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Research Article

Vitamin D Receptor Gene Polymorphisms and Cardiovascular Risk in Elderly

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Abstract

Introduction: Studies show an inverse association between 25 (OH) D concentrations and occurrence of risk for cardiovascular disease.

Objective: To identify the frequency of VDR gene FokI and BsmI polymorphism in the elderly and to determine the existence of a relationship with cardiovascular risk.

Materials and Methods: Cross-sectional, descriptive and analytical study. Sample composed of 359 elderly men and women. Information was collected: sociodemographic; cardiovascular risk assessment using the online calculator of the Brazilian Society of Cardiology; biochemical and molecular evaluation in a subsample of 100 elderly. The BsmI and FokI were genotyped by the Restriction Fragment Length Polymorphism technique. Fisher's Exact Test was applied to evaluate association between categorical variables in the SPSS software, version 22.0.

Results: 61.6% of the sample were female (n = 221). The mean value of 25 (OH) D was 22.4 (8.0) ng/mL, representing vitamin D insufficiency. In BsmI polymorphism, 57% have heterozygous (Bb) genotype and in FokI polymorphism, 47% have genotype. dominant (FF) and 50% the heterozygous genotype (Ff). The genotypes FF and Bb were the only ones to present elderly with low cardiovascular risk, however, heterozygote (Bb) presented higher percentage for intermediate and high cardiovascular risk.

Discussion: Studies show that the BsmI polymorphism increases the susceptibility to CVD, and the association of the BB genotype with greater carotid artery thickness. While studies of the FokI polymorphism show a greater association of the ff genotype with CVD risk.

Conclusion: There was a high prevalence of hypovitaminosis D and risk of cardiovascular disease in the study population.

Keywords: Polymorphism; Seniors; Vitamin D

Introduction

Population aging results in changes in the population's health profile, favoring an increase in the occurrence of Cardiovascular Diseases (CVD) [1]. CVD are the main causes of death in men and women in the five regions of Brazil [1]. Numerous studies demonstrate an inverse association between low concentrations of 25-hydroxyvitamin D [25 (OH) D] and occurrence of risk for CVD [2-5].

In this context, it is worth noting that insufficient or deficient concentrations of 25 (OH) D are common in the elderly. The low endogenous production and/or insufficient consumption of vitamin D, stand out among the factors that favor hypovitaminosis D, as well as genetics and the environment (exposure to the sun) [6-9]. Therefore constituting a challenge in the field of public health and a concern in the scientific community in gerontology and geriatrics [10].

To perform its function, vitamin D requires that its receptor (VDR) is produced and that it works properly. As a result, VDR polymorphisms, genetic variations in the gene in VDR that occur in more than 1% of the population, have been the subject of an increasing number of researches in recent years, due to their ability to alter the functionality of 1,25-dihydroxyvitamin D decreasing its activity, thereby generating effects of hypovitaminosis [11,12].

According to the United States National Biotechnology Information Center (NCBI), more than 180 polymorphisms in the VDR gene have already been identified [13,14]. Most of these are concentrated in exons 2 and 3, responsible for encoding the DNA binding domain. Changes in these two exons modify the zinc finger that binds to DNA, generating a deformation in the receptor, which prevents the vitamin from binding.

Therefore, studies investigate whether polymorphisms in VDR are associated with CVD [11,15].

Aim of the Study

The aim of this study is to identify the frequency of polymorphism FokI (rs2228570) and BsmI (rs1544410) of the VDR gene in

the elderly, as well as to determine the existence of a relationship between these polymorphisms with cardiovascular risk.

Materials and Methods

This is a cross-sectional, descriptive and analytical study, part of a thesis project linked to the Graduate Program in Food and Nutrition at UFPI.

The sample consisted of 359 elderly men and women, registered in the Family Health Strategy Program in Teresina, PI. To calculate the sample size, the prevalence estimate of 32.3% of overweight for the Brazilian elderly population was used, as studies show that from this prevalence of nutritional status, vitamin D levels can be found if reduced. The confidence interval used was 95%, the estimated error was 5%, obtaining a sample number of 336. The elderly should be physically independent, with no inflammatory bowel diseases and without the use of drugs that influence the nutritional status related to vitamin D. Considering the inclusion and exclusion criteria, the possible losses and refusals, the total sample was defined in 359 elderly people.

Socioeconomic information was collected through questionnaires. Whereas, cardiovascular risk assessment was performed using an online calculator provided by the Brazilian Society of Cardiology [16]. The assessment was performed by entering the values corresponding to the risk factors, obtained by applying a socioeconomic questionnaire and biochemical examination (gender, age, systolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, diabetes, smoking, use of drugs to treat hypertension and statin use), in the cardiovascular risk calculator.

For the biochemical and molecular evaluation, blood was collected in a sub-sample composed of 100 elderly people, dimensioned by the estimate of the standard deviation of 28.5 ng/mL of 25 (OH) D, based on the study by Saraiva., *et al*. [17], adopting the 95% confidence interval, with an estimated error of 5.6 ng/mL. Serum concentrations of 25 (OH) D were classified as adequate (≥ 30 ng/mL), insufficient (between 20 and 29 ng/mL) and deficient (< 20 ng/mL) [30]. For DNA extraction, the Quiagen kit was used, following the manufacturer's instructions.

BsmI (rs1544410) and FokI (rs10735810) were genotyped by the Restriction Fragment Length Polymorphism (RFLP) Technique, being considered for BsmI, elderly with dominant genotype (BB - 825 bp), heterozygous (Bb - 825, 650 and 175 bp) and recessive (bb - 650 e175 bp), using 2% agarose gel electrophoresis. For FokI, the dominant (FF - 265 bp), heterozygous (Ff - 265, 196 and 69 bp) and recessive (ff - 196 and 69 bp) genotype were considered, using 2% polyacrylamide gel electrophoresis.

The BsmI and FokI genetic variables were in Hardy-Weimberg equilibrium ($p > 0.05$). Fisher's Exact Test was applied to assess the association between categorical variables in the Statistical Package for the Social Sciences software version 22.0. The ethical aspects met Resolution 466/2012, of the National Health Council and the project was approved by the UFPI Ethics Committee (CAAE: 60364016.3.0000.5214) and all participants signed the free and informed consent form.

Results

Of the 359 elderly people who participated in the study, 61.6% were female (n = 221), 87.1% were non-Caucasian. The mean age was 71.6 (7.8) for men and 70.0 (7.5) for women, with no statistically significant difference ($p = 0.055$). Among the elderly, married and widowed marital status predominated (38.9% for both), with complete elementary education (66.6%) and family income of 1 to 2 minimum wages (58.8%).

Regarding the serum vitamin D level, the mean value of 25 (OH) D obtained was 22.4 (8.0) ng/mL, which represents insufficiency of vitamin D; in which elderly females had lower values than males, 20.17 (6.17) ng/mL and 25.75 (9.19) ng/mL, respectively. It was observed that 82% of the elderly had inadequate plasma vitamin D values, showing significant statistical differences between the sexes, with a higher proportion of inadequacy in women (65.9%) when compared to men (34.1%).

Figure 1a and 1b shows the genotype frequency of the BsmI and FokI polymorphism, respectively, in which, most of the samples presented heterozygous genotype for both polymorphisms. Regarding cardiovascular risk, none statistically significant difference was found in the association of polymorphisms and cardiovascular risk.

In BsmI polymorphism (Figure 2b), the heterozygous genotype (Bb) was the only one to present elderly people with low cardiovascular risk. However, the heterozygous genotype also had a higher percentage in all cardiovascular risk classifications.

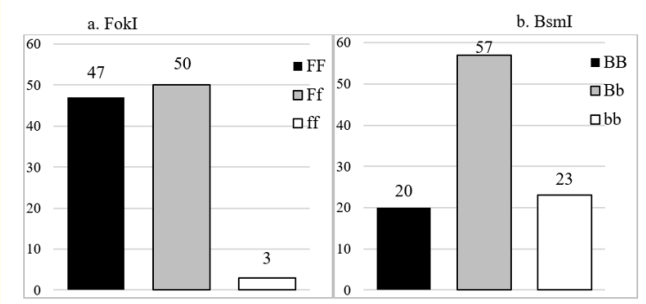

Figure 1: Genotypic percentage frequency of the BsmI and FokI polymorphism of the elderly.

Discussion

The mean value of 25 (OH) D found representing insufficiency of vitamin D is justified by the physiological changes resulting from aging that contribute to insufficiency of vitamin D, as well as the reduction of sun exposure due to changes in the lifestyle of the elderly, low consumption of sources of this vitamin [18] and use of multiple drugs that interfere with the absorption and metabolism of vitamin D. Many still have renal impairment, which causes a decrease in 1α-hydroxylase and consequently less renal production of 1.25 (OH) D [10].

Most of the samples showed heterozygous genotype for both polymorphisms (Figure 1). In BsmI polymorphism, 20% of the samples had a dominant genotype (BB); 57% heterozygous genotype (Bb) and 23% recessive genotype (bb). While, in the FokI polymorphism, 47% of the elderly studied have the dominant genotype (FF), 50% the heterozygous genotype (Ff) and 3% the recessive genotype (ff). This result was similar to that obtained by Beckett., *et al*. [19] who evaluated the genotypic frequency for the BsmI polymorphism and observed a greater predominance of the Bb genotype (53.5%), followed by bb (34.5%) and BB (12.0%). As well as in relation to the FokI polymorphism, which in a study carried out by Gussago., *et al*. [20] presented genotype FF (47.4%), Ff (42.1%) and ff (10.5%).

Regarding the FokI polymorphism (Figure 2a), none of the elderly with the Ff genotype had low cardiovascular risk, as well as the ff genotype. Therefore, the FF genotype is the only one to present elderly people with low cardiovascular risk. However, the FF genotype was the one that had the highest percentage of elderly people with high cardiovascular risk (19%), followed by the Ff and ff genotype. Of the elderly with very high cardiovascular risk, half have the FF genotype and the other half have the Ff genotype.

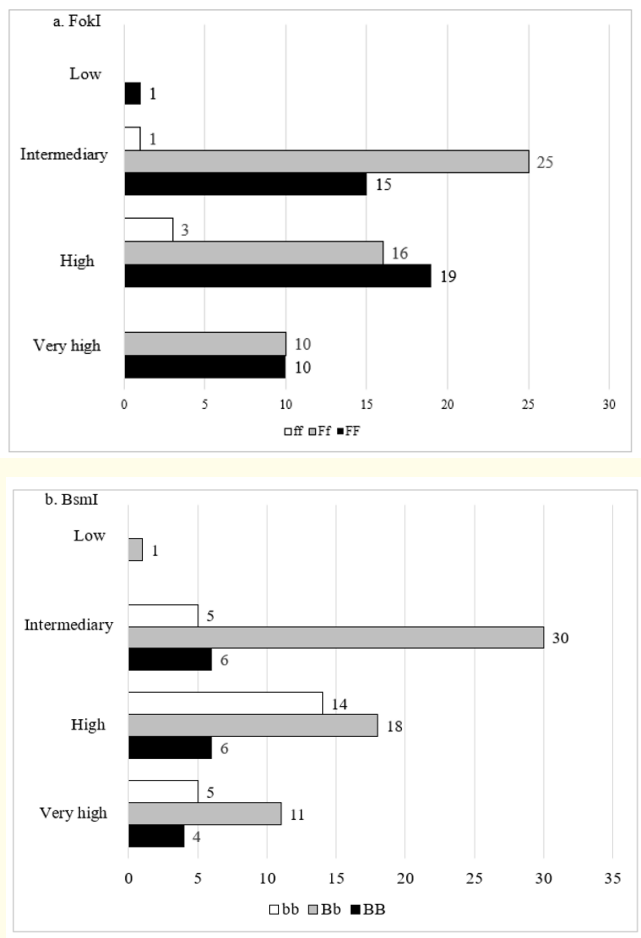

Figure 2: Association between cardiovascular risk and FokI and BsmI polymorphism in the elderly.

Regarding the relationship between VDR polymorphisms and CVD, studies show that in BsmI polymorphism, there is an increased susceptibility to CVD in the presence of the B [21-23] allele. Kammerer., *et al.* [24] demonstrated an association of the BB genotype with greater thickness of the intimate layer -medium of

the carotid artery. While studies of the FokI polymorphism show a greater association of the ff genotype with CVD risk [25-27]. In research developed by Mory., *et al*. [28] and Abd-Allah., *et al*. [29] it has been reported that individuals with the ff and Ff genotype tend to have lower pancreatic beta cell function.

Conclusion

As shown in the literature, in the present study there was a high prevalence of hypovitaminosis D and risk of cardiovascular diseases in the population studied, showing the importance of scientific studies, including nutrigenetics, on this theme. In view of the still controversial and divergent results regarding VDR polymorphisms and their association with CVD, further studies should be encouraged.

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