

## Artículo de Revisión / Review Article

### Effect of vitamin D3 supplementation on 25 OHD plasma levels in the presence of VDR gene polymorphisms

### Efecto de la suplementación con vitamina D3 en los niveles plasmáticos de 25 OHD, en presencia de polimorfismos del gen VDR

#### ABSTRACT

The objective of this review was to investigate the effect of vitamin D3 supplementation on serum 25-hydroxyvitamin D concentration in individuals with single-nucleotide polymorphisms in the vitamin D receptor gene. The research was conducted on 241 articles found in the PubMed, Scopus, Science Direct, and Cochrane Library databases between November and December 2018. After article screening, three randomized double-blind placebo-controlled clinical trials were identified as eligible for this review. Participants were Australian, Brazilian, and Chinese individuals, who ingested doses of vitamin D<sub>3</sub> ranging from 2000 IU to a megadose of 200,000 IU. The presence of the BB/Bb genotype of the BsmI polymorphism and the FokI G allele caused an increase in the serum concentrations of vitamin D after supplementation. Nonetheless, the few studies on this subject are not unanimous in their results. It is possible that differences among populations, sample sizes, doses, and time of supplementation have an impact on data and outcomes.

Keywords: BsmI; FokI; Randomized clinical trial; Vitamin D receptor; 25(OH) D.

#### RESUMEN

El objetivo de esta revisión fue investigar el efecto de la suplementación con vitamina D3 sobre la concentración sérica de 25-hidroxivitamina D en individuos con los polimorfismos de un solo nucleótido en el gen del receptor de la vitamina D. La investigación se realizó en 241 artículos encontrados en las bases de datos PubMed, Scopus, Science Direct y Cochrane Library entre noviembre y diciembre de 2018. Después de la selección del artículo, se identificaron tres ensayos clínicos aleatorios, controlados con placebo, doble ciego, como elegibles para esta revisión. Los participantes fueron australianos, brasileños y chinos, quienes ingirieron dosis de vitamina D<sub>3</sub> que iban desde las 2000 UI hasta una megadosis de 200,000 UI. La presencia del genotipo BB / Bb del polimorfismo BsmI y el alelo FokI G causó un aumento en las concentraciones séricas de vitamina D después de la suplementación. No obstante, los pocos estudios sobre este tema no son unánimes en sus resultados. Es posible

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que las diferencias entre poblaciones, tamaños de muestra, dosis y tiempo de suplementación tengan un impacto en los datos y resultados de la investigación.

Palabras clave: BsmI; Ensayo clínico aleatorizado; FokI; Receptor de vitamina D; 25 (OH) D.

#### INTRODUCTION

Vitamin D (25-hydroxyvitamin D: 25(OH) D) deficiency is a worldwide public health problem, affecting several population groups in various parts of the world<sup>1</sup>. It is considered a significant etiological factor in the pathogenesis of clinical conditions related to bone metabolism and chronic diseases such as obesity, type 2 diabetes mellitus, cardiovascular and autoimmune diseases, and some types

of cancer<sup>2</sup>. In the evaluation of vitamin D status, despite the controversies, 25(OH) D has been found to be inversely associated with many diseases and with mortality, especially in extraskelatal diseases<sup>3,4</sup>, whose mechanisms have not yet been fully elucidated<sup>5</sup>, thus rendering the establishment of causality difficult<sup>6</sup>.

The biological actions of vitamin D occur when the active form, 1,25-dihydroxyvitamin D<sub>3</sub>, binds to the nuclear vitamin D receptor (VDR)<sup>7</sup>, a member of the superfamily of steroid hormone receptors found in the nuclei of almost all cells and in all tissues<sup>8</sup>. The VDR gene is located in chromosomal region 12q12.14 and is composed of eight exons coding for proteins (exons 2–9) and of six nontranslated, alternately spliced exons<sup>9</sup>. Hence, more than 25 genetic variants of VDR are possible, among which those caused by single-nucleotide polymorphisms (SNPs) may have significant consequences for health<sup>10</sup>.

In the VDR gene, SNPs—such as rs1544410 (BsmI), located in an intron and involving a substitution of adenine for guanine (A>G)<sup>11</sup>, and rs2228570 (FokI), located in exon 2 and resulting in the synthesis of a protein with three extra amino acid residues—appear to impair the mechanism of action of vitamin D<sup>12</sup>. BsmI and FokI possibly alter the concentrations of 25(OH) D and an individual's sensitivity to vitamin D<sub>3</sub> supplementation<sup>13</sup>. The objective of this review was to investigate the positive effect of vitamin D<sub>3</sub> supplementation on the serum concentration of 25(OH) D in individuals with VDR gene polymorphisms.

## MATERIALS AND METHODS

This systematic review was performed through analysis of double-blind placebo-controlled randomized clinical trials (RCTs), with no restriction by publication year, conducted exclusively in healthy humans, regardless of gender, age, and ethnicity of the individuals, via the PICO strategy<sup>14</sup> (patient, intervention, comparison, and outcomes) to answer the guiding question of whether vitamin D<sub>3</sub> supplementation has different effects on individuals with the VDR SNPs.

In each PICO dimension, the following elements were defined: (P) patients with VDR polymorphisms, (I) supplementation with vitamin D<sub>3</sub>, (C) placebo, and (O) differences in concentrations of 25(OH) D.

The online search for the articles was performed between November and December 2018, in the PubMed, Scopus, Science Direct, and Cochrane Library databases. We used two groups of keywords: 1) polymorphism, VDR, supplementation, and vitamin D; 2) polymorphism, VDR, supplementation, and cholecalciferol.

Publications were excluded from this study if they met one or more of the following criteria: the publication was not available as full text, the publication was not in English, the study was based on animal or *in vitro* tests, the study did not analyze serum concentrations of 25(OH) D, the intervention was based only on food enrichment with vitamin D<sub>3</sub>, and studies that included children, adolescents, and pregnant women. Included in the research were

studies conducted on healthy adults and seniors, without references to autoimmune diseases, osteoporosis, cancer, diabetes, tuberculosis, and other diseases and pre- and postmenopausal periods.

The titles and abstracts of the articles selected were independently analyzed by two researchers. In the case of divergence, a third and fourth researcher were consulted to verify the adequacy of the eligibility criteria. Nevertheless, to make the choice even more stringent, a fifth researcher also analyzed the articles to assist with the consensual decision.

The quality of the systematic review was ensured via the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol<sup>15</sup>. In the qualitative classification of publications, the Jadad scale<sup>16</sup> was employed independently and by blinded researchers. RCTs were assumed to have good quality when they reached 3–5 points, and the risk of bias was analyzed using the Cochrane Collaboration Tool<sup>17</sup>.

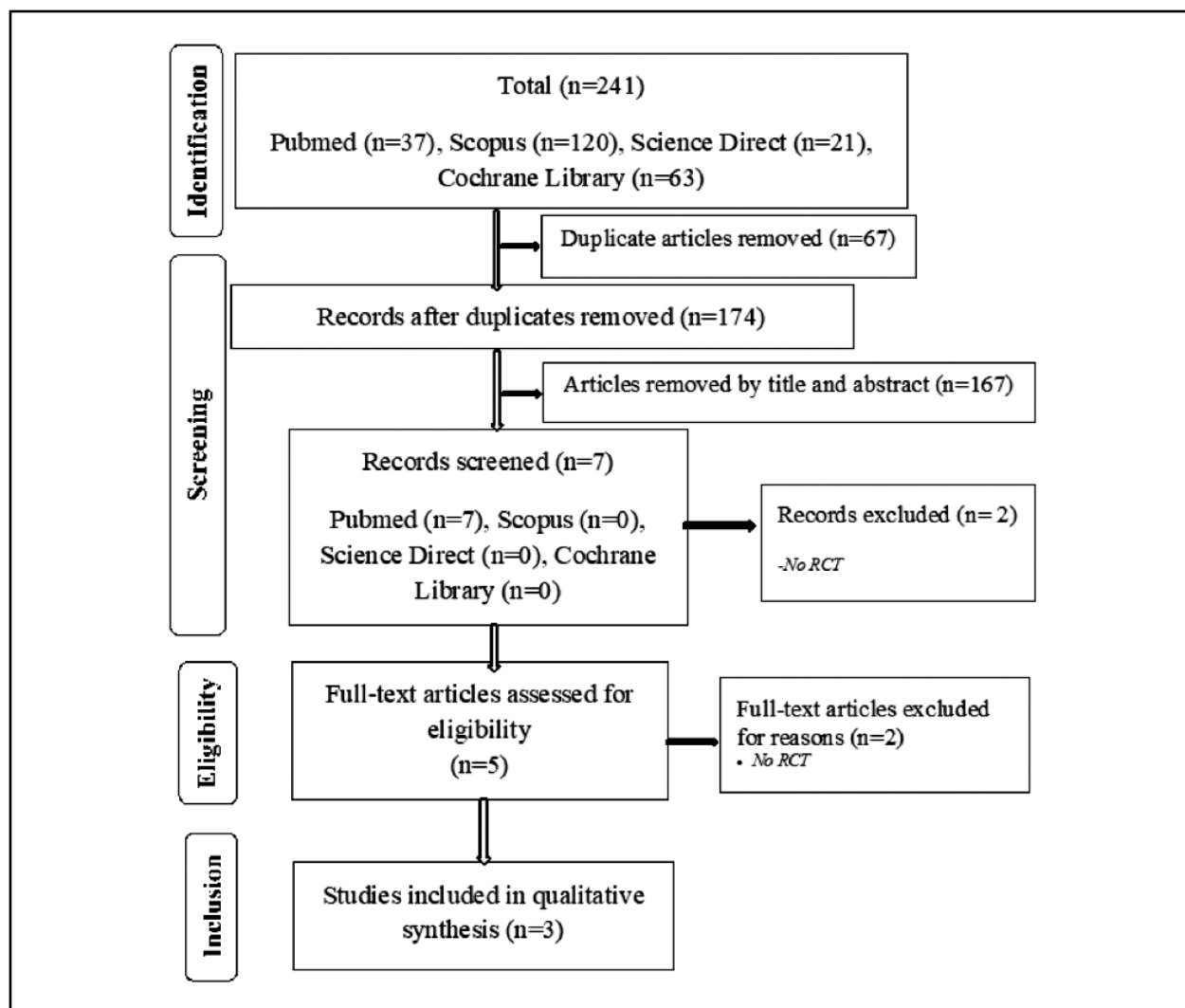
## RESULTS

The bibliographic research, which was carried out from March to November 2018 according to the pre-established strategy, resulted in 241 articles. The distribution of articles by database was as follows: 37 in PubMed, 120 in Scopus, 21 in Science Direct, and 63 in the Cochrane Library.

After selection and removal of duplicate trials, three randomized, double-blind, placebo-controlled trials met the predefined high-quality criteria for this systematic review. Figura 1 shows the flowchart of the search results on the sources of information and the selection and inclusion of the original articles for this systematic review, according to the PRISMA statement protocol.

The research showed homogeneous methodological quality in the evaluation of bias risk (Table 1). The low risk ratios were 100% (n= 3) for random generation sequence, concealment of allocation, blinding of participants and professionals, selective reporting of outcomes, and other sources of bias and 1:3 (n= 2) for blinding of outcome assessors and incomplete outcomes. Table 2 summarizes the results of the reviewed articles and lists the authors, year of publication, research site, sample size, sex, dose, duration of vitamin D supplementation, and main outcomes, as well as quality evaluations on the Jadad scale.

There is still a shortage of data in the literature on this subject. The studies analyzed originated in different countries and different continents (South America, Australia, and Asia), were published in the last 3 years, and included genotyping of VDR SNPs (BsmI and FokI) and included both sexes. The lowest number of participants was 20 and the highest was 448. The age of participants ranged from 20 to 84 years, i.e., the studies included adults and the elderly. The weekly doses of vitamin D<sub>3</sub> supplementation ranged from 2000 IU/day for 20 weeks (and monthly doses ranged from 30,000 to 60,000 IU/month for a year) to a single megadose of 200,000 IU.



**Figure 1:** Flowchart of the search. Legends: RCT- Randomized controlled trials.

**Table 1.** Analysis of the methodological quality and risk of bias proposed by the Cochrane collaboration.

Evaluated item	Waterhouse et al <sup>18</sup>	Cavalcante et al <sup>19</sup>	Yao et al <sup>20</sup>
Random sequence generation	Low risk	Low risk	Low risk
Allocation concealment	Low risk	Low risk	Low risk
Blinding of participants and personnel	Low risk	Low risk	Low risk
Blinding of outcome evaluators	Uncertain	Low risk	Low risk
Incomplete outcome data	Low risk	Low risk	Uncertain
Selective outcome reporting	Low risk	Low risk	Low risk
Other sources of bias	Low risk	Low risk	Low risk

**Table 2.** Summary of studies evaluated on the effect of supplementation with vitamin D<sub>3</sub>.

First Author/ Year/ Country	SNP-VDR	Sample	Age (Years)	Intervention with Vitamin D3	Outcomes	Jadad Scale
Waterhouse <sup>18</sup> / (2014) Australia	FokI	Female (n=179) Male (n= 206)	60–84	Monthly doses for 12 months: Group 1: 30,000 IU Group 2: 60,000 IU Placebo	SNP FokI was not associated with changes in 25(OH) D concentration	5 points
Cavalcante <sup>19</sup> / (2015) Brazil	BsmI	Female (n= 20)	60–68	• Megadose: √200,000 √Placebo	The women with the BB/Bb genotype had a greater increase in 25(OH) D levels	5 points
Yao <sup>20</sup> / (2017) China	FokI	Female (n= 307) Male (n= 141)	20–45	• 20 weeks: √2000 IU/d √Placebo	The G allele of the FokI SNP was associated with an increase in 25(OH) D levels.	5 points

Legends: to convert nmol/L to ng/mL divide by 2.5. To convert ng/mL to nmol/L multiply by 2.5. SNP: single-nucleotide polymorphisms.

Waterhouse et al<sup>18</sup> reported a beneficial effect of monthly supplementation for 12 months. Serum levels of 25(OH) D increased from 42.0 ± 13.0 nmol/L (16.8 ± 5.2 ng/mL) to 64.0 ± 17.0 nmol/L (25.6 ± 6.8 ng/mL) in the group receiving 30,000 IU of vitamin D<sub>3</sub> and from 42.0 ± 4.0 nmol/L (16.8 ± 5.6 ng/mL) to 78.0 ± 20.0 nmol/L (31.2 ± 8.0 ng/mL) in the group receiving 60,000 IU of vitamin D<sub>3</sub>. In the comparison between the supplementation and control groups in relation to VDR polymorphism (FokI), the differences in responses to supplementation were not significant among Australians.

Cavalcante et al<sup>19</sup> evaluated the effect of the BsmI VDR gene polymorphism and observed that the mean values of 25(OH) D in Brazilian individuals with the BB/Bb genotype rose from 63.75 ± 7.25 nmol/L (25.5 ± 2.9 ng/mL) to 80 ± 17.75 nmol/L (32.0 ± 7.1 ng/mL) after supplementation with a megadose of 200,000 IU.

Yao et al<sup>20</sup> observed an increase in 25(OH) D levels (p= 0.009) in Chinese individuals with the G allele of rs2228570 (FokI) after the 20th week of supplementation with 2,000 IU of vitamin D<sub>3</sub>.

## DISCUSSION

This systematic review was conducted to investigate the effects of vitamin D supplementation in humans. Regarding the effect of the intervention due to the presence of VDR gene polymorphisms, there were divergent effects among clinical trials. In addition, few studies investigated the subject, and there was no research evaluating the joint influence of

these two SNPs on response to supplementation.

Vitamin D supplementation has been used as a strategy for reducing the causes of disease-associated mortality in different populations around the world, but the mechanisms that account for the actions of the supplements are still a subject of speculation. Intervention with vitamin D supplements is relatively low risk and without major drawbacks, provided it is at the tolerable level of ingestion because the excess can lead to intoxication, hypercalcemia, and soft tissue calcification<sup>21</sup>.

The clinical trial by Waterhouse et al<sup>18</sup> evaluated the effect of vitamin D supplementation at serum concentrations of 25(OH) D in healthy elderly Australians, mostly of European-descent (93%), men (n= 206) and women (n= 179), aged 60–84 years, using monthly doses of 30,000 IU (n= 189) or 60,000 IU (n= 196). The supplementation groups had higher serum concentrations of 25(OH) D as compared to the placebo control group (n= 207).

The results of the abovementioned study<sup>18</sup> did not show any differences in 25(OH) D levels (within the groups that received the two types of vitamin D supplementation relative to the control group) with respect to SNPs rs10766197 (CYP2R1), rs12203592 (IRF4), rs1805009 (MC1R), rs10877012 (CYP27B1), rs1408799 (TYRP1), rs182549 (MCM6), and rs1667394 (HERC2), as well as the VDR gene SNP rs2228570 (FokI). In contrast, the SNPs of CYP2R1, which encodes the enzyme responsible for the hydroxylation of vitamin D to 25(OH) D, yielded statistically significant differences (p< 0.05).

The response to vitamin D supplementation could be explained in 24% of the cases by the supplementary dose and the initial serum concentration of 25(OH) D. Regression analyses performed by Waterhouse et al<sup>18</sup> confirmed the hypothesis that genetic variation among individuals determines the differences seen after supplementation, thus explaining why some people require higher doses to reach normal values of 25(OH) D as well as the inter-individual variation of values that can be considered physiologically normal.

The findings of Waterhouse et al<sup>18</sup> revealed that the variation observed in the response to vitamin D<sub>3</sub> supplementation is also due to familial predisposition to deficiency and saturation of the process of conversion of vitamin D<sub>3</sub> to 25(OH) D in the liver<sup>21</sup>. In addition, baseline values of 25(OH) D and body-mass index (BMI) negatively correlated with the change in serum concentrations of 25(OH) D although they made little contribution.

Women with ideal BMI had a greater response to vitamin D supplementation than did overweight and obese women, probably owing to the volumetric dilution of vitamin D<sup>18</sup>. It is believed that the amount of body fat affects serum concentrations of 25(OH) D, suggesting that supplementation with this vitamin should be planned by assessing total body fat mass<sup>22</sup>.

Baseline serum level of 25(OH) D, BMI, and ambient UV radiation (RUV) negatively correlated with the change in the serum 25(OH) D level. Persons who received the highest dose and those with a self-reported health status of “fair” or “poor” experienced a greater change than did those who received the lowest dose and those with good self-reported health, respectively<sup>18</sup>.

The increase in the serum 25(OH) D level was 1.5 to 2.5 nmol/L for every 100 IU/d, although the mean increase per 100 IU of vitamin D per day in the 60,000 IU group was slightly lower than in the 30,000 IU group (1.8 vs 2.2 nmol/L). It seems that the process by which vitamin D<sub>3</sub> is converted to 25(OH) D is saturable, a factor that may explain the weaker response per 100 IU per day in the group receiving a higher dose than in those randomized to the lowest dose<sup>23</sup>. Thus, it should be reiterated that the only polymorphism of the VDR gene evaluated by the authors of ref.<sup>18</sup>—FokI—did not influence serum vitamin D concentrations in the evaluated Australian elderly.

Waterhouse’s<sup>18</sup> study has limitations such as the small sample size and the 25(OH) D dosing method, because the mean baseline level was somewhat lower than expected—a possible influence of specific medications or pathologies—and study participants represented an older population of predominantly European-descent (95%), making the results not generalizable to other populations.

The study by Yao et al<sup>20</sup> lasted for 20 weeks and was conducted on 411 Han Chinese adults with baseline 25(OH) D levels between 12.5 and 50 nmol/L and BMI between 18.5 and 28 kg/m<sup>2</sup>. Patients were randomized into two groups to receive doses of vitamin D<sub>3</sub> in capsules (placebo=0 and group 2= 2,000 IU) at weeks 0 and 20 of treatment.

The results showed that the three FokI genotypes, AA, GA, and GG, were associated with an increase in 25(OH) D levels to 28.2 ± 3.6 ng/mL, 33.8 ± 2.1 ng/mL, and 39.6 ± 3.0 ng/mL, respectively, indicating that the G allele actually had a greater, statistically significant effect on vitamin D<sub>3</sub> supplementation efficacy.

In this randomized trial<sup>20</sup>, authors evaluated the effects of genetic and non-genetic factors on 25(OH) D and on 25(OH) DBio, which represents both free forms and those bound to albumin and appears to be biologically more active in tissues. It can be calculated using the equation proposed by Bhan et al<sup>24</sup> from the concentrations of 25(OH) D, vitamin D-binding protein, and albumin.

Daily supplementation with 2,000 IU of vitamin D<sub>3</sub> for 20 weeks significantly increased total concentrations of 25(OH) D in 75% of the sample, where vitamin D deficiency was not corrected. In this case, genetic factors were found to have a stronger impact than non-genetic factors on responses to supplementation. The GF allele of the FokI SNP was assumed to pose a risk, and when it co-occurs with other polymorphisms, such as CYP27B1 and CYP24A1 SNPs, there is an additional need for vitamin D to achieve adequate serum concentration<sup>20</sup>.

Regarding non-genetic determinants, the increase in 25(OH) D concentration was much lower in overweight participants, confirming the importance of taking weight into account (for the most reliable evaluation of vitamin D) in the effects of genetic and non-genetic factors on the responses in terms of serum 25(OH) D and 25(OH)-DBio to identify a better intervention strategy<sup>20</sup>.

It is worth mentioning that the study by Yao et al<sup>20</sup> has some limitations: all participants were Chinese adults (20–45 years of age), and therefore the findings may not be generalizable to other ethnic groups or different age groups; 25(OH) DBio concentrations were calculated instead of direct measurement and only the current Tolerable Upper Intake Level (UL) in China was used for supplementation, and thus the effects of other doses on responses after vitamin D<sub>3</sub> supplementation should be evaluated.

Another VDR SNP evaluated for 25(OH) D upregulation after supplementation in this systematic review was BsmI, a polymorphism located in the 3′UTR region of intron 8; this polymorphism does not alter the structure and function of VDR but is strongly related to the poly(A) tail, potentially affecting mRNA stability<sup>25</sup>.

In this context, Cavalcante et al<sup>19</sup> evaluated 40 Brazilian women randomly distributed into two groups: the treatment group (where the women received a megadose of 200,000 IU of vitamin D<sub>3</sub> [69.3 ± 6.6 years]) and a placebo group (67.3 ± 5.0 years). The intervention did not cause renal disorders, because levels of alanine amino transferase, aspartate amino transferase, urea, creatinine, and uric acid did not differ statistically significantly before and after supplementation. In addition, serum 25(OH) D levels increased significantly in the supplementation group (31.48 ± 6.0 ng/mL) compared to placebo (24.42 ± 3.8 ng/mL) after the intervention (p=

0.0001). Additionally, this value remained higher in the supplementation group at the end of the study ( $p = 0.0003$ ).

In the supplementation group, 63.2% ( $n = 12$ ) of the elderly had the BB/Bb genotype and 36.8% ( $n = 7$ ) had the BsmI genotype. In the placebo group, 47.4% ( $n = 9$ ) of the individuals had the BB/Bb genotype and 52.6% ( $n = 10$ ) the bb genotype. At the beginning of the study, mean values of 25(OH) D were similar between women with genotype BB/Bb ( $25.5 \pm 2.9$  ng/mL) and genotype bb ( $25.6 \pm 4.6$  ng/mL;  $p > 0.05$ ). After four weeks of vitamin D megadose supplementation, there was a significant increase in serum 25(OH) D levels in the elderly with the BB/Bb genotype, but not genotype bb ( $p = 0.009$ ). Thus, individuals with the BB/Bb genotype were more sensitive to supplementation than those with genotype bb<sup>19</sup>.

Elnenaei et al<sup>26</sup> also found that the BB/Bb genotype in postmenopausal women is more responsive to vitamin D supplementation. Thus, considering that VDR is involved in the regulation of many genes, different biological responses can be identified for the same genotype<sup>27</sup>. In addition, genes associated with individual variables (gender, origin, and ethnicity) and environmental non-genetic variables (BMI and the percentage of body fat) play a major role in vitamin D metabolism<sup>28</sup>.

Thus, in the three studies covered by this review, diverse treatment protocols were followed, a fact which requires attention and indicates that the results should be evaluated with caution, even though vitamin D supplementation resulted in an increase in 25(OH) D. Only the Chinese intervention was in accordance with the guidelines on the pleiotropic effects of vitamin D, which recommend doses between 400 and 2000 IU / day depending on age, ethnicity, body weight, and presence of disease<sup>29</sup>.

In addition, another study, that of Sari et al.<sup>30</sup>, on the BsmI polymorphism aimed to evaluate the effect of vitamin D supplementation in women from North Sumatra, Indonesia, aged 20–50 years, with a BMI of 23 kg/m<sup>2</sup> (overweight, according to the Asia Pacific guidelines by Gill)<sup>31</sup>. The type of capsule used for supplementation had a variation in gel consistency, being pink and hard for the placebo group ( $n = 17$ ), and soft and yellow for the group receiving vitamin D<sub>3</sub> ( $n = 19$ ).

The results demonstrated that vitamin D supplementation for 28 days did not significantly increase serum vitamin D levels in the women, with values in the test group being  $20.4 \pm 5.4$  ng/mL and in the placebo group  $19.9 \pm 4.1$  ng/mL: after supplementation, there was only a small increase in vitamin D levels in the test group ( $22.3 \pm 4.4$  ng/mL;  $p = 0.04$ ). This result is justified by the fact that all the women from this region of Indonesia are heterozygous for the BsmI polymorphism (Bb). The drawback of this study was the short intervention time.

The effects of the FokI and BsmI SNPs were not conclusive. This can be explained by the genetic variation between the Australian, Chinese, and Brazilian populations and also by varying familial predisposition to vitamin D deficiency,

reiterating the need for further studies. In addition, it is suggested that an individual's VDR gene polymorphisms should be analyzed prior to supplementation, as there are also other SNPs (DBP, CYP2R1, etc.) that may affect vitamin D levels and response to supplementation.

In a survey conducted on Arabs regarding the FokI and BsmI SNPs, only rs2228570 was associated with low concentrations of 25(OH) D<sub>3</sub>. However, in an African-American or Hispanic population the FokI SNP did not influence the level of vitamin D<sup>33</sup>. In studies in the Chinese population, results were less promising: Li et al<sup>34</sup> and Robien et al<sup>35</sup> found no interaction between 25(OH) D and the genetic variations FokI and BsmI.

It is important to highlight that two of the studies analyzed earlier were conducted in the elderly, a population group that has a higher risk of vitamin D deficiency compared to younger populations. This age-specific occurrence could be due to the unique characteristics of the aging process, which is marked by reduced skin synthesis, low food intake, increased body adiposity, lower sun exposure, decreased calcium absorption, reduced VDR, and renal production of 1,25(OH)<sub>2</sub>D<sup>36</sup>. Furthermore, it is possible to design experiments for a systematic exploration of any potential association between low levels of 25(OH) D and aging-related diseases, such as depression, osteoporosis, cardiovascular disease, type 2 diabetes, cancer, and hypertension<sup>37</sup>.

Therefore, observations from the present research is envisioned to enhance knowledge about the specific subject, particularly with respect to the insights on VDR genetic variants and supplementation effects. However, the study has some limitations, such as the exclusive use of works in the English language and the limited number of available electronic databases for this purpose.

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