LUMEN ET VIRTUS

Insufficient serum levels of 25-hydroxyvitamin d are associated with dyslipidemia in the elderly

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ABSTRACT
Objective: To identify possible associations between serum levels of 25-hydroxyvitamin D and dyslipidemia in the elderly. Method: A cross-sectional study. For sample consisted of 80 elderly people monitored at a Geriatric Outpatient Clinic of the University Hospital in Alagoas, Brazil. In this study

sociodemographic variables, lifestyle, health conditions, anthropometrics, body composition and biochemical tests were collected (serum lipid profile, 25-hydroxyvitamin D, us-RCP, PTH and calcium). Results: It was observed that the concentrations of 25-hydroxyvitamin D correlated negatively with the serum concentrations of total cholesterol and LDL-c. There was no association between HDL-c, triglyceride concentrations and the variables studied (p>0.050). 25-hydroxyvitamin D was associated with the diagnosis of dyslipidemia (p=0,032). Discussion: Vitamin D was shown to be a protective factor for the development of dyslipidemia in the elderly studied and the insufficiency in serum level of vitamin D seemed to exert an influence on lipid metabolism, making the elderly even more vulnerable cardiovascular diseases.

Keywords: Vitamin D. Aging. Hyperlipidemias. Cardiometabolic risk factor.;

1 INTRODUCTION

The world's elderly population grows at a fast pace and Brazil follows this trend, and may become one of the countries with the largest number of elderly people in the world (1-3). The population aging process constantly increases the need for knowledge on the factors that affect the prevalence of chronic degenerative diseases associated with age. Among these is dyslipidemia, which is a risk factor for cardiovascular disease (CVD) (4,5).

In addition to the increased prevalence of chronic diseases, nutritional deficiencies are observed in this population, such as hypovitaminosis D, which can be partly explained by decreased sun exposure and aged skin, which delay the conversion of the precursor to vitamin D (cholecalciferol), by ultraviolet light, leading to a reduction in the serum levels of this vitamin (6).

Studies suggest a strong association between hypovitaminosis D and dyslipidemia (7,8). However, the mechanism of interrelation between 25(OH) D and lipid profile serum is not clear, although some hypotheses have already been formulated (9,10).

Thus, the present study aimed to identify possible associations between serum levels of 25-hydroxyvitamin D and dyslipidemia in the elderly registered in a Nutrition Laboratory at a Brazilian Federal University, as well as the prevalence of hypovitaminosis D in this group.

2 METHODS

This is an observational, cross-sectional study. The sample consisted of elderly people monitored at the Geriatric Outpatient Clinic of the University Hospital Prof. Alberto Antunes/HUPAA at the Federal University of Alagoas/UFAL, Brazil, from May 10, 2016 to March 30, 2018, and was guided by the STROBE tool (*Strengthening the Reporting of Observational Studies in Epidemiology*) (11).

For sample calculation, a prevalence of 56% of hypovitaminosis D (disability + insufficiency) was used as a reference in the elderly treated at outpatient clinics in the city of São Paulo – Brazil (12), a sampling error of 10% and confidence level of 95%.

Individuals of both sexes, aged over 60 years or older, who were not using supplements containing vitamins and / or minerals during the period considered were included, by signing the informed consent form.

Elderly people with physical disabilities and/or uncontrolled chronic diseases (tumor diseases, heart disease, chronic gastrointestinal disease, kidney disease, or liver failure) and patients with metabolic diseases that compromise organic vitamin D homeostasis (thyroid diseases, liver diseases, nephropathies) were not included. In this study, there were no dropouts and no elderly people were excluded after being included in the research.

As a research tool, a previously prepared questionnaire was applied during the nutritional consultation, in which sociodemographic variables, lifestyle, health conditions, anthropometrics, body composition and biochemical tests were collected (serum lipid profile, 25-hydroxyvitamin D, us-RCP, PTH and calcium).

Sociodemographic variables were collected: sex (male and female), age (continuous variable), marital status (married or not married = divorced/ widowed/ single), education (in years of study, categorized as < 5 years and ≥ 5 years) and income; The variable "race/skin color was self-reported by the elderly, and for bivariate analyzes they were grouped in black and not black (brown and white).

Regarding lifestyle and health conditions, the following variables were collected: lifestyle (living alone or with family / caregiver), history of self-reported diseases or with a proven medical diagnosis [osteoporosis (yes, no), high blood pressure (yes, no), diabetes (yes, no), stroke (yes, no)]; number of medications currently in use (≤3 or ≥4); smoking history (yes = currently smokes and no = has smoked, never smoked), history of alcoholism (yes = currently drinks, and no = already drank, never drank); practice physical activity (yes or no, regardless of intensity and frequency).

Body mass was measured with the aid of a calibrated digital platform scale, with a capacity of 200 kg and a resolution of 100g. The individuals were weighed without shoes and without adornments, keeping in an orthostatic position (standing, in an upright position; feet apart at hip width; with the weight divided onto both feet), relaxed shoulders and arms laterally loose when reading the weight (13).

Height was estimated by measuring knee height, applying the equations proposed by Chumlea et al. (14).

The knee height was verified with the aid of an anthropometric ruler from the Sanny® brand (São Paulo - SP, Brazil). The individual was instructed to sit or lie down, with the leg bent, forming a 90º angle with the knee. The fixed part of the ruler was placed under the heel and the furniture was brought to two to three fingers of the patella. The reading was taken on the nearest millimeter.

The Body Mass Index (BMI) was calculated by dividing weight (in kilograms) by square height (in meters), expressed in kg/m². For the classification, the Lipschitz (15) criterion was adopted: low

weight with BMI < 22kg/m²; eutrophy, BMI between 22kg/m² and 27kg/m²; and overweight BMI > 27kg/m².

The thickness of the subscapular skinfold was obtained 2 cm below the scapula, obliquely to the longitudinal axis, following the orientations of the costal arches. The individual was instructed to keep his shoulders and arms relaxed for the application of the calibrator.

To measure waist circumference (WC), the protocol by Martins and Lopes (16) was used, which suggests the measurement of WC in the smallest perimeter of the waist. For this, a measuring tape was used for anthropometric measurements (0.1 mm scale).

WC $\geq$ 80cm for women and $\geq$ 90cm for men were considered borderline values for risk of cardiovascular events (17).

The electrical bioimpedance test (BIA) was performed with the individual lying on a non-conductive surface, in the supine position, with arms and legs abducted at 45º. The volunteers were instructed to follow some pre-examination procedures: an eight-hour fast; not performing strenuous physical exercises in the 12 hours prior to the test; not to drink alcohol 48 hours before the test; empty the bladder at least 30 minutes before the evaluation; and, remove metallic objects from the place where the electrodes were placed at the time of the test.

To blood collection and analysis of biochemical parameters, 20mL of blood were collected by a trained health professional, with the participants fasting for 8 hours. Tubes without anticoagulant were used, which, after collection, were wrapped with aluminum foil to avoid incidence of light. Then, the blood was separated with the aid of a centrifuge (SORVALL®, São Paulo-SP, Brazil) at 3,000 rpm, for 15 minutes, to obtain the serum, which was transferred to polypropylene tubes with a capacity of 1.5 ml.

The analysis of this material were performed immediately after collection, in the clinical analysis laboratory of Hospital Universitário Prof. Alberto Antunes (HUPAA) at the Federal University of Alagoas (UFAL). Biochemical analysis of 25-hydroxyvitamin D were performed in an outsourced clinical laboratory in the city of Maceió, state of Alagoas. All analyzes performed were supervised and followed the methods described below.

Tha serum level of 25-hydroxyvitamin D was obtained by a quantitative determination method, which is a direct, competitive test, based on the chemiluminescence principle (CLIA). The 25-hydroxyvitamin D dosing kit (DiaSorin®) was used, with an intra-assay coefficient of variation (CV) of 8.4% to 12.5% and an interassay CV of 8.6% to 11.0%. The cutoff points used to classify the nutritional status in vitamin D were those proposed by Bischoff-Ferrari et al. (18), who defined vitamin D insufficiency when serum level of 25(OH) D are between 10 and 30ng/mL, and sufficiency when levels are above 30 ng/mL.

The lipidogram measurements were performed in the equipment Automation ViteK Systems Clinline 150 (Biomerieux®). Total cholesterol, High Density Lipoproteins – cholesterol (HDL-c) and triglycerides were measured using the enzymatic colorimetry method, while Low Density Lipoproteins – cholesterol (LDL-c) concentration was calculated according to the equation proposed by Friedwald (19).

The values proposed by the update on the Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention of the Brazilian Society of Cardiology were adopted as reference standards (20).

The determination of total serum calcium was performed using an automated colorimetric method, with a range of 8.6 to 10.3 mg/dL being considered normal (21).

To determine the concentrations of us-CRP, the nephelometric method was used, which measures the agglutination of particles covered by antibodies, through the intensity of the reflected light (22). Values up to 5.0 mg/L were considered normal.

For the measurement of parathormone, the electrochemiluminescence technique was used. The incubation time was 18 minutes, the analytical sensitivity was 1.2 ng/L. The reference value of 4 to 58 pg/dL was used.

The collected data were organized in an electronic database, by typing in a spreadsheet of the statistical program SPSS (Statistical Package for Social Sciences), version 20.0®, to obtain the results and later descriptive statistical analysis (frequency, mean / median, interval interquartile - IQ or standard deviation - SD). For all analyzes, an alpha value equal to 5% was adopted. The normality of the distribution of variables was assessed using the Shapiro-Wilk test.

The association between the frequency of categorical variables was determined using Pearson's chi-square test or Fisher's exact test. Correlation measures between continuous variables were measured by Pearson or Spearman correlation, respecting the distribution behavior of the variables. To assess the difference between the means of continuous quantitative variables, the Student's t test was used for parametric variables and the Mann-Witney test for non-parametric variables. The results were expressed as mean ± SD or median + IQ, respectively.

Multivariable regression models, adjusted by sex, age, education, income, alcohol consumption, physical activity, diagnosis of DM, BMI, WC and body fat percentage were proposed to estimate the effect of serum level of 25-hydroxyvitamin D on the serum profile of total cholesterol, LDL-c and HDL-c. The explanatory variables of this study that present biological plausibility for the occurrence of dyslipidemia were inserted in the regression models, according to data from scientific literature, regardless of the alpha value.

As they have a parametric distribution, possible effects between serum levels of 25-hydroxyvitamin D and serum concentrations of lipoproteins (HDL-c and LDL-c) and cholesterol were determined by multivariable linear regression analysis.

Logistic regression analysis was proposed to model possible associations between the occurrence of dyslipidemia (yes = 1; no = 0) and the serum levels of 25-hydroxyvitamin D. Likewise, the explanatory variables of this study that present plausibility were inserted in this model. biological basis for the occurrence of dyslipidemia, according to scientific literature data, regardless of the alpha value.

3 RESULTS

The total sample consisted of 80 elderly people, of both sexes, aged 60 years or older, with 47 dyslipidemic elderly (58.75%) and 33 non-dyslipidemic elderly (41.25%). In the sample, there was a predominance of married women with an income greater than 1 (one) minimum wage, of "non-black" ethnicity. Regarding the socioeconomic, anthropometric, clinical, and biochemical characteristics of the elderly, there was no statistically significant difference between the groups (dyslipidemic and non-dyslipidemic) in any of the variables (Table 1).

There were no statistically significant differences between groups for the variables: age, BMI, WC, body fat percentage, CRP, calcium and PTH (Table 2). In preliminary analyzes of the present study, there was no association between vitamin D insufficiency and dyslipidemia classifications according to the Brazilian Guideline on Dyslipidemia and Atherosclerosis Prevention of the Brazilian Society of Cardiology (data not shown).

It was observed that the concentrations of 25-hydroxyvitamin D correlated negatively with the serum concentrations of total cholesterol and LDL-c, in all models presented. The HDL-c concentration was not influenced by the 25-hydroxyvitamin D concentrations (Table 3).

There was no association between triglyceride concentrations and the variables studied (p> 0.050).

In logistic regression analysis, adjusted for sex, age, education, BMI, WC, body fat percentage, physical activity and diabetes diagnosis, it was observed that the concentration of 25-hydroxyvitamin D was associated with the diagnosis of dyslipidemia ; for each 1 ng / mL of this vitamin, a reduction of approximately 5% in the chance of the elderly being classified as dyslipidemic was observed (OR = 0.931; CI = 95% = 0.873 - 0.994; p = 0.032).

Table 1. Sociodemographic characteristics, anthropometrics, health conditions, lifestyle and biochemical tests of the elderly participants in the study.

	Non-dyslipidemic n=33 (%)	**Dyslipidemic n=47 (%)**	**OR**	**p**
Sex				
Male	7 (21.21)	12 (25.53)	0.78	0.655¥

Female	26 (78.78)	35 (74.46)		
Race/skin color				
Black	4 (12.12)	6 (12.76)	1.06	0.932¥
Not black	29 (87.87)	41 (87.23)		
Educational (years of study)				
<5 years	14 (42.42)	29 (61.70)	0.46	0.089¥
≥5 years	19 (57.57)	18 (38.29)		
Income				
≥ 1 MS	26 (78.78)	37 (78.72)	1.00	0.994¥
< 1 MS	7 (21.21)	10 (21.27)		
Marital status				
Married	11 (33.33)	16 (34.04)	0.97	0.947¥
Not married	22 (66.66)	31 (65.95)		
Smoker				
Yes	1 (3.03)	0 (0.00)	-	-
No	32 (96.96)	47 (100.00)		
Alcohol				
Yes	8 (24.24)	12 (25.53)	1.07	0.896¥
No	25 (75.75)	35 (74.46)		
Physical activity				
Yes	20 (60.60)	26 (55.31)	1.24	0.638¥
No	13 (39.39)	21 (44.68)		
Hypertension				
Yes	22 (66.66)	34 (72.34)	1.31	0.586¥
No	11 (33.33)	13 (27.65)		
Diabetes				
Yes	4 (12.12)	13 (27.65)	2.77	0.107#
No	29 (87.87)	34 (72.34)		
Vitamin D				
>30 ng/mL	26 (78.78)	27 (57.44)	2.75	0.047¥
<30 ng/mL	7 (21.21)	20 (42.55)		
BMI				
Eutrophy and low weight	19 (57.57)	23 (48.93)	1.42	0.446¥
Overweight	14 (42.42)	24 (51.06)		
WC				
Normal	9 (27.27)	8 (17.02)	1.83	0.270¥
High	24 (72.72)	39 (82.97)		
us-RPC				
Normal	32 (96.96)	43 (91.48)	2.97	0.399#
High	1 (3.03)	4 (8.51)		
Calcium				
Normal	32 (96.96)	47(100.00)	-	-
Low	1 (3.03)	0 (0.00)		
PTH				
Normal	29 (87.87)	40 (85,10)	1.26	0.999#
High	4 (12.12)	7 (14,89)		

BMI: Body Mass Index; WC: waist circumference; us-RPC: *Ultra-sensitive C-Reactive Protein*; PTH: parathyroid hormone; MS 1 MS (minimal salary) = US$ 192.24; OR: *odds ratio*.
¥Pearson; #Fisher.

Table 2. Association between antropometric and biochemical variables with dyslipidemia in the elderly participants in the study.

	Non-dyslipidemic (n=33) mean (SD) or median (min/máx)	**Dyslipidemic (n=47)** mean (SD) or median (min/máx)	**CI (95%)**	**p**
Age (years)	66.00 (60.00/78.00)	66.00 (60.00 / 80.00)	–	0.666#
BMI (kg/m^2)	26.21 (4.28)	27.57 (5.23)	-3.55 – 0.85	0.225*
WC (cm)	91.10 (12.53)	93.11 (10.95)	-7.26 – 3.24	0.449*

Body fat (%)	36.48 (7.41)	37.90 (7.01)	-5.33 – 2.47	0.467*
total cholesterol (mg/dL)	200.24 (37.09)	225.37 (41.00)	-42.96 – -7.29	0.006*
LDL-c (mg/dL)	112.27 (31.15)	145.04 (43.20)	-50.27 – -15.26	<0.001*
VLDL-c (mg/dL)	21.00 (11.40/28.80)	32.80 (18.00/110.00)	–	<0.001#
HDL-c (mg/dL)	67.27 (20.35)	55.29 (16.80)	3.68 – 20.27	0.005*
Triglycerides (mg/dL)	101.00 (57.00/144.00)	179.00 (91.00/607.00)	–	<0.001#
us-RCP (mg/dL)	1.10 (0.10/7.20)	1.40 (0.10/8.50)	–	0.531#
Vitamin D (ng/dL)	39.59 (12.60)	34.26 (10.45)	0.19 – 10.48	0.032*
Calcium (mg/dL)	9.95 (0.64)	9.83 (0.57)	-0.14 – 0.39	0.361*
PTH (pg/dL)	38.82 (14.22)	40.38 (15.84)	- 8.43 – 5.30	0.651*

BMI: Body Mass Index; WC: waist circumference; us-RPC: *Ultra-sensitive C-Reactive Protein*; PTH: parathyroid hormone; HDL-c: High Density Lipoproteins - cholesterol; LDL-c: Low Density Lipoproteins - cholesterol; VLDL-c: Very Low Density Lipoproteins - cholesterol. OR: *odds ratio*; SD = Standard desviation; CI: Confidence interval; #Mann Whitney; *Teste T.

Table 3. Linear regression coefficients for serum level of the total cholesterol, LDL-c and HDL-c.

	B	***p***	***R²***	R² *adjusted*
Dependent variable – Total Cholesterol (n = 80)*				
Vitamina D	-0.313	0.030	0.236	0.102
Dependent variable - LDL-c (n = 80)*				
Vitamina D	-0.367	0.013	0.204	0.064
Dependent variable - HDL-c (n = 80)*				
Vitamina D	-0.005	0.971	0.299	0.175

BMI: Body Mass Index; WC: waist circumference; HDL-c: High Density Lipoproteins - cholesterol; LDL-c: Low Density Lipoproteins - cholesterol.
*The models were adjusted for sex, age, education, income, alcohol, physical activity, body fat (%) and diabetes diagnosis;

4 DISCUSSION

The present study evaluated possible associations between serum level of vitamin D and dyslipidemia in the elderly, and observed important relationships between these two variables.

The frequency of individuals classified as having vitamin D insufficiency was higher among dyslipidemic elderly people, when compared to the group with normal serum lipid profile. There were no significant differences between the two groups regarding sociodemographic, anthropometric variables and the frequency of diabetes and hypertension.

Studies on the association between serum level of vitamin D and dyslipidemia in the elderly such as the present study were not found. In the context of the metabolic syndrome, the study by Lima et al. (23), which evaluated 205 volunteers with an average of 57 years of age, found an inversely proportional correlation between serum levels of vitamin D and triglycerides ($r = -1.54$; $p = 0.030$). In another cross-sectional study carried out by Kayaniyil et al. (24), an inverse association was also found between serum levels of 25(OH) D and triglycerides, in patients with metabolic syndrome, from a multiethnic sample.

In the present study, the serum concentration of total cholesterol showed a negative association with the concentrations of 25(OH) D. Similar to cholesterol concentrations, it was observed that LDL-c concentrations were influenced by the levels of 25(OH) D (negative association). Triglycerides and VLDL were not influenced by vitamin D and no relationship was observed between these variables and the other variables studied.

Data similar to those obtained here were found by Chiu et al. (25), in a study with 126 individuals with a mean age (± SD) 26 ± 6 years, where a negative relationship of serum levels of 25(OH) D with CT and LDL-c was observed. In that same study, there was also no association between 25(OH) D and TG.

The relationship between the increase in serum concentrations of atherogenic lipids (total cholesterol and/or LDL-c) and insufficiency in vitamin D, observed in the present study, can be explained by a series of events, which result from the relationship between serum concentrations of vitamin D and PTH. It is suggested that low serum concentrations of 25(OH) D increase serum PTH concentrations, promoting the influx of calcium in adipocytes, which leads to an increase in lipogenesis and consequently, to an alteration in the lipid profile (9,26,27).

The increase in PTH, in addition to promoting lipogenesis (28,29), can modulate adipogenesis by suppressing the vitamin D receptor, which inhibits compounds involved in adipocyte differentiation and maturation (29,30). In general, it is clear that the increase in body fat, common in the aging process, can worsen vitamin D deficiency.

No association was observed between serum concentrations of HDL-c and vitamin D. Lupton (31) observed that individuals deficient in this vitamin (<20 ng/mL) had lower serum levels of HDL-

c (-10.4%, -5.5 mg/dL) and higher levels of all atherogenic lipids. These differences were statistically significant for all lipid variables, in crude analyzes, and remained significant after adjusting for confounding factors ($p < 0.001$ for all variables, in both analyzes).

Although there was no relationship between HDL-c and 25(OH) D, a study by Lee et al. (32), which evaluated 3069 elderly men, observed that individuals with high serum concentrations of 25(OH) D tended to have higher concentrations of HDL-c, than those with lower serum concentrations of 25(OH) D. However, the association between 25(OH) D and HDL-c was not significant after adjusting confounding factors. Likewise, Lupton (31) observed that individuals with deficient levels of this vitamin (<20 ng/mL) had lower serum levels of HDL-C. Supposedly, this relationship can be explained by the fact that vitamin D can increase the concentrations of Apo A-1, which is the main protein component of HDL-c (7,32,33).

In the present study, through logistic regression, an important association was observed between the concentrations of 25(OH) D and dyslipidemia in the elderly; the increase in the concentration of this vitamin was shown to be a protective factor for the development of this disorder.

Although Jorde and Grimnes (7), indicate that high levels of 25(OH) D are associated with a favorable serum lipid profile, it is still not possible to determine the cause-effect relationship between these variables.

The role of vitamin D in inflammation has also been extensively investigated. Vitamin deficiency is associated with increased inflammation and expression of inflammatory cytokines, directly involved with cardiovascular risk (34). Amer and Qayyum (35) observed that C-Reactive Protein (CRP) decreased as the serum level of 25(OH) D increased to 21 ng/ml. There was also a direct relationship between serum levels of 25(OH) D above average and CRP, after adjusting for the traditional cardiovascular risk factors. In the present study, higher levels of us-CRP were observed in the elderly group insufficient in vitamin D, when compared to sufficient (data not shown).

It is important to highlight that due to natural changes in human metabolism over the years, the aging process makes the individual more susceptible to the appearance of chronic non-communicable diseases. In this context, the insufficiency in serum level of vitamin D in the studied population seemed to exert an influence on lipid metabolism, making the elderly even more vulnerable to dyslipidemias and, therefore, to atherogenesis and cardiovascular diseases.

Despite its important contribution to the discussion, this study has some limitations, among them the sample size, the lack of evaluation of food consumption, family history for dyslipidemia, investigation of sun exposure and use of sunscreen. In addition, it is a cross-sectional model, so it is not possible to determine a cause and effect relationship between variables.

5 CONCLUSION

Vitamin D was shown to be a protective factor for the development of dyslipidemia since there was an important association between the concentrations of 25(OH) D and dyslipidemia in the elderly studied. In the present study, a relationship was observed between the increase in serum concentrations of atherogenic lipids, notably total cholesterol and LDL-c, and insufficiency in vitamin D. No associations were observed between serum concentrations of HDL-c, triglycerides, and VLDL-c with this vitamin. Prospective intervention studies to better establish this relationship in the elderly population should be carried out.

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