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Vitamin D role in smoking women and cardiac remodeling

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Abstract

Background: The objective of the study is to evaluate the influence of serum vitamin D concentrations and smoking status in cardiac structure and function.

Methods: The participants of this study were healthy women smokers ($n = 18$, mean age 52.8 years), ex-smokers ($n = 18$, mean age 51.7 years), and never smokers ($n = 19$, mean age 44.4 years). All participants underwent assessment of body composition, dietary intake, sun exposure frequency, vitamin D serum determination, and echocardiographic assessment. All data underwent statistical analysis.

Results: The three groups were classified as overweight. The group of ex-smokers showed significantly higher vitamin D serum concentrations. Smoker group showed a higher posterior wall thickness (PW), left ventricular mass, and left ventricular mass index (LVMI). We identified positive correlations between LVMI and smoking history, PW and vitamin D serum, and body mass index and time of smoking history. Multiple linear regressions showed positive association of smoking history and LVMI and PW, also that serum vitamin D has a positive association with PW. PW was associated with smoking history and serum vitamin D, showing a deleterious effect on the heart of both variables.

Conclusions: Smoking habit in adult women was associated with cardiac remodeling, and excess of vitamin D is associated with the action of smoking on cardiac variables. Thus, higher serum vitamin D values have a deleterious effect on the heart in this model.

Keyword: Smoking, Nutrition, Myocardial dysfunction, Vitamin D

Background

More than one billion individuals worldwide are estimated to have vitamin D deficiency [1]. Additionally, the list of disorders associated with vitamin D deficiency continues to grow [2]. In addition to its classical functions, vitamin D deficiency is associated with cancer, neurodegenerative diseases, cardiovascular diseases, and mortality of all causes [3–6]. Vitamin D deficiency is described as a potential risk factor for cardiovascular disease, primarily ventricular hypertrophy and congestive heart failure [3, 7, 8]. Recently, an experimental study showed that vitamin D-deficient-diet-fed rats presented with cardiac hypertrophy as well as reduced left ventricular fractional shortening and ejection fraction [9]. Furthermore, Mancuso et al. [10] showed an attenuation of cardiac hypertrophy when rats with heart failure received chow with vitamin D supplementation.

Together with deficiency/excess vitamin D, smoking is a risk factor for cardiovascular disease and is the primary cause of preventable death worldwide [11]. Cigarette smoke is thrombogenic, atherogenic, and promotes direct aggression to the heart [12]. Experimental studies showed that animals exposed to cigarette smoke have cardiac alterations also known as cardiac remodeling [13–16]. Clinical studies also showed the effects of cigarette smoking on ventricular remodeling and heart function [17, 18].

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Several authors studied the association between vitamin D and tobacco smoke exposure. Hill et al. [19] observed in a clinical study that smoking was negatively associated with serum vitamin D concentrations in Irish women and in Australia, smokers had lower levels of serum vitamin D [20]. Moreover, Rafacho et al. [16] supplemented cigarette-smoke-exposed rats with vitamin D and observed an attenuation of cardiac remodeling. This study suggests that vitamin D status could influence cardiac alterations caused by tobacco smoke. Thus, the hypothesis of this study is that vitamin D deficiency could worsen cardiac alterations induced by cigarette smoke.

Objective

The objective of the study is to evaluate the influence of serum vitamin D concentrations and smoking status in cardiac structure and function.

Methods

The study was approved by the ethics committee, and the written informed consent was obtained from all of the participants. The sample size was calculated based on the average serum vitamin D concentration, an expectation of a 3 ng/mL difference and a residual expected standard deviation of 2.8 ng/mL for comparing the three groups. Assumptions made were 80 % power and a significance value of <0.05. Using these values, we obtained 18 subjects per group.

A total of 18 active female smokers and 18 female ex-smokers, who were participating in a smoking cessation group, were evaluated. All of the participants, whether smokers or ex-smokers, presented with a history of smoking greater than ten pack-years. Ex-smokers were defined as those who had stopped smoking for more than 6 months before enrollment. Only women were evaluated because of their higher prevalence in our smoking cessation program and to obtain greater homogeneity between groups. The control group consisted of 19 healthy women that were never smokers. Exclusion criteria were as follows: presence of severe or chronic diseases such as hypertension, diabetes, and respiratory diseases; supplementation of calcium and vitamin D; age below 30 years old; body mass index (BMI) higher than 30 kg/m^2; and menopause.

Body composition assessment

Participant weight and height were measured, and BMI was calculated (kg/m^2). BMI was classified according to the cutoff suggested by the WHO [21]. The fat-free mass index (FFMI) and fat mass index (FMI) were estimated (FFM/height^2 and FMI/height^2) based on dual-energy X-ray absorptiometry exam (DXA) using the Hologic instrument, model Discovery A, Bedford, MA, USA. Automated quantification of regional body tissue weights was performed with APEX System software version 2.3.1.

Dietary intake assessment

To assess dietary vitamin D intake, a 24-h recall was used in triplicates. Data from the three food records were calculated using the Nutrition Data System for Research-Grad Pack Software, which was developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN.

Sun exposure assessment

A sun exposure frequency questionnaire was used to analyze the sun exposure of participant. Each answer contained a value defined as an index of sun exposure ranging from 0 (no sun exposure) to 38 (high sun exposure) [22].

Biochemical assessment

Peripheral venous blood was obtained after a 12-h fast in the early morning (8:00 to 10:00 a.m.) to collect 25(OH) vitamin D_3, calcium, and parathyroid hormone (PTH) levels. 25(OH) vitamin D_3 levels were measured by chemiluminescence (Abbott®). Vitamin D deficiency was defined as serum vitamin D levels lower than 12 ng/mL. Risk for inadequacy was defined as serum levels of 25(OH) vitamin D_3 from 12 to 20 ng/mL, and sufficient levels were above 20 ng/mL [23].

Echocardiographic assessment

Transthoracic echocardiography was performed to evaluate cardiac morphology and function by the same operator. The echocardiograph was a General Electric (GE) equipment Vivid 6S with phased-array multifrequency transducers of 2.5 to 3.5 MHz and an image registration system. Images were obtained and analyzed following the recommendations of the American Society of Echocardiography [24]. Intraobserver variability was lower than 3 %. Left ventricular systolic function was evaluated by measuring the ejection fraction according to the Simpson method.

Statistical analysis

ANOVA test was used to compare means between the three groups when the distribution was normal, followed by Tukey's test for pairwise comparisons. The Kruskal-Wallis test followed by Dunn's test was used to compare variables with nonparametric distribution. Pearson's or Spearman's correlation coefficients were used to examine associations between continuous variables according to their distribution. χ^2 was used to compare proportions. Multiple linear regression analyses were used to evaluate the influence of vitamin D and smoking status on echocardiographic variables. Statistical significance was considered when $p < 0.05$. SPSS version 12.0 was used (Statistical Package for Social Science, IBM).

Results

We evaluated 64 women, of whom nine were excluded due to diabetes (two subjects), chronic obstructive pulmonary disease (one subject), and BMI > 30 kg/m^2 (six subjects). Thus, 55 women completed the study protocol.

The average age of the women smokers and ex-smokers was greater than 50 years old. The women in the three groups were classified as overweight. The history of smoking was similar between smokers and ex-smokers (Table 1).

There were no differences in body composition variables (FFMI and FMI) and vitamin D intake among the three groups. The sun exposure frequency questionnaire showed that the smoking subjects (smokers and ex-smokers) had a higher total score compared with the control subjects (Table 1).

Generally, most women studied showed sufficient vitamin D concentrations 65.5 %), and the proportions among the groups were not different. Furthermore, ex-smokers showed significantly higher vitamin D concentrations than the control group.

Echocardiographic morphometric variables are presented in Table 2. The smoker group showed a higher posterior wall thickness (PW), left ventricular mass (LVM), and left ventricular mass index (LVMI) compared with the control group. No differences were observed when comparing the other variables among the groups.

Variables to evaluate systolic and diastolic function are also presented in Table 2. We observed that the ex-smoker group had shorter *E* waves compared with the control group. No differences were observed in other diastolic function variables among the groups. There were also no differences in systolic function variables among the groups.

Correlations between LVMI, PW, serum vitamin D concentrations, vitamin D intake, body composition, and time of smoking are shown in Table 3. We identified positive correlations between LVMI and smoking history, PW and serum vitamin D concentration, and BMI and time of smoking history. Smoking history was used in statistical models because of the higher correlation coefficient obtained in the univariate analysis (Table 3).

Multiple linear regressions revealed a positive association of smoking history, LVMI, and PW (Table 4). Moreover, serum vitamin D concentration was positively associated with PW. Only PW was associated with smoking history and serum vitamin D concentration, showing a deleterious effect of both variables on the heart.

Discussion

The aim of this study was to evaluate the influence of serum vitamin D concentrations and smoking status in cardiac structure and function. Our results suggest that tobacco smoke and higher vitamin D levels induced cardiac remodeling.

Generally, the results showed that smokers and ex-smokers were older than subjects in the control group. The mean BMI classified the subjects as overweight, although the literature cited studied smokers who were underweight or are of normal weight [25]. Differences in fat mass were not observed among groups. The groups were also similar with respect to vitamin D intake; all of them ingested vitamin D below the recommended amount [23].

We observed significantly higher sun exposure indices in the smoker and ex-smoker groups compared with the control group. One possible explanation would be the largest solar exposition caused by smoking habit. In São Paulo state, an established law that prohibits smoking in collective public or private environments forced smokers to smoke in outdoors.

Circulating 25(OH) vitamin D_3 concentration is the most suitable indicator of vitamin D status. This prohormone is stable and has a half-life of approximately 3 weeks [26]. However, the cutoff to define hypovitaminosis D is still not well established. Some authors consider levels higher than 30 ng/ml to define sufficiency [5], while others consider higher than 20 ng/mL an adequate cutoff level [23]. In this study, we used the most recent classification of the IOM

Table 1 Clinical characteristics, smoking, and vitamin D status in the 55 women studied

Variables	Control ($n = 19$)	Smokers ($n = 18$)	Ex-smokers ($n = 18$)	p
Age (years)	44.4 ± 11.0a	52.8 ± 7.0b	51.7 ± 8.0b	0.011*
Smoking time (years)	0	31.3 ± 10.9	28.4 ± 9.0	0.896
BMI (kg/m^2)	25.6 ± 3.7	26.0 ± 3.4	26.6 ± 2.7	0.636
FMI (kg/m^2)	8.0 ± 2.6	8.6 ± 2.2	9.2 ± 1.5	0.262
FFMI (kg/m^2)	16.9 ± 1.6	17.2 ± 2.1	17.4 ± 1.6	0.745
Vitamin D serum (ng/mL)	21.5 ± 6.4a	26.2 ± 10.4ab	30.2 ± 11.9b	0.033*
Vitamin D intake (μg/d)	4.2 ± 2.4	3.3 ± 2.7	3.15 ± 1.9	0.327
Freq sun expo	9.6 ± 4.5a	12.3 ± 4.6b	13.3 ± 3.9b	0.035*

Values followed by different letters (a, b) differ at 5 % by the multiple comparison test (Tukey's test)
BMI body mass index, *FMI* fat mass index, *FFMI* fat-free mass index, *Freq Sun Expo* frequency of sun exposure questionnaire
*$p < 0.05$

Table 2 Cardiac structure and diastolic and systolic functions of the 55 women studied, assessed by the echocardiography

Variables	Control ($n = 19$)	Smokers ($n = 18$)	Ex-smokers ($n = 18$)	p
LVD (mm)	37.0 ± 9.0	45.5 ± 4.41	44.5 ± 4.25	0.213
LVS (mm)	22.8 ± 1.78	26.8 ± 3.06	27.4 ± 3.75	0.493
PW (mm)	8.60 ± 0.54a	10.2 ± 2.13b	9.41 ± 1.53ab	0.023*
2PW/VED	0.49 ± 0.18	0.44 ± 0.66	0.42 ± 0.95	0.788
LVM (g)	115 ± 37.5a	208 ± 89.5b	173 ± 34.7ab	0.008*
LVMI	79.8 ± 21.8a	112 ± 36.4b	99.8 ± 18.6ab	0.002*
AD (mm)	27.2 ± 2.68	29.5 ± 2.34	29.4 ± 3.58	0.061
LAD (mm)	32.2 ± 2.04	35.7 ± 2.16	34.1 ± 3.83	0.175
LAD/AD	1.18 ± 0.96	1.21 ± 0.46	1.17 ± 0.20	0.844
Ejection fraction	0.77 (0.75–0.80)	0.77 (0.75–0.81)	0.77 (0.73–0.81)	0.985
Shortening fraction	0.33 ± 0.26	0.40 ± 0.61	0.38 ± 0.65	0.583
HR (bpm)	70.6 ± 4.09	72.0 ± 11.5	67.4 ± 8.88	0.391
CO (ml/min)	4562 ± 1405	4949 ± 1498	5002 ± 1333	0.550
E (cm/s)	84.4 ± 14.5a	71.8 ± 19.3ab	68.9 ± 19.1b	0.024*
A (cm/s)	74.0 ± 22.4	72.0 ± 18.4	59.9 ± 17.5	0.841
E/A	1.40 ± 0.57	1.01 ± 0.46	1.18 ± 0.53	0.196

Values followed by different letters (a, b) differ at 5 % by the multiple comparison test (Tukey's test)
Abbreviations: LVD left ventricular diastolic diameter, *LVS* left ventricular systolic diameter, *PW* posterior wall thickness, *2PW/LVS* relative wall thickness, *LVM* left ventricular mass, *LVMI* left ventricular mass index, *AD* aortic diameter, *LAD* left atrium diameter, *LAD/AD* left atrium diameter corrected by aorta, *HR* heart rate, *CO* cardiac output, *E* mitral E wave, *A* mitral A wave, *E/A* E wave/A wave ratio
*$p < 0.05$

[23]. This classification considered serum levels of 25(OH) vitamin D_3 lower than 12 ng/mL as vitamin D deficiency and lower than 20 ng/mL as risk of vitamin D inadequacy.

Studies showed high prevalence of hypovitaminosis D in different populations worldwide, including Brazil. In certain Asian, European, and Latin American countries, hypovitaminosis D (<20 ng/mL) prevalence ranged from 20 to 83 % depending on the populations studied [27]. In Brazil, the rate of vitamin D deficiency ranged from 42 to 86 % [28–30]. In the present study, 34.5 % of participants

Table 3 Correlation analysis for the left ventricular mass index and posterior wall thickness

Variables	r	p
LVMI		
Vitamin D serum (ng/mL)	0.263	0.0526
Vitamin D intake (μg/d)	−0.173	0.206
BMI (kg/m^2)	0.143	0.297
FMI (kg/m^2)	0.097	0.478
FFMI (kg/m^2)	0.127	0.356
Smoking time (years)	0.437	0.0009*
PW (mm)		
Vitamin D serum (ng/mL)	0.314	0.0200*
Vitamin D intake (μg/d)	−0.198	0.146
BMI (kg/m^2)	0.294	0.0293*
FMI (kg/m^2)	0.172	0.209
FFMI (kg/m^2)	0.261	0.0543
Smoking time (years)	0.345	0.0102*

PW posterior wall thickness, *LVMI* left ventricular mass index, *Freq Sun Expo* frequency full sun exposure, *PTH* parathyroid hormone, *BMI* body mass index, *FMI* fat mass index, *FFMI* fat-free mass index
*p < 0.05

Table 4 Multiple linear regression model for the left ventricular mass index and posterior wall thickness

Model	R^2	Adjusted (95 % confidence interval)	p
LVMI			
Smoking time (years)	0.229	1.002 (0.48–1.524)	<0.001*
LVMI			
Vitamin D serum (ng/mL)	0.0759	0.776 (−0.016–1.568)	0.056
LVMI			
Smoking time (years)	0.249	0.918 (0.378–1.458)	0.001*
Vitamin D serum (ng/mL)		0.433 (−0.317–1.183)	0.253
PW (mm)			
Smoking time (years)	0.224	0.0416 (0.0148–0.0684)	0.003*
PW (mm)			
Vitamin D serum (ng/mL)	0.245	0.0534 (0.0156–0.0912)	0.007*
PW (mm)			
Smoking time (years)	0.310	0.0337 (0.0067–0.0607)	0.016*
Vitamin D serum (ng/mL)		0.0408 (0.0034–0.0782)	0.034*

Adjusted for age and BMI
PW posterior wall thickness, *LVMI* left ventricular mass index
*p < 0.05

had 25(OH) vitamin D_3 serum levels <20 ng/mL. The proportion of subjects at risk for vitamin D inadequacy was also not different among the groups. The majority of the subjects in the present study had an adequate vitamin D status.

Brot et al. [31] observed a higher frequency of vitamin D deficiency (20.9 %) in the smokers compared with the non-smokers group (13.7 %); however, we did not observe any difference. This finding and the similar serum 25(OH) vitamin D_3 levels between control and smoking groups shows that the smoking habit does not influence vitamin D status. However, the ex-smoker group had higher serum vitamin D levels than the control group. This difference could be due to the higher sun exposure observed in ex-smokers.

The interest in the association of vitamin D and cardiovascular diseases came from animal models and epidemiological studies reporting increased cardiovascular events in subjects with vitamin D deficiency [4, 32–34]. Several studies showed that vitamin D exerts a biphasic "dose-response" curve on cardiovascular physiopathology with deleterious consequences not only in the case of vitamin D deficiency but also when it is in excess [35, 36]. Both vitamin D deficiency [37–41] and high vitamin D levels [42–46] can be associated with structural and functional cardiovascular alterations. In the present study, we observed that serum 25(OH) vitamin D_3 levels were associated with PW using the linear multiple regression model. An increase of 1 ng/mL in serum 25(OH) vitamin D_3 caused a 0.05-mm increase in PW thickness. This finding suggests a deleterious consequence of high serum vitamin D levels on the heart.

Among the cellular and molecular changes that occur in the process of cardiac remodeling by vitamin D excess is oxidative stress. Chen and DeLuca [47] identified a gene (vitamin D upregulated (VDUP-1)) which is positively regulated by vitamin D promyelocytic cell line (HL-60). The VDUP-1 has been identified in several tissues including the heart [48–51]. The protein encoded by VDUP-1 is also known as the thioredoxin-binding protein (TBP-2) or more days, as protein interactions with thioredoxin (TXNIP). It was given these names because, among other functions, it was identified as an endogenous negative regulator of protein thioredoxin (Trx), an important antioxidant protein in the heart [52]. This interaction blocks the binding of Trx with other factors, reducing their reducing activity [53, 54]. Another mechanism that might explain cardiac structural abnormalities could be the increased secretion of fibroblast growth factor 23 (FGF-23). Increased FGF-23 is associated with left ventricular hypertrophy in patients with chronic kidney disease [55, 56] and in patients with systolic heart failure [57]. In an experimental study in which FGF-23 was administered into mice atrium, the induction of cardiac hypertrophy was observed [58]. FGF-23 is one of the hormones that contributes to the regulation of serum phosphorus concentration [59], and it is also known that increasing the concentration of vitamin D increases intestinal absorption and serum phosphorous concentration [46, 60].

A main health disorder linked to smoking is cardiovascular disease [12, 13]. Smoking habits are reportedly associated with cardiac remodeling [12, 13, 61], which is associated with increased risk of heart failure and mortality. In the present study, we observed that the smoking group had higher values of PW thickness, left ventricle mass, and LVM index compared with the control group. In the multiple linear regression model in which LVMI was associated with time of smoking, each 1 year of smoking history increased the LVMI by 1.0 g. In another model, PW was associated with time of smoking, and each year in smoking history increased PW thickness by 0.04 mm. These higher LVM and PW values in smoking subjects were also observed in other studies [17, 62, 63].

The vitamin D-mediated protection effect against the smoking aggression [16] was not observed in the present study. In multiple linear regression models, we showed that vitamin D is another factor associated with the smoking effect in the heart.

What is new/novel about this research? Vitamin D and smoking are risk factors for cardiovascular disease. The present study suggests the deleterious effect of vitamin D to the heart. High serum vitamin D concentration is another factor associated with the action of smoking on cardiac variables.

Some limitations of this study have to be considered. Our study included a small number of women per group. Furthermore, the majority of women assessed were obese, which negatively correlates with vitamin D concentrations. The enrollment of only women limits the generalization of the study.

Conclusions

The smoking habit of adult women was associated with cardiac remodeling, and excess of vitamin D is associated with the action of smoking on cardiac variables. Thus, higher serum vitamin D values have a deleterious effect to the heart in this model.

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Authors' contributions

MPF was responsible for the experimental design, preparation, coordination, and for conducting the study. She performed the statistical analysis and the manuscript redaction. SET was co-advisor, participating of the preparation and coordination of the research. She assisted in the statistical analysis and correction of the text. MGR realized the echocardiogram exams and supported in the interpretation of these results. CBM performed the spirometry tests used as an exclusion criterion, assisting in the interpretation of these results. KNMS conducted the exam requests, the interpretation of the biochemical tests, and the medical examination used as exclusion criteria. BFP supported the text revision. PSAG contributed with the elaboration of the study and text correction. MFM contributed with the results interpretation and text correction. LAMZ helped in the cardiac remodeling data interpretation. SJP was a co-advisor, participating of the preparation and coordination of the study. She also supported the interpretation of the results and text correction. IG contributed with the discussions about the research. SARP was an advisor, helping in the experimental design, preparation, and conducting the study. He also contributed to the statistical analysis and revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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