Association between polymorphisms in the gene encoding the vitamin D receptor, lipid profile and anthropometric parameters in elderly Brazilians

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ABSTRACT

Polymorphisms in the vitamin D receptor gene are associated with the severities of several diseases, including overweight and cardiovascular disease. In addition, vitamin D is an important determinant of health and has several functions in bone homeostasis and in various physiological and metabolic mechanisms. From this perspective, this study aimed to evaluate whether there is an association between the genetic variants Fok1 (rs2228570) and Bsm1 (rs1544410) with circulating metabolic markers of the lipid profile and anthropometric measurements in the elderly. This is a cross-sectional study conducted with 173 elderly people from Teresina, Piauí State, Brazil, whose sociodemographic and health characterization occurred through interviews. 25-hydroxyvitamin D [25(OH)D] was measured by chemiluminescence. The cut-off values used as a reference for serum lipids were from the Update of the Brazilian Guideline on Dyslipidemias and Prevention of Atherosclerosis. Genotyping was performed using the restriction fragment length polymorphism technique. The results showed that there were no statistically significant differences between the association of VDR FokI and BsmI gene polymorphisms with BMI, blood pressure and vitamin D concentrations. However, elderly carriers of the BsmI genotype, specifically Bb heterozygotes, were associated with lower values of triglycerides and HDL-cholesterol.

Keywords: Dyslipidemias, Vitamin D, Polymorphism, Vitamin D Receptor.

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INTRODUCTION

Most of the biological functions of the active form of vitamin D are mediated by the VDR nuclear receptor that regulates the transcription of target genes. This receptor is found in several organs, which implies a broad action of vitamin D, in the regulation of many physiological and metabolic processes, with important repercussions on human health.

The VDR gene is located on chromosome 12q12-q14 and comprises 11 exons and 11 introns, with more than 600 identified single nucleotide polymorphisms (SNPs) in its coding region, however, FokI (rs2228570) and BsmI (rs1544410), located in intron 8, are arguably the most studied SNPs. VDR gene variants have the potential to influence biological outcomes (Abouzid et al., 2018; Jolliffe et al., 2016), as demonstrated its effect on skeletal muscles independent of vitamin D, and decreased expression of the VDR protein is related to the development of various diseases and aging (Manuel et al., 2018).

Studies have related vitamin D deficiency with a higher prevalence of abdominal obesity and/or dyslipidemia in several populations, where blood concentrations of this vitamin have been inversely associated with the atherogenic lipid profile (Cheng et al 2010; Jorde et al., 2010; Skaaby et al., 2012; Ponda et al., 2012; Wang et al., 2016). This type of association has been a cause for concern, since the expression of some genes related to lipid metabolism is regulated by calcitriol (Ramagopalan et al., 2010) and some are activated by VDR (Martínez-Sena et al., 2020), demonstrating that both vitamin D status and VDR function have the potential to affect gene expressions associated with lipid metabolism (Mei et al., 2022).

However, for each of the lipid parameters, such as triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL), the results are inconsistent, as suggested by Dibaba 2019; Wang et al., 2012 in a human study and meta-analyses.

When verifying the effect of polymorphisms on Body Mass Index (BMI), the ff/FF (FokI) and Bb/BB (BsmI) genotypes and the F and B alleles were related to higher BMI (De Oliveira, 2018; Swapna et al., 2011). Another study revealed an association between serum concentrations of 25(OH)D, VDR SNPs (FokI and BsmI) with nutritional status (Bienertová-Vasku et al., 2017).

Although research indicates genetic interactions between the VDR and the lipid profile, anthropometric changes, development of overweight and associated diseases, the results are not consistent. In this scenario, the objective of this study was to evaluate whether there is an association between the genetic variants Fok1 (rs2228570) and Bsm1 (rs1544410) with circulating metabolic markers of the lipid profile and anthropometric measurements in the elderly.

METHODOLOGY

STUDY DESIGN

This study is an excerpt from the doctoral thesis entitled "Global nutritional status of the elderly: Association with sociodemographic factors, Vitamin D Status, arterial hypertension and genetic polymorphisms" of the Graduate Program in Food and Nutrition (PPGAN) of the Federal University of Piauí (UFPI).

POPULATION AND SAMPLE

For this study, the data correspond to a sample composed of 173 (one hundred and seventy-three) elderly people of both sexes, living in the city of Teresina, Piauí, Brazil, where only the variables defined to meet the objectives of this research are included.

SAMPLE SELECTION

Elderly people aged 60 years or older were selected through a random sample from the elderly identification database. The sample calculation was based on the estimate of the standard deviation of 9.3 ng/mL of 25(OH)D, from the population-based study with the elderly in São Paulo, adopting a confidence interval of 95% and an error of 1.39 ng/mL. The distribution of the number of individuals was calculated according to the proportion of elderly people registered in each health care zone, as follows: Central-North (32.6%; n=59), East-Southeast (32.1%; n=58) and South (35.1%; n=64). Data collection took place between 2017 and 2018, at the home, of the elderly randomly selected from the list provided by the health units.

ANTHROPOMETRIC ASSESSMENT AND NUTRITIONAL DIAGNOSIS

For anthropometric evaluation, weight (kg) and height (cm) were measured according to the recommendations of Chumlea; Roche; Steinbaugh (1985). Waist circumference (WC) was obtained by measuring the abdominal region, in its smallest perimeter and was classified as recommended by the World Health Organization (2000): no risk (< 94 cm for men and < 80 cm for women); increased risk (> 94 cm for men and > 80 cm for women) and very high risk (> 102 cm for men and > 88 cm for women).

The Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the height in meters squared. The classification of nutritional status was according to the Pan American Health Organization (2002) for the elderly, which considers the following values and classification: underweight ($\leq$ 23 kg/m^2), normal weight (> 23 and < 28 kg/m^2), overweight ($\geq$ 28 and < 30 kg/m^2) and obesity ($\geq$ 30 kg/m^2).

BLOOD PRESSURE MEASUREMENT

Initially, arterial hypertension was defined based on the medical diagnosis and use of antihypertensive drugs reported by the patients. In addition, the measurement of diastolic and systolic blood pressure (mmHg) was performed in triplicate, as recommended by the Brazilian Guideline on Arterial Hypertension of the Brazilian Society of Cardiology – SBC (2021), using a stethoscope and an aneroid sphygmomanometer of the Premium® brand.

BIOCHEMICAL PARAMETERS

Blood collection was performed by a nursing technician with experience in the area, on the premises of the Basic Health Unit (BHU) to which the elderly person was registered or at the participant's home. The appointment was made by telephone call, one week in advance. Individuals received orientations, following a standardized script, including: fasting for 8 hours from non-alcoholic foods and beverages, fasting for 72 hours for alcoholic beverages, and not performing physical activities or physical exertion on the day scheduled for collection.

For the biochemical evaluation, a 10 mL blood sample was collected by venipuncture, in plastic test tubes with a vacuum polyethylene cap (*vacutainer* type), with separator gel, using disposable plastic syringes, stainless steel and sterile needles. Tubes without anticoagulant were used to determine the lipid profile and with EDTA to evaluate vitamin D and genetic polymorphisms. The transport to the laboratory took place immediately after the harvest, under refrigeration, in a Styrofoam box closed with ice. The samples were analyzed on the day of collection, in a specialized private laboratory according to the methods standardized by the laboratory, using an immunoassay analyzer (Architect c8000).

Serum concentrations of total cholesterol, high-density lipoprotein (HDL-c) and triglycerides (TG) were determined by the colorimetric enzymatic method, using Labtest kits®. The low-density lipoprotein (LDL-c) fraction was calculated according to the formula of Friedwald, Levy & Fredrickson (1972): LDL-c = CT – HDL-c – TG/5.

Vitamin D was measured using the Diasorin LIAISON TM (USA) method. The standardized assay is based on the recognition of vitamin D binding proteins through chemiluminescence. Hypovitaminosis D was defined when 25(OH)D concentrations were < 30 ng/mL and sufficiency occurred when it was ≥ 30 ng/mL, based on the stratified reference intervals for the elderly population according to the Brazilian Society of Endocrinology and Metabolism (2018).

GENOTYPING

Genomic DNA from peripheral blood was extracted using the QIAGEN kit. The evaluation of purity and quality were defined after quantification in the NanoDrop 2000 spectrophotometer, whose 260/280 ratio should be ≥ 1.8 and have a defined band in 1.5% agarose gel. DNA samples were normalized to 20 ng and conventional polymerase chain reaction (PCR) was performed in a Bioer Gene Pro® thermal cycler. and for PCR, 5 µL of Solis BioDyne 5xFIREPol® master mix and 0.8 µL of Forward and Reward primers were used for each SPNs. In all samples, the endogenous gene (GADPH) was tested and the reactions included a negative control.

The products amplified in the PCR of BsmI (825 bp) and FokI (265 bp) were visualized in 1.5% agarose gel in UV light in a MiniBIS Pro photodocumenter. To determine the genotypes of the SNPs, the samples were submitted to restriction by the Restriction Fragment Length Polymorphism (RFLP) method, using 1 µL of the fast digest enzyme for FokI. and for BsmI. The products of FokI digestion were submitted to electrophoresis in 8% polyacrylamide gel (80 v) and those of BsmI in 1.5% agarose gel (100v). For staining of the gels and subsequent visualization of the DNA fragments, ethidium bromide was used.

STATISTICAL ANALYSIS

The data were entered and calculated using *the Statistical Package for the Social Sciences (SPSS)* software, version 22.0, which calculated the data with the presentation of the results in tables expressed in numbers and percentages for categorical variables. The Hardy-Weinberg equilibrium was tested by the chi-square test, and was considered an imbalance when $p<0.05$.

For the quantitative variables, the measures of central tendency (means) and dispersion (standard deviation) were calculated. To compare the mean of a continuous variable in two independent groups, the Student's t-test was performed. Pearson's chi-square test was used to evaluate differences between the variables. In cases in which more than 25% of the cells presented values below 5, Fisher's Exact Test was applied. Thus, in the results section, the statistical methods used for each of the variables presented are specified. For the statistical tests, the level of significance adopted was 5% or $p<0.05$.

ETHICAL ASPECTS

The approval of the UFPI Research Ethics Committee was obtained in the original project (opinion no. 2.216.538).

RESULTS AND DISCUSSION

CLINICAL, BIOCHEMICAL AND ANTHROPOMETRIC CHARACTERISTICS OF THE ELDERLY

The study sample consisted of 173 elderly people, of both sexes, aged between 60 and 93 years, with a predominant age group of 60 to 70 years (52.6%). Among the elderly, the majority were female (68.2%), reflecting the phenomenon of feminization of old age, that is, a higher proportion of women than men, especially at more advanced ages. In all regions of the world, the proportion of women exceeds half of the elderly population (Cortez et al., 2019; Ferreira et al., 2018) and this needs to be considered in studies on aging.

The data regarding the study variables are described in Table 1. The mean age was approximately 72 and 70 years for men and women, respectively. Regarding BMI, it was found that the mean remained similar for both sexes, around 24 kg/m2, with a predominance of adequate values. It is noteworthy that overweight and obesity were present in 20.2% of the elderly (Data not shown in the table).

The waist circumference measurement was higher in males, as in the study by Alves et al. (2021), being within the increased risk category (97.99 cm), while the mean value of women presented a very increased risk (93.67 cm), according to the WHO classification (2000).

Table 1. Mean and standard deviation of the variables studied in the group of elderly people. Teresina, PI, 2020-2021.

Variables	**Sex**	**N**	**Average**	**Standard Deviation**	**P* value**
Age	But	55	72,35	8,44	0,296
	Fem	118	70,95	7,44	
	But	55	24,90	4,24	
IMC	Five	118	24,30	4,95	0,421
	But	55	97,99	9,09	
Waist circumference	Five	118	93,67	12,11	**0,020**
	But	55	135,85	14,95	
Systolic Blood Pressure	Five	118	136,16	20,98	0,91
	But	55	84,05	9,92	
Diastolic Blood Pressure	Five	118	82,91	8,22	0,426
	But	55	47,80	8,20	
HDL	Five	118	49,75	10,74	0,234
	But	55	224,61	36,84	
Colesterol Total	Five	118	191,27	38,53	**<0,001**
	But	55	173,61	40,12	
Triglycerides	Five	118	147,28	56,11	**0,001**
	But	55	141,88	32,92	
LDL	Five	118	112,19	33,35	**<0,001**
	But	55	35,02	15,64	
25-Hydroxyvitamin D	Five	118	23,84	10,97	**<0,001**

Legend: But: Male; Female: Female; BMI: Body Mass Index; HDL: High-intensity lipoprotein; LDL Low-density lipoprotein; * Student's t-test. Source: Survey data.

In addition, the categorization of WC data indicated that 41.8% of men presented increased risk and 30.9% very increased risk. For the elderly, the values were 9.3% and 75.4%, respectively (Data not shown in the table). Jansen et al. (2020) and Souza et al. (2013) explain that in addition to the increase in adipose tissue, in aging there is also a redistribution of abdominal fat, thus, with increasing age, subcutaneous fat becomes more centralized, leading to an increase in abdominal fat, a fact observed in the population in question.

The accumulation of fat in the abdominal region is an important risk factor for several diseases, which is differentiated when compared to other forms of body fat distribution (Da Silva et al., 2017; Rocha, 2013). There is a correlation between waist circumference measurement and the development of dyslipidemia, hypertension, and insulin resistance, in addition to an association with alterations in biochemical tests (Bueno et al., 2017; Rossi; Caruso; Galante, 2015).

Similar values were verified by Oliveira et al. (2014), in a study with 359 elderly people from Teresina-PI, assisted by teams of the Family Health Strategy (ESF), where the mean BMI of the elderly was 25.2 for both sexes, and a higher percentage of men with high weight compared to women, 33.8% and 29.5%, respectively. And similar values of waist circumference were observed in men, with a mean of 96.8 cm. However, contrary to the present study, elderly women had a higher mean abdominal circumference value, which was 98.5 cm.

Also in relation to Table 1, it is observed that the mean values of Systolic and Diastolic Pressure (mm Hg) were normal in both sexes, and there was no statistical difference between men and women. Arterial hypertension occurred in more than half of the elderly (56.1%). Bento, Mambrini, and Peixoto (2020) evaluated factors associated with hypertension in older adults and report that there is no significant difference between men and women. However, they state that there are generally higher rates of hypertension among women and this can be explained by a greater tendency to self-care and a greater perception of their health status, that is, women tend to make medical visits more frequently than men.

Medeiros (2018) in a study carried out with 179 elderly people in Paraíba identified a high prevalence of arterial hypertension (AH), and observed that the main factors associated with AH were non-white race/color and high triglyceride levels. In a study with 273 elderly people in Teresina-PI, Rocha et al. (2020), observed biochemical changes mainly in increased levels of triglycerides and SBP, between both sexes.

Table 1 also shows the means and standard deviations of the lipid profile of the elderly, where it is evident that the concentrations of cholesterol, triglycerides and LDL-c for males were significantly higher, and HDL-c was lower. According to the V Brazilian Guideline on Dyslipidemias and Prevention of Atherosclerosis, of 2017, the reference values of the lipid profile desirable for individuals over 20 years of age (including the elderly) are: TC: < 200; TG: < 150; HDL-c: > 40 and

LDL-c: < 100. Therefore, both sexes had desirable HDL concentrations, men had total cholesterol and triglyceride concentrations above the desired levels, in contrast to the data for women, and both groups had LDL-c concentrations above the desired levels. Different results were found in the study by Neves-Souza et al. (2015), with lipid profile values above the desirable values most prevalent in the female group.

Changes in serum concentrations of cholesterol, triglycerides, LDL-c and HDL-c are among the main risk factors for the development of cardiovascular diseases, including hypertension and atherosclerosis (SANTOS; CHIACHIO, 2020; BASIC et al., 2019; GUEDES et al., 2016). In addition, low concentrations of vitamin D are related to increased risk of hyperlipidemia. A correlation was found between vitamin D deficiency and increased total cholesterol and LDL-c.

On the other hand, a decrease in HDL-c concentration was observed. However, the mechanism of vitamin D's lipid-lowering effect remains unknown. Vitamin D probably increases serum calcium by increasing intestinal calcium absorption, which in turn reduces serum triglycerides by suppressing the formation and secretion of hepatic triglycerides. Another explanation may be through the inhibitory effect of vitamin D on serum PTH concentrations. The low concentration of this hormone can reduce TG by increasing its peripheral absorption.

ASSOCIATION BETWEEN POLYMORPHISMS AND THE VARIABLES ANALYZED

The frequency distribution of genotype characteristics and alleles of the polymorphisms verified in the present study are described in Table 2.

Table 2. Frequency distribution of traits of genotypes and SNP alleles of the VDR gene.

Feature	**N**	**%**
GENOTYPE		
FF	80	46,2
Ff	79	45,7
Ff	14	8,1
ALLELE		
F		
f		
GENOTYPE		
BB	34	19,7
Bb	95	54,9
bb	44	25,4
ALLELE		
B		
b		

Source: Survey data.

The association between the genotypes in the sample and the variables analyzed: BMI, serum vitamin D concentration, blood pressure values and alteration in the lipid profile of the elderly are shown in tables 3 and 4.

Of the 173 elderly people analyzed, 20.2% were overweight or obese, according to BMI. Of these, a higher frequency of overweight/obesity can be observed in relation to the FF genotype (12.7%) (Table 3) and the Bb genotype (10.4%) (Table 4). However, no statistically significant association was found (Table 3).

Table 3. Association between FokI genotypes (rs2228570) and anthropometric and clinical variables in the elderly. Teresina, PI, 2020-2021.

Variables	FF n = 80		Ff n = 79		Ff n = 14		Total n=173		p
N		%	N	%	N	%	N	%	
IMC									
Non-obese	58	33,5%	69	39,9%	11	6,4%	138	79,8%	0,053
Overweight/obesity	22	12,7%	10	5,8%	3	1,7%	35	20,2%	
Vitamin d									
Inadequacy	57	32,9%	48	27,7%	10	5,8%	115	66,5%	0,381
Sufficiency	23	13,3%	31	17,9%	4	2,3%	58	33,5%	
Hypertension									
No	37	21,4%	36	20,8%	4	2,3%	77	44,5%	0,484
Yes	43	24,9%	43	24,9%	10	5,8%	96	55,5%	
Dyslipidemia									
No	39	22,5%	46	26,6%	5	2,9%	90	52,0%	0,221
Yes	41	23,7%	33	19,1%	9	5,2%	83	48,0%	

Fisher's exact. Source: Survey data.

Table 4. Association between BsmI genotypes (rs1544410) and anthropometric and clinical variables in the elderly. Teresina, PI, 2020-2021.

Variables	BB n=34		Bb n= 95		bb n= 44		Total n=173		p
N		%	N	%	N	%	N	%	
IMC									
Non-obese	26	15,0%	77	44,5%	35	20,2%	138	79,8%	0,849
Overweight/obesity	8	4,6%	18	10,4%	9	5,2%	35	20,2%	
Vitamin d									
Inadequacy	24	13,9%	63	36,4%	28	16,2%	115	66,5%	0,811
Sufficiency	10	5,8%	32	18,5%	16	9,2%	58	33,5%	
Hypertension									
No	14	8,1%	45	26,0%	18	10,4%	77	44,5%	0,705
Yes	20	11,6%	50	28,9%	26	15,0%	96	55,5%	
Dyslipidemia									
No	15	8,7%	49	28,3%	26	15,0%	90	52,0%	0,419
Yes	19	11,0%	46	26,6%	18	10,4%	83	48,0%	

Chi-square. Source: Survey data.

Some studies have shown that FokI and BsmI are genetic variants associated with markers of adiposity (Al-Daghri et al., 2014; Ochs-Balcom, 2011). While, others reported a lack of association

(Khan et al., 2016; Maria et al., 2018). Although some VDR variants are associated with high BMI and WC, however, in relation to VDR BsmI and FokI were also not related to BMI and WC in the studies by Dorjgochoo et al. (2012), Walsh et al. (2016) and Pramono et al. (2021).

Thus, the evidence for the relationship between VDR genetic variants and obesity remains inconclusive. It should be noted that adiposity based only on BMI does not take into account the more accurate determination of body composition.

Regarding the association with plasma vitamin D concentration, of the 66.5% who had vitamin D insufficiency, a greater relationship was also observed with the FF (32.9%) and Bb (36.4%) genotypes, but without significant association. A non-association of these polymorphisms with circulating vitamin D concentrations was also verified by Al-Ghafari, Balamash, and Al Doghaither (2019). In addition, Rai et al. (2017) mention that little is known about how these polymorphisms affect circulating vitamin D levels.

The association of genotypes with blood pressure values showed a greater relationship between the FF and Ff genotypes, both with 24.9%, and the Bb genotypes (28.9%) with the elderly who had Arterial Hypertension. With the analysis of the alteration in the lipid profile, it was found that dyslipidemia was present in 48% of the elderly analyzed, and of these there was a greater relationship with the FF genotype (23.7%). The relationship between dyslipidemia and the Bsml polymorphism was more frequent in the Bb genotype (26.6%).

In all the variables analyzed, the relationship with the genotype evaluated was higher in the most frequent genotypes, genotypes "FF" and "Bb", but in none of the associations analyzed was a statistically significant difference found. The results found differ from other studies that; found an association between polymorphisms and changes in the lipid profile (Jin et al., 2021; Kazemian et al., 2019) and association between FokI and the risk of hypertension (Wang et al., 2013).

Table 5 shows the relationship between the lipid profile and the genotypes of FokI (rs2228570) and BsmI (rs1544410). A statistically significant relationship between triglycerides and low HDL-c was identified with the Bb genotype of the BsmI polymorphism. There was no significant relationship between the lipid profile and the genotypes of the Fokl polymorphism. The literature is still scarce in the study of genetic variations related to the vitamin D pathway, so the evidence of the findings of the present study strengthens this relationship. Although the physiological mechanism responsible for the relationship between vitamin D and cholesterol is not well understood, it is important to mention that both molecules have the same precursor, 7-dehydrocholesterol (Grave et al., 2016).

Table 5. Lipid profile in relation to VDR genotypes. Teresina, PI, 2020-2021.

Genotypes	**TG N / %**	**p**	**CT N / %**	**p**	**LDL-c alto N / %**	**p**	**HDL-c baixo N / %**	**p**
FokI (rs2228570)								
FF	18 / 22,5		15 / 18,8		9 / 11,3		22 / 27,5	
Ff	13 / 16,5	0,13	14 / 17,7	0,89	11 / 13,9	0,57	18 / 22,8	0,94
Ff	7 / 50,0		4 / 28,6		2 / 14, 3		3 / 21,4	
BsmI (rs1544410)								
BB	9 / 26,5		7 / 20,6		4 / 11,7		9 / 26,5	
Bb	15 / 15,8	**0,01***	14 / 14,7	0,15	10 / 10,6	0,48	30 / 31,6	**0,02***
bb	14 / 31,8		12 / 27,3		8 / 18,1		4 / 9,1	

Fischer's Exato test. Legend: TG: Triglycerids; CT: Total cholesterol; HDL: High-intensity lipoprotein; Low-density LDL Lipoprotein.

Source: Survey data

The study by Gussago et al. (2016) revealed a significant impact of VDR gene polymorphisms in an older population on some variables measured in the study, including HDL-c. In addition, VDR polymorphisms are known to have an impact on BMI, triglycerides, and HDL-c (Carvalho, 2015).

Evidence has shown that the BsmI polymorphism of the VDR gene may be closely associated with dyslipidemia. Karonova et al. (2018) and Sangkaew, Nuinoon, Jeenduang (2018) observed the relationship of BsmI with hypertriglyceridemia. Jin et al. (2021) found that HDL-c levels were lower in individuals in BsmI genotypes. A previous study revealed the similar finding that BsmI genotypes were associated with lower HDL-c and obesity, respectively (Al-Daghri et al., 2014).

From a biological point of view, the active form of vitamin D (1,25-dihydroxyvitamin D) contributes to obesity and alterations in lipid metabolism through several pathways, including increased adipocyte apoptosis; activation of fatty acid oxidation; upregulation of uncoupling protein expression and reduction of lipolysis (Beydoun et al., 2018; Morrison et al., 2005).

BsmI, positioned in the 3' region of the VDR affects the stability of the VDR mRNA and its transcriptional activity. Therefore, any change in this axis, including vitamin D concentrations or in the variation of VDR genes, can modify energy production, lipid metabolism and cause an increase in VDR expression in adipocytes. In addition, longer and repeated BsmI genes represent less mRNA stability and reduced VDT protein traction, resulting in reduced vitamin responses such as adipocyte inhibition and muscle mass differentiation (Kazemian et al., 2019; Al-Daghri et al., 2014).

In addition, according to Wang et al (2016) and Sharif-Askari et al (2020), 25(OH)D deficiency is associated with an unfavorable lipid profile, particularly HDL-c, especially in people with risk factors associated with cardiovascular diseases, such as obesity, for example. On the other hand, the study by Gendy et al. (2019) did not demonstrate an association between lipid concentrations and VDR polymorphisms. However, vitamin D is associated with regulation of lipid metabolism, fatty acid oxidation, and inhibition of lipid synthesis (San et al., 2004).

In this context, Alquaiz et al. (2020) found a strong relationship between vitamin D deficiency and dyslipidemia and proposed several mechanisms that probably work simultaneously, such as the role of vitamin D in altering the function of pancreatic cells causing metabolic disorders in lipoproteins, eventually with greater alteration in TG and lower concentrations of HDL-c. In addition, The vitamin may also play a role in the synthesis of bile acids in the liver with a direct impact on lipid metabolism. These findings suggest that low concentrations of 25(OH)D function as a predictor of increased atherogenic lipoproteins.

These mismatches in the results of the studies are often totally misunderstood for several reasons such as: variations in genetic characteristics, different ethnicities and geographic areas and different individuals may be exposed to different environmental factors, in addition to the design of the studies that may present limitations or be unsatisfactory in relation to sampling and the biases presented. Future research on deep sequencing is needed

CONCLUSION

It was observed that there were no statistically significant differences between the association of VDR FokI and BsmI gene polymorphisms with BMI, blood pressure and vitamin D concentrations. It is understood that the results of this study provide important information about the relationship between polymorphisms in the lipid profile and suggest that the presence of the Bb allele can predict the risk of association, however, more studies addressing the same theme are needed to verify these results in different ethnic groups.

REFERENCES

1. Al-Daghri, N. M., Al-Attas, O. S., Alokail, M. S., Alkharfy, K. M., Yakout, S. M., Aljohani, N. J., ... & Kumar, S. (2014). Vitamin D receptor gene polymorphisms are associated with obesity and inflammosome activity. *PloS one*, 9(7), e102141.

2. Alimirah, F., Peng, X., Murillo, G., Mehta, R. G., & Mehta, R. R. (2011). Significado funcional do polimorfismo FokI do receptor da vitamina D em células de câncer de mama humano. *PloS one*, 6(1), e16024.

3. Alves, L. F., Bueno, D. R., Farias, J. P., Peixoto, S. V., & Mambrini, J. V. M. (2021). Performance of adiposity indicators in predicting metabolic syndrome in older adults. *Archives of Endocrinology and Metabolism*.

4. Basic, J., Zdravković, M., Ivanović, I., Stojanović, R., Pavlović, D., Jevtović Stoimenov, T., & Jovanović, I. (2019). Vitamin D receptor gene polymorphism influences lipid profile in patients with juvenile idiopathic arthritis. *Clinical Rheumatology*, 38, 117-124.

5. Bento, I. C., Mambrini, J. V. M., & Peixoto, S. V. (2020). Contextual and individual factors associated with arterial hypertension among Brazilian older adults (National Health Survey-2013). *Revista Brasileira de Epidemiologia*, 23.

6. Beydoun, M. A., Boueiz, A., Shroff, M. R., Beydoun, H. A., Wang, Y., & Zonderman, A. B. (2018). Vitamin D metabolism-related gene haplotypes and their association with metabolic disturbances among African-American urban adults. *Scientific Reports*, 8(1), 1-11.

7. Bienertová-Vašků, J., Zlámal, F., Tomášková, V., Nezhybová, H., Táborská, K., Vcelák, J., & Šerý, O. (2017). Variantes alélicas no gene do receptor de vitamina D estão associadas a medidas de adiposidade na população da Europa Central. *BMC Medical Genetics*, 18(1), 1-9.

8. Bueno, D. R., Marucci, M. F. N., & Gobbo, L. A. (2017). Abdominal obesity and healthcare costs related to hypertension and diabetes in older adults. *Revista de Nutrição*, 30, 209-218.

9. Carvalho, L. S. F., & Sposito, A. C. (2015). Vitamin D for the prevention of cardiovascular disease: are we ready for that? *Atherosclerosis*, 241(2), 729-740.

10. Cortez, A. C. L., Silva, R. A. D., Pinheiro, M. C. F., & Monteiro, W. M. (2019). Aspectos gerais sobre a transição demográfica e epidemiológica da população brasileira. *Enfermagem Brasil*, 18(5).

11. Da Silva, L. A. R., Oliveira, G. B. V. P., Santos, L. F., & Furtado, L. M. (2017). Correlação entre índice de massa corporal e circunferência abdominal em adultos e idosos. *Revista Brasileira de Ciências do Envelhecimento Humano*, 14(3).

12. De Oliveira, G. B. V. P., Furtado, L. M., Da Silva, L. A. R., & Santos, L. F. (2018). Relação dos índices antropométricos e Vitamina D com o desempenho funcional de idosos. *Estudos Interdisciplinares sobre o Envelhecimento*, 23(1).

13. Elamin, M. B., Abu Elnour, N. O., Elamin, K. B., Fatourechi, M. M., Alkatib, A. A., Almandoz, J. P., ... & Montori, V. M. (2011). Vitamina D e desfechos cardiovasculares: uma revisão sistemática e meta-análise. *The Journal of Clinical Endocrinology & Metabolism*, 96(7), 1931-1942.

14. Faludi, A. A., Izar, M. C. O., Saraiva, J. F. K., Chacra, A. P. M., Bianco, H. T., Afiune Neto, A., & Bertolami, M. C. (2017). Atualização da diretriz brasileira de dislipidemias e prevenção da aterosclerose – 2017. *Arquivos Brasileiros de Cardiologia*, 109(2), 1-76.

15. Ferreira, C. E. S., Maeda, S. S., Batista, M. C., Lazaretti-Castro, M., Vasconcellos, L. S., Madeira, M., ... & Borba, V. Z. C. (2018). Posicionamento oficial da Sociedade Brasileira de Patologia Clínica/ Medicina Laboratorial e da Sociedade Brasileira de Endocrinologia e Metabologia. Intervalo de referência de vitamina D – 25(OH)D. *Atualização*.

16. Ferreira, N., Souza, D. L. B., & Santiago, L. M. (2018). Envelhecimento ativo: prevalência e diferenças de gênero e idade em estudo de base populacional. *Cadernos de Saúde Pública*, 34(11), 1–16.

17. Grave, N., Costa, J. A., Silva, R. P., Vieira, V. G., & Borges, R. M. (2016). A vitamin D pathway gene-gene interaction affects low-density lipoprotein cholesterol levels. *The Journal of Nutritional Biochemistry*, 16(9), 1-21.

18. Guedes, R. F., Santos, L. R., Rodrigues, C. G., & Lima, V. F. (2016). Análise do perfil lipídico e dos fatores de risco associados a doenças cardiovasculares em acadêmicos da área da saúde. *HU Revista*, 42(2).

19. Gussago, C., Nocella, C., Nocentini, G., & Pignatelli, P. (2016). Impact of vitamin D receptor polymorphisms in centenarians. *Endocrine*, 53(2), 558-564.

20. Issa, C. T. M. I., Vieira, V. C., Santos, D. M., & Silva, M. S. (2016). Relationship between cardiometabolic profile, vitamin D status and BsmI polymorphism of the VDR gene in non-institutionalized elderly subjects: Cardiometabolic profile, vitamin D status and BsmI polymorphism of the VDR gene in non-institutionalized elderly subjects. *Experimental Gerontology*, 81, 56-64.

21. Jansen, A. K., Melo, M. C., Souza, T. F., & Lima, S. R. (2020). Comparação da estatura aferida e estimada em idosos com diferentes classificações funcionais. *O Mundo da Saúde*, 1(44), 445-453.

22. Jin, T., Zhang, X., Tong, L., & Zhang, M. (2021). Association of vitamin D receptor polymorphisms with metabolic syndrome-related components: A cross-sectional study. *Journal of Clinical Laboratory Analysis*, 35(1), e23829.

23. Jorde, R., & Grimnes, G. (2010). Rastreamento dos níveis séricos de 25-hidroxivitamina D durante 14 anos em um estudo de base populacional e durante 12 meses em um estudo de intervenção. *Jornal Americano de Epidemiologia*, 171(8), 903-908.

24. Jorde, R., & Grimnes, G. (2011). Vitamin D and metabolic health with special reference to the effect of vitamin D on serum lipids. *Progress in Lipid Research*, 50(4), 303-312. doi: 10.1016/j.plipres.2011.05.001. PMID: 21640757.

25. Jorge, A. J. L., Soares, R. P., & Silva, M. R. (2018). Deficiência da Vitamina D e doenças cardiovasculares. *International Journal of Cardiovascular Sciences*, 31(4), 422-432.

26. Karonova, T., Zhukova, E., Rozhinskaya, L., Vasil'eva, E., & Gurevich, M. (2018). Relationship between vitamin D status and vitamin D receptor gene polymorphisms with markers of metabolic syndrome among adults. *Frontiers in Endocrinology*, 9(1), 1-7.

27. Kazemian, E., Mahjub, R., Rafatmanesh, A., Fakhari, S., & Hashemi, S. (2019). Vitamin D receptor gene polymorphisms affecting changes in visceral fat, waist circumference and lipid profile in breast cancer survivors supplemented with vitamin D3. *Lipids in Health and Disease*, 18(1), 1-10.

28. Medeiros, J. B. (2018). Fatores associados à hipertensão arterial em idosos longevos residentes em um município do nordeste brasileiro. (Dissertação de mestrado, Programa de Pós-Graduação em Saúde Pública, Universidade Estadual da Paraíba).

29. Milani, P. (2014). Correlação da vitamina D com o perfil lipídico e glicídico em indivíduos com síndrome metabólica. (Dissertação de mestrado, Universidade Federal da Fronteira do Sul, Chapecó).

30. Morrison, N. A., Qi, J. C., Tokita, A., Kelly, P. J., & Eisman, J. A. (2005). Vitamin D receptor genotypes influence the success of calcitriol therapy for recurrent vertebral fracture in osteoporosis. *Pharmacogenetics and Genomics*, 15(2), 127-135.

31. Nam, S. W., Choi, J., Jeon, H. J., Oh, T. K., & Lee, D. H. (2021). The Associations Between Vitamin D Receptor BsmI and ApaI Polymorphisms and Obesity in Korean Patients with Type 2 Diabetes Mellitus. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 14, 557–564.

32. Neves-Souza, R. D., Guimarães, A. C., Andrade, C. R., & Sichieri, R. (2015). Associação entre perfil lipídico, estado nutricional e consumo alimentar em idosos atendidos em unidades de saúde, Londrina, Pr. *Estudos Interdisciplinares sobre o Envelhecimento*, 20(1).

33. Neyestani, T. R., Nikooyeh, B., Alavi-Majd, H., & Shariatzadeh, N. (2013). O polimorfismo Fok-I do receptor de vitamina D modula a resposta do hospedeiro diabético à ingestão de vitamina D: necessidade de uma abordagem nutrigenética. *Cuidados com a Diabetes*, 36(3), 550-556.

34. Norman, P. E., & Powell, J. T. (2014). Vitamina D e doenças cardiovasculares. *Circulation Research*, 114(2), 379-393.

35. Oliveira, G. B. V. P., Guedes, D. P., & Souza, K. S. (2014). Perfil antropométrico e níveis séricos de vitamina D de idosos participantes do programa saúde da família de Teresina. *Revista Interdisciplinar Ciências da Saúde*, 1(1), 48-55.

36. OPAS - Organização Pan-Americana da Saúde. (2003). *Doenças crônico-degenerativas e obesidade: estratégia mundial sobre alimentação saudável, atividade física e saúde*. Brasília.

37. Peters, B. S. E., Giudici, K. V., & Martini, L. A. (2017). Vitamina D e doenças crônicas não transmissíveis. [S.l.: s.n.].

38. Rocha, F. L., Corrêa, H. L., & Silva, A. M. (2013). Correlação entre indicadores de obesidade abdominal e lipídeos séricos em idosos. *Revista da Associação Médica Brasileira*, 59(1), 48-55.

39. Rocha, M. S., Silva, T. P., & Barbosa, A. R. (2020). Síndrome metabólica e estado nutricional de idosos residentes em capital do nordeste brasileiro. *Research, Society and Development*, 9(10), e8029109161.

40. Rossi, L., Caruso, L., & Galante, A. P. (2015). *Avaliação Nutricional: novas perspectivas* (2nd ed.). Guanabara Koogan.

41. Rodríguez-Carrio, J., Prado, C., López, P., & Suárez, A. (2019). O polimorfismo do receptor da vitamina D e o DHCR7 contribuem para a interação anormal entre a vitamina D e o perfil lipídico na artrite reumatóide. *Scientific Reports*, 9(1), 1-11.

42. Sangkaew, B., Nuinoon, M., & Jeenduang, N. (2018). Association of vitamin D receptor gene polymorphisms with serum 25(OH)D levels and metabolic syndrome in Thai population. *Gene*, 659, 59-66.

43. Santos, T. O., & Chiachio, N. C. F. (2020). Fatores de Risco Associados a Dislipidemia entre os Funcionários Atendidos no SESI–Serviço Social da Indústria de Vitória da Conquista, Bahia/Risk Factors Associated with Dyslipidemia among Employees Served at SESI-Social Service of the Victory Industry of Conquista, Bahia. *ID on line Revista de Psicologia*, 14(51), 191-201.

44. Souza, R., Oliveira, D., & Carvalho, A. (2013). Avaliação antropométrica em idosos: estimativas de peso e altura e concordância entre classificações de IMC. *Revista Brasileira de Geriatria e Gerontologia*, 16, 81-90.

45. Swapna, N., Vamsi, U. M., & Usha, A. (2011). Risco conferido pelo polimorfismo FokI do gene do receptor da vitamina D (VDR) para hipertensão essencial. *Journal of Indian Society of Human Genetics*, 17(3), 201.

46. Wang, L., Manson, J. E., Song, Y., & Sesso, H. D. (2013). Um estudo prospectivo dos metabólitos da vitamina D no plasma, polimorfismos do gene do receptor da vitamina D e risco de hipertensão em homens. *European Journal of Nutrition*, 52, 1771-1779.

47. World Health Organization. (1995). *Physical status: the use and interpretation of anthropometry*. WHO Technical Report Series, 452.

48. World Health Organization. (2000). *Obesity: preventing and managing the global epidemic*. Report of a World Health Organization Consultation, 284, 256.

49. Al-Ghafari, A. B., Balamash, K. S. A. L., & Doghaither, H. A. (2019). Relationship between Serum Vitamin D and Calcium Levels and Vitamin D Receptor Gene Polymorphisms in Colorectal Cancer. *Biomed Research International*, 2019, Article 8571541.

50. Rai, V., Abdo, J., Agrawal, S., & Agrawal, D. K. (2017). Vitamin D Receptor Polymorphism and Cancer: An Update. *Anticancer Research*, 37(8), 3991-4003.

51. Sun, X., & Zemel, M. B. (2004). Role of Uncoupling Protein 2 (UCP2) Expression and 1alpha, 25-Dihydroxyvitamin D3 in Modulating Adipocyte Apoptosis. *The FASEB Journal*, 18, 1430–1432.

52. Gendy, H. I., Sadik, N. A., Helmy, M. Y., & Rashed, L. A. (2019). Vitamin D Receptor Gene Polymorphisms and 25(OH) Vitamin D: Lack of Association to Glycemic Control and Metabolic Parameters in Type 2 Diabetic Egyptian Patients. *Journal of Clinical and Translational Endocrinology*, 15, 25.

53. Wang, Y., Si, S., Liu, J., Wang, Z., Jia, H., Feng, K., ... Song, S. J. (2016). The associations of serum lipids with vitamin D status. *PLoS One*, 11(10), e0165157.

54. Alquaiz, A. M., Kazi, A., Youssef, R. M., Alshehri, N., & Alduraywish, S. A. (2020). Association between standardized vitamin 25(OH)D and dyslipidemia: a community-based study in Riyadh, Saudi Arabia. *Environmental Health and Preventive Medicine*, 25(1), 4.

55. Saheb Sharif-Askari, F., Saheb Sharif-Askari, N., Halwani, R., Abusnana, S., Hamoudi, R., & Sulaiman, N. (2020). Low vitamin D serum level is associated with HDL-C dyslipidemia and increased serum thrombomodulin levels of insulin-resistant individuals. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 13, 1599-1607.