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Trabajo Original

Pediatría

Vitamin D levels and their association with oxidative stress and inflammation markers in patients with cystic fibrosis

Niveles de vitamina D y su asociación con marcadores de estrés oxidativo e inflamatorios en pacientes con fibrosis quística

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Abstract

Introduction: cystic fibrosis is a disease that causes inflammation, oxidative stress and metabolic changes that lead to nutrient deficiency, such as vitamin D deficiency. On the other hand, it is suggested that vitamin D has anti-inflammatory and antioxidant actions.

Objective: to evaluate the prevalence of hypovitaminosis D and the association between serum 25 hydroxyvitamin D levels with markers of oxidative stress and inflammation in patients with cystic fibrosis.

Method: a cross-sectional study was carried out with 48 patients with cystic fibrosis including children, adolescents and adults in the northeast region of Brazil. Blood collection was performed for analysis of 25-hydroxyvitamin D, calcium, parathyroid hormone, inflammatory process (C-reactive protein [CRP] and alpha-1-acid glycoprotein-A1 [A1GPA]) and oxidative stress (malondialdehyde (MDA) and total antioxidant capacity [CAOT]). The statistical analysis was performed using the "Statistical Package for the Social Sciences", adopting a significance level of $p < 0.05$.

Results: vitamin D insufficiency/deficiency was found in 64.6 % of patients. After multiple linear regression analysis, MDA showed an inverse association with blood values of 25-hydroxyvitamin D ($p < 0.05$) conditioned by the presence of inflammatory process markers. When only oxidative stress was evaluated, this association disappeared.

Conclusion: in conclusion, there was a high prevalence of hypovitaminosis D, with 25(OH)D levels associated with greater oxidative stress when combined with inflammatory markers. Improved vitamin D levels may be an alternative to reduce the damage caused by excess oxidative stress and inflammation in CF patients.

Keywords:

Vitamin D. Cystic fibrosis. Oxidative stress.

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Resumen

Introducción: la fibrosis quística es una enfermedad que cursa con inflamación, estrés oxidativo y cambios metabólicos que conducen a deficiencia de nutrientes como la vitamina D. Por otro lado, se sugiere que la vitamina D tiene acción antiinflamatoria y antioxidante.

Objetivo: evaluar la prevalencia de hipovitaminosis D y la asociación entre los niveles séricos de 25 hidroxivitamina D con los marcadores de estrés oxidativo e inflamación en pacientes con fibrosis quística.

Método: estudio transversal realizado con 48 pacientes con fibrosis quística, niños, adolescentes y adultos, de la región nordeste de Brasil. Se realizó una extracción de sangre para el análisis de 25-hidroxivitamina D, calcio, hormona paratiroidea, proceso inflamatorio (proteína C-reactiva [PCR] y alfa-1-glucoproteína ácida-A1 [A1GPA]) y estrés oxidativo (malondialdehído [MDA] y capacidad antioxidante total [CAOT]). El análisis estadístico se realizó utilizando el "Paquete Estadístico para las Ciencias Sociales", adoptando un nivel de significancia de $p < 0,05$.

Resultados: se encontró insuficiencia/deficiencia de vitamina D en el 64,6 % de los pacientes. Después de un análisis de regresión lineal múltiple, la MDA mostró una asociación inversa con los valores sanguíneos de 25-hidroxivitamina D ($p < 0,05$) condicionado a la presencia de marcadores de proceso inflamatorio; cuando solo se evalúa el estrés oxidativo, esta asociación desaparece.

Conclusión: en conclusión, hubo una alta prevalencia de hipovitaminosis D, con niveles de 25(OH)D asociados a mayor estrés oxidativo cuando se combina con marcadores inflamatorios. La mejora de los niveles de vitamina D puede ser una alternativa para reducir el daño causado por el exceso de estrés oxidativo y la inflamación en pacientes con FQ.

Palabras clave:

Vitamina D. Fibrosis quística. Estrés oxidativo.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disease characterized by pulmonary hyperinflammation followed by destruction of airway walls and fibrosis, resulting in a gradual decline in lung function, high oxidative stress, and impaired antioxidant/oxidant balance, among other systemic alterations (1-2). It is caused by mutations in the Cystic Fibrosis Transmembrane Regulatory Protein (CFTR), leading to absent or diminished CFTR protein function on the cell surface (2). Dysfunction in this protein affects the respiratory, gastrointestinal, hepatobiliary and immune systems (2,3,17).

The inflammatory process in CF behaves chronically, promoting an imbalance between pro- and anti-inflammatory mediators (3,4). It is believed that the inflammatory response and excess oxidative stress play a decisive role in the progression of lung damage and CF severity (5,6). Some studies have already demonstrated a relationship between HR and oxidative stress, and the role of antioxidants (2-6). However, the role of vitamin D has not yet been investigated in CF patients.

Most CF patients are at risk for vitamin D deficiency due to poor nutrient absorption, caused by pancreatic insufficiency, impaired metabolism, and lack of sun exposure (6,7). The prevalence of vitamin D deficiency/insufficiency in the CF population ranges from 23 % to up to 95 % (3,8,26). Vitamin D is a fat-soluble vitamin that has a known role in the development and maintenance of calcium and bone health (7). In addition to its known bone role, vitamin D may have anti-inflammatory properties, immune function and immune system actions with an antioxidant role (8,9,10).

In view of the immunomodulating role of vitamin D, it is relevant to assess the status of vitamin D in these patients and the possible association of serum levels with markers of oxidative stress and inflammation. Thus, the aim of the study was to assess the prevalence of vitamin D insufficiency/deficiency and to verify its association with markers of inflammatory status and oxidative stress in patients with cystic fibrosis.

METHODS

TYPE OF STUDY AND CASUISTRY

A cross-sectional study with a sample of patients diagnosed according to the criteria of the Cystic Fibrosis Foundation (11). Two important centers of reference in the treatment and monitoring of patients with CF were part of this research: the University Hospital Lauro Wanderey (HULW), located in João Pessoa, PB, the largest of the two centers located in the state of Paraíba, and the Integral Medicine Institute Professor Fernando Figueira (IMIP), located in Recife, PE, the only center of its type located in the state of Pernambuco.

A probabilistic sample value was obtained by the allocation method proportional to the stratum size (12), identifying two strata with different finite populations for the calculation: João Pessoa-PB and Recife-PE. The percentages, as well as the population size of the extracts, were chosen taking into account the population of CF patients in Brazil in 2016, and the distribution by regions listed until the beginning of the study in the latest edition of the document (13). The chosen margin of error was 4.5 %. In order to correct any losses, an increase by 10 % was made, resulting in a sample size calculation of at least 38 patients for a significant representation of this population.

Patients older than 5 years of age with a diagnosis of CF who were under outpatient follow-up at the two hospitals were invited. Patients with indication for or undergoing lung transplantation, with pulmonary exacerbation and/or with renal or hepatic dysfunction were not included. After inclusion and exclusion criteria, data from 48 patients were collected.

Data were collected between August 2018 and December 2019 after the parents or guardians of children and adolescents and the adults signed the Informed Consent Form (FICF) and the Informed Consent Term (TALE, in Portuguese), in compliance with Resolution 466, of December 12, 2012 of the National Health Council (14). The study was previously approved by the ethics committee of the two institutions with the CAE number 87354018.1.0000.5183 and CAE number 12994619.6.1001.5201, respectively.

ASSESSMENT OF CLINICAL, SOCIAL AND NUTRITIONAL FACTORS

The patients were interviewed through a previously structured questionnaire for clinical and nutritional evaluation, through an interview using a previously elaborated form.

The skin phototype was classified from I to VI, as proposed by Fitzpatrick (15), where the patient was asked about the description of their skin, whether it burns easily, rarely, or never, and also about its sensitivity to the sun, ranging from slightly sensitive to very sensitive. With this information, the skin phototype was classified ranging from white (I) to black (VI).

Participants were weighed on a digital anthropometric scale, with the patient standing upright in the center of the equipment, with his back to the scale, feet together, barefooted, wearing light clothing, and arms extended along the body. To measure the height of the patients they were placed in an orthostatic position, in respiratory apnea, barefooted, with no head decorations. The measurement was read by touching the cursor to the highest point of the head at the end of an inspiration. Ideally, they had to touch the heels, calves, buttocks, scapulae, and back of the head to the stadiometer. When it was not possible to touch these five points, they had to place at least three of them against the stadiometer (16). The classification of nutritional status was performed using the indicators weight/age, BMI/age and height/age, evaluated according to the WHO-2006/2007 curves for patients aged 5 to 18 years (17). For the classification of adult patients (over 18 years and under 60 years), the values proposed by the World Health Organization were used (18).

Vitamin D intake was assessed by applying a 24-hour recall with all participants and a second recall with 40 % of the population studied (19), keeping a minimum period of 30 and a maximum of 45 days between the application of a recall and the next one. Vitamin D intake was calculated using the Virtual Nutri plus software. The residual nutrients method (MSM) (20) was used to control the effect of intrapersonal energy consumption in the evaluation of micronutrients.

BIOCHEMICAL COLLECTION AND ASSESSMENT

Approximately 20 ml of blood were collected from patients fasting for 8 to 12 hours, informed in advance by a trained team at each pole. Serum levels of 25-hydroxyvitamin D (25(OH)D), parathyroid hormone (PTH) and calcium were measured by chemiluminescent immunoassay (Liaison XL Diasorin). The classification of vitamin D levels was performed based on the reference values used by the Cystic Fibrosis Foundation (12) — sufficient levels above 30.0 ng/mL, insufficient 25(OH)D levels below 30.0 ng/mL, and deficiency below 20.0 ng/mL.

Inflammatory markers (ultra-sensitive C-Reactive Protein (US-CRP), alpha-1-acid glycoprotein [A1GPA]) were analyzed by the immunochemical method of turbidinomotry. For oxidative stress, the analysis was through the evaluation of an oxidizing marker, malondialdehyde (MDA), analyzed by the thiobarbituric acid reaction method (TBARS) (21), and total antioxidant capacity (CAOT), analyzed by the DPPH method (22). Tests were also performed to assess liver function (alanine transaminase [ALT], aspartate transaminase [AST]), renal function (urea, creatinine, uric acid), in order to evaluate patients regarding inclusion criteria.

STATISTICAL ANALYSIS

A descriptive analysis of all study variables was performed, data were analyzed using the Statistical Package for Social Sciences for Windows, version 22.0 (SPSS Inc., Chicago, IL). All data were checked for normal distribution using the Kolmogorov-Smirnov test. To assess the existence of possible differences between the means of patients according to vitamin D status, Student's T-test or the Mann-Whitney test were used.

Simple linear regression analyses were performed to identify the variables associated with serum 25(OH)D levels to develop the multiple linear regression model, which also included variables that, despite not having associations, have an association already reported in the literature (8,9). The existence of colinearity between the explanatory variables was assessed. Throughout the study, tests whose p-value was less than 0.05 were considered significant.

RESULTS

This study evaluated 48 patients who met all the inclusion criteria, 26 of whom were male (54.2 %). Among these individuals, 56.4 % were adolescents, followed by 27.1 % of children between 5 and 10 years of age and 16.7 % of adults between 20 and 45 years old. The mean age of the studied group was 14.85 ± 7.04 years and 62.5 % reported < 30 minutes of sun exposure per day. The majority of the research population (54%) declared themselves to be of mixed race (n = 26) or (31 %) white (n = 15) (Table I). As for the use of vitamin supplementation, only 35.4 % (n = 17) reported using some vitamin supplementation according to medical prescription, and 3 participants used vitamin D daily (800 to 2000 IU/day). Regarding nutritional status, more than 40 % of patients were considered to have a low-weight nutritional status.

Vitamin D insufficiency/deficiency was observed in 64.6 % (n = 31) of patients, and there was no statistically significant difference between genders and age groups. As for the dietary intake of vitamin D, the participants consumed an average of 4.80 ± 2.15, with no difference between the sufficiency and hypovitaminosis D groups (p = 0.81). Vitamin D levels were grouped into two classes: sufficient (25(OH)D ≥ 30 ng/mL) and insufficient/deficient (25(OH)D < 30 ng/mL). Mean serum 25(OH)D levels were 33.84 ± 3.10 ng/mL in the sufficient group, and 22.41 ± 5.0 ng/mL in the vitamin D insufficiency/deficiency group. No significant differences were found between anthropometric parameters, skin phototype, exposure time, serum calcium levels and consumption, inflammatory markers and oxidative stress with nutritional status of vitamin D (insufficient/deficient or sufficient) (Tables II and III).

Table I. General characteristics of and vitamin D status in patients with cystic fibrosis in northeastern Brazil

Characteristics	Total
n (%)	
Number of patients	48
Gender	
Female	22 (45.8)
Male	26 (54.2)
Color	
Mixed race	26 (54.2)
Black	7 (14.6)
White	15 (31.3)
Others	0 (0)
Degree of education of persons responsible	
Illiterate	1 (2.1)
Elementary School	19 (40.4)
High School	18 (38.3)
≥ Graduation	9 (19.2)
Skin phototype	
Type 1	5 (10.4)
Type 2	9 (18.8)
ype 3	17 (35.4)
Type 4	8 (16.7)
Type 5	5 (10.4)
Type 6	4 (8.3)
*Status of 25 OH D**	
Sun exposure	
< 30 minutes/day	30 (62.5)
> 30 minutes/day	18 (37.5)
25 (OH) D status	
Vitamin D insufficient/deficient, < 30ng/mL	31 (64.6)
Sufficient vitamin D, ≥ 30 ng/Ml	17 (35.4)

*Data presented in number (n) and percentage (%). *Parameters adopted from Cystic Fibrosis Foundation (18). 25(OH)D: 25-hydroxyvitamin D.*

Table II. Association between 25(0H)D status and metabolic parameters in patients with cystic fibrosis treated in northeastern Brazil

Serum 25-hydroxyvitamin D concentrations				
	Total of variables n = 48	**Insufficient/Disabled† n = 31**	**Enough† n = 17**	**p***
Age (years)	14.85 ± 7.04	14.53 ± 7.89	15.03 ± 6.61	0.82
Time of sun exposure (minutes/day)	45.2 ± 57.32	48.10 ± 64.33	39.41 ± 42.89	0.54
Vitamin D consumption (mcg)	4.80 ± 2.15	4.400 ± 8.43	5.03 ± 8.74	0.81
Calcium consumption in mg	1096.80 ± 736.87	10077 ± 638.99	1107.21 ± 7995.00	0.89
Serum calcium (mg/dL)	9.52 ± 0.51	9.50 ± 0,65	9.53 ± 0.42	0.85
PTH (mg/dL)	46.17 ± 25.75	44.84 ± 30.46	46.89 ± 23.41	0.80
CRP (mg/dL)	11.25 ± 17.69	11.31 ± 16.40	11.20 ± 18.62	0.98
A1GPA (mg/dL)	115.5 ± 47.47	115.97 ± 50.66	114.21 ± 46.48	0.93
MDA (µmol/L)	3.71 ± 0.92	3.425 ± 0.60	3.870 ± 1.03	0.72
CAOT (%)	18.7 ± 8.47	18.46 ± 8.97	19.25 ± 8.32	0.77

*Data presented as mean ± standard deviation. *Significant p with $p < 0.05$. †Parameters based on Cystic Fibrosis Foundation (18). A1GPA: alpha 1 acid glycoprotein; CAOT: total antioxidant capacity; MDA: malondialdehyde; CRP: C-reactive protein; PTH: parathyroid hormone. T-test or its non-parametric Mann-Whitney match.*

Table III. Multiple linear regression model to predict serum 25(OH)D levels

Variables	Coefficient	p	r^2
Model 1			
Serum calcium	2.395	0.28	0.179
MDA	-3.318	0.14*	
CAOT	-0.150	0.23	
CRP	3.651	0.57	
Model 2			
Serum calcium	1.465	0.66	0.128
MDA	-3.019	0.04*	
CAOT	-0.109	0.40	
A1GPA	0.034	0.25	
Model 3			
Serum calcium	0.841	0.69	0.098
MDA	-2.053	0.84	
CAOT	-0.134	0.30	

*Multiple linear regression models. The variables age and gender, height and gender were inserted as confounding variables to adjust the linear regression models. *Significant value, p-value < 0.05. Dependent variable: A1GPA: alpha 1 acid glycoprotein; CAOT: total antioxidant capacity; MDA: malondialdehyde; CRP: C-reactive protein; 25(OH)D: 25-hydroxyvitamin D.*

When performing multiple regression analysis to estimate the association of variables with serum 25(OH)D levels, variables with associations reported in the literature were considered. Variables were adjusted for gender and age. The variable BMI showed multicolinearity and was removed from the model, and the variables A1GPA and CRP were analyzed in different models for also presenting multicolinearity (> 0.800). Sun exposure values were not included in the model due to the presence of outliers. MDA levels showed a negative association with serum 25(OH)D levels when associated in the model with the inflammatory process markers CRP ($p = 0.14$) and A1GPA ($p = 0.40$). When evaluated without the presence of inflammatory markers, this association did not remain ($p = 0.84$).

DISCUSSION

Individuals with CF have difficulty maintaining vitamin D status due to malabsorption induced by pancreatic insufficiency, low sun exposure, and insufficient intake of vitamin D-containing foods (23). The present study found a high prevalence of vitamin D insufficiency/deficiency. The study (11) investigated 45 patients with CF in the São Paulo region regarding the association of vitamin D levels, and observed a percentage of 43.56 % of hypovitaminosis D in children and preschool children. Similar data (24) were collected in the state of Rio Grande do Sul, where the authors evaluated 37 children and adolescents with cystic fibrosis, finding a prevalence of 54 %. They also found 59 % ($n = 35$) of adults with CF with less than ideal levels of 25 hydroxyvitamin D (25). Therefore, based on these previous data, we can classify the prevalence of the present study as HIGH.

In addition to decreased intestinal absorption, poor nutritional intake and poor adherence, other factors that contribute to vitamin D deficiency in CF include decreased outdoor activity and exposure to sunlight (23). Northeastern Brazil has a sunlight exposure for most of the year that is more accentuated than in the regions already studied, which could positively favor the maintenance of serum vitamin D concentrations, but this study showed that the fact of living in a sunny region was not enough to have adequate levels of vitamin D. Although sun exposure is an influencing variable in vitamin D status, results still diverge in studies on other populations in sunny locations (26,27). In the CF population (27) an association of vitamin D status with sun exposure was shown in the last 3 years, counteracting our results. Thus, studies are suggested to standardize the time of assessment of sun exposure and its association with characteristics such as pathophysiology, season of the year, and skin phototype.

Inflammation is an important contributor to CF disease progression, and anti-inflammatory therapies can improve clinical outcomes (4-10). The resulting chronic infection and airway inflammation can lead to progressive lung destruction, increasing the severity of the disease(28). In the present study, it was possible to observe that, although the relationship between the inflammatory character of CF and the association of inflammation with hypovitaminosis is already known, in this study patients with CF showed no differences between the group with vitamin D sufficiency and insufficiency, but it did influence the marker of oxidative stress MDA in the multivariate analysis. A study in CF respiratory epithelial cells showed that the active form of vitamin D, 1,25 dihydroxyvitamin D, significantly reduced inflammatory cytokines (IL-6 and IL-8) stimulated by antigens (29). A double-blind (12), controlled clinical trial with 30 adults with CF pulmonary exacerbation used a single vitamin D3 megadose for 12 weeks. After 12 weeks in the supplemented group there was a trend towards a reduction in IL-6 and TNF-α, but not in the other interleukins evaluated.

Chronic infection and common inflammation in CF patients generate an increase in reactive oxygen species and thus an increase in oxidative stress (2,30,31) playing a role in the progression of lung damage in these individuals (6). Our data indicate the role of inflammation in oxidative stress, since the association of MDA was significant in multivariate models, when associated with the inflammatory process markers evaluated in this study. Larger studies with a greater number of inflammatory and oxidative stress markers are needed to test this hypothesis and the anti-inflammatory and antioxidant role of vitamin D.

Only one (1) study was found evaluating MDA as a marker of lipid peroxidation in CF patients. Lezo and collaborators (2) investigated oxidative stress in 70 patients with CF aged 1 to 18 years. The study evaluated whether supplementation with antioxidant vitamins (A, C and E) can be tailored to individual needs and oxidative status. Oxidative stress markers, lipid 4-hydroxynonenal (HNE-L) and MDA, had an inverse relationship with antioxidant vitamins, particularly vitamin C. No studies were found evaluating the role of vitamin D and oxidative stress in this population.

This is a pioneering study in finding an association between vitamin D levels and markers of oxidative and inflammatory stress in CF patients. However, this claim needs to be validated through further research. The main limitation of our study is the restricted number of oxidative and inflammatory stress markers analyzed. Furthermore, the association found was weak, increasing the need for further studies. Another limitation was that the study was cross-sectional, which could infer causality for the outcome (vitamin D deficiency).

Our study has interesting implications for the scientific community and clinical practice by demonstrating a high prevalence of hypovitaminosis D in patients with CF, a treatable condition that should be better monitored and whose treatment should focus on maintaining serum vitamin D levels within normal levels. The results suggest that further studies should be carried out in order to verify whether the treatment of hypovitaminosis D is able to reduce the classic oxidative stress that normally affects patients with CF.

CONCLUSION

We conclude that most CF patients have insufficient vitamin D levels and that hypovitaminosis D was associated with greater oxidative stress when associated with inflammatory markers. We suggest greater attention should be paid to vitamin D levels and more clinical studies should be performed for a possible role of correcting vitamin D status in improving common oxidative stress in these patients.

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