	135 (132-139)	135 (132-140)	134 (132-137)	137 (132-140)	ns
Albuminemia (g/dl)	3.1 (2.5-3.4)	3.1 (2.5-3.5)	2.8 (2.5-3.3)	3.1 (2.6-3.6)	ns
Total proteins (g/dl)	6.3 (6.0-6.9)	6.4 (5.9-6.9)	6.3 (6.0-6.9)	6.3 (6.1-7.0)	ns
Aspartate transaminase (mUI/ml)	23.0 (16.0-39.5)	23.0 (17.5-39.5)	23.0 (16.0-49.5)	17.0 (12.5-38.5)	ns
Alanine transaminase (mUI/ml)	22.0 (17.0-38.5)	22.0 (18.0-30.5)	22.0 (15.0-55.0)	23.0 (13.5-32.5)	ns
Total alkaline phosphatase (UI/l)	133 (84-205)	139 (89-209)	108 (74-190)	158 (87-231)	ns
Arterial pH	7.42 (7.39-7.45)	7.42 (7.38-7.45)	7.43 (7.40-7.45)	7.43 (7.40-7.48)	ns
PO_2	72.0 (63.0-89.0)	74.0 (62.0-89.0)	70.5 (58.5-86.8)	76.0 (64.5-87.5)	ns
PCO_2	32.6 (28.1-36.0)	33.0 (28.0-37.0)	32.3 (29.3-35.0)	33.0 (28.0-34.0)	ns
HCO_3	21.0 (19.2-23.3)	21.0 (18.3-23.3)	21.0 (20.0-23.0)	21.5 (19.9-24.5)	ns
% sat	95.0 (92.0-96.7)	94.4 (92.0-96.0)	94.1 (90.0-97.0)	95.5 (93.5-97.0)	ns
C-reactive protein (mg/dl)	35 (17-106)	41 (21-110)	27 (10-110)	49 (10-86)	ns
ESR (mm/h)	56 (25-82)	58 (30-83)	55 (23-78)	75 (27-94)	ns

*Mean±standard deviation (SD) for normally distributed data or media (25th-75th percentiles) for sewed data. ESR: eritrosedimentation rate; CURB-65: Confusion, Urea, Respiratory rate, Blood pressure, age ≥65. *Comparison between the three 25-hydroxyvitamin D categories.*