

Review - Human & Animal Health

Influence of Polymorphism of Vitamin D Receptor (*Fok I*) on Hypertension

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HIGHLIGHTS

- Polymorphisms in *FokI* encoding a VDR affects blood pressure.
- The FF genotype appears to increase the risk of hypertension.

Abstract: Evidence suggests that polymorphisms in the gene encoding a vitamin D receptor might affect blood pressure. The objective of this systematic review was to investigate the association between hypertension and vitamin D receptor (*Fok I*) gene polymorphism. A literature search was performed according to the PRISMA guidelines using the MEDLINE®/PubMed, Scopus, Cochrane Library CENTRAL, SciELO, and LILACS databases. The quality of case-control or cohort studies and studies based on cross-sectional methodology was evaluated using the Newcastle-Ottawa Scale and the protocol of Loney and coauthors [25], respectively. In this systematic literature search, 215 publications were identified, of which 10 were analyzed, including seven case-control studies, two cross-sectional studies, and one cohort study. The association between *Fok I* polymorphism and hypertension was reported in 60% of the publications and the risk for hypertension was shown to be related to FF and ff genotypes. In addition, *Fok I* polymorphism was shown to increase plasma renin activity, which plays an important role in regulating blood pressure. However, no association was observed between *Fok I* polymorphism and serum vitamin D levels. In conclusion, *Fok I* polymorphism plays an important role in hypertension.

Keywords: single nucleotide polymorphism; rs228570; blood pressure; 25 (OH) D; renin.

INTRODUCTION

Arterial hypertension (AH) is considered to be a risk factor for cardiovascular diseases and is a public health concern. The prevalence of AH is high among the elderly because it is known to progressively increase with age [1]. Recent studies have demonstrated an association between AH and vitamin D [2,3]. Moreover, individuals with low levels of 25-hydroxyvitamin D (25 (OH) D, a biomarker of vitamin D status in the body) are at a higher risk of developing AH than those with normal levels of 25 (OH) D [4–7]. Vitamin D plays an important role in regulating endothelial function, inflammation, and the activity of the renin-angiotensin-aldosterone system (RAAS) [8], which regulates blood pressure [5]. The active form—1,25 di-hydroxyvitamin D (1,25 (OH)₂ D₃)—binds to the nuclear vitamin D receptor (VDR) to produce a biological effect. Studies with VDR and 1 α -hydroxylase knockout mice indicated that inadequate activation of RAAS influences hypertension. Renin expression and plasma angiotensin II production are increased in null VDR mice, leading to hypertension, cardiac hypertrophy, and increased water intake. In wild mice, i.e., mice with intact VDR, inhibition of calcitriol synthesis also leads to increased renin expression, whereas calcitriol injection leads to renin suppression [9].

VDR is expressed in several types of tissues, including the bone, adipose, immune system [4], as well as components of the cardiovascular system, such as aortic endothelium [10] and vascular smooth muscle [11]. In addition, VDR is highly expressed in pancreatic beta cells, small and large intestine, kidney tubular cells, bronchial and skin epithelial cells, endocrine glands, and certain reproductive tissues [12].

In humans, the regulation of blood pressure has a genetic influence of about 30–50% [13]. The *VDR* gene is located on chromosome 12q13.1, and single nucleotide polymorphisms (SNPs) of this gene can affect blood pressure [14]. One of the most studied SNP of the *VDR* gene is *Fok I* (rs228570 or rs10735810). *Fok I* polymorphism can generate truncated proteins and is associated with increased risk for hypertension [14–16]. *Fok I* polymorphism is caused by a thymine-to-cytosine transition, which leads to a translational frameshift characterized by an extension of the open reading frame to the next initiation codon (ATG), resulting in the synthesis of a truncated 424-amino acid protein. In the 427-amino acid protein, ATG-encoded methionine (M1 form) was present in the f allele, whereas ACG-encoded methionine (M4 form) was present in the F allele [17].

The truncated protein in individuals with the FF genotype is thought to promote the development of AH by increasing the production of renin and angiotensin II [18]. The transcriptional activity of the truncated protein is suggested to be higher than that of the full-length protein. Moreover, the increased responsiveness of the truncated protein to 1,25 (OH)₂ D₃ might alter the function of VDR and vitamin D in cells and tissues [19].

Low levels of 25 (OH) D combined with *Fok I* polymorphism have been associated with increased plasmatic renin activity and RAAS activity [20]. This suggests that 1,25 (OH)₂ D₃ can downregulate renin expression in humans, and increase cardiovascular and metabolic disease risk [21].

An *in vitro* study from the mid-2000s has described the functional significance of variable protein length by demonstrating that the transcriptional activity of VDR with *Fok I*-f SNP was lower than that of TFIIB factor (an RNA polymerase II specific transcript) with *Fok I*-F SNP [22]. Thus, due to the importance of the association between AH and *Fok I* polymorphism, we performed a systematic literature search to validate the hypothesis that patients with *Fok I* polymorphism have an increased risk for hypertension.

MATERIAL AND METHODS

Search strategy

The text continues here. A literature search was performed according to the PRISMA guidelines [23]. Two independent researchers (IFOCN and CMRGC) systematically searched the MEDLINE® (Medical Literature Analysis and Retrieval System Online)/PubMed, Scopus, Cochrane Library CENTRAL, SCIELO (Scientific Electronic Library Online), and LILACS (Latin American and Caribbean Literature in Health Sciences) databases between June 17, 2017 and December 9, 2018, with the combined use of the following three sets of keywords: (Genetic and Hypertension and Polymorphism VDR); (Vitamin D and Hypertension and Polymorphism); (VDR and Hypertension and Fok I).

Inclusion and exclusion strategy

No limits were set for the publication year of articles, or for the sex, age, and ethnicity of subjects. Original research studies in humans, available in full and published in English, were included. Review studies, studies conducted in pregnant women, animal studies, and *in vitro* studies were excluded. In cases where the

publication was found on more than one platform, the publication from the first search was selected for analysis and the duplicates were excluded.

Analysis of studies

The selected manuscripts were analyzed by the authors of the present review for the method of patient selection, population characteristics, and study results. The quality of case-control and cohort studies was evaluated using the Newcastle-Ottawa scale [24] and that of cross-sectional studies was assessed according to the protocol of Loney and coauthors [25].

RESULTS

A total of 215 publications were selected from the database search. To complement the study information, a publication from another online source was added. The quality of 10 publications was evaluated, as shown in Figure 1 and Tables 1, 2, and 3, and it was found that the studies were carried out in male and female subjects from Europe ($n = 4$), Asia ($n = 2$), Africa ($n = 1$), and North America ($n = 3$).

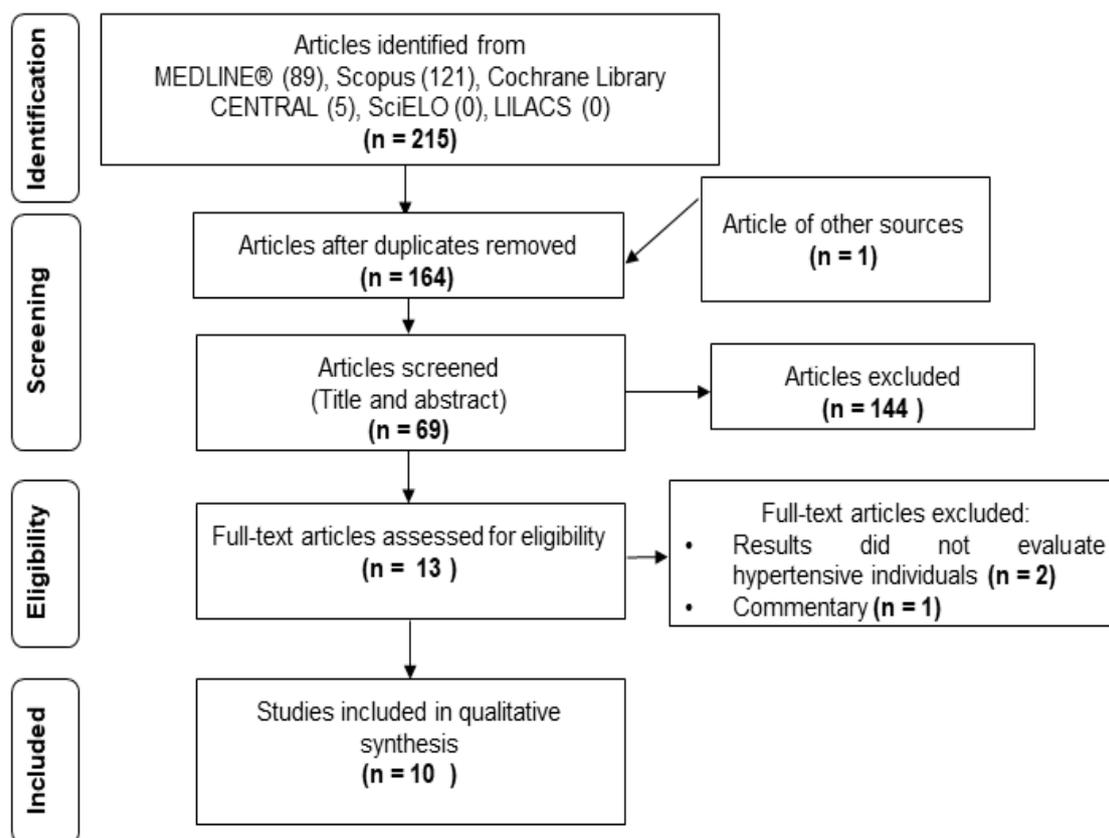


Figure 1. Research flow chart

Table 1. Quality of case-control research evaluated.

Items	Ref. [26]	Ref. [27]	Ref. [28]	Ref. [29]	Ref. [30]	Ref. [31]	Ref. [32]
Selection							
Is the case definition adequate?	–	–	–	–	–	–	–
Representativeness of the case	*	*	*	*	*	*	*
Selection of controls	*	*	*	*	*	–	*
Definition of controls	*	*	–	*	*	*	*
Comparability							
Comparability of cases and controls on the basis of the design or analysis	**	**	**	**	**	**	**
Exposure							
Ascertainment of exposure	–	*	–	*	–	–	–
Same method of ascertainment for the cases and controls	–	*	–	*	–	–	*
Non-response rate	*	*	*	*	*	*	*
Score	6	8	5	8	6	5	7

Subtitle: (*) = 1 star = 1 point; (**) = 2 stars = 2 points; (–) = zero point.

Table 2. Quality of cross-sectional surveys evaluated.

Items	Ref. [33]	Ref. [34]
Are the study Methods valid?		
Are the study design and sampling method appropriate for the question?	1	1
Is the sampling frame appropriate?	1	1
Is the sample size adequate?	1	1
Are objective, suitable and standard criteria used for measurement of the health outcome?	1	1
Is the health outcome measured in an unbiased fashion?	1	1
In the response rate adequate? Are the refusers described?	1	1
What is the interpretation of the results?		
Are the estimates of prevalence or incidence given with confidence intervals and in detail by subgroup, if appropriate?	1	1
What is the applicability of the results?		
Are the study subjects and the setting described in detail and similar to those of interest to you?	1	1
Score	8	8

Subtitle: number (1) = 1 point

Table 3. Quality of the cohort study evaluated.

Items	Ref. [35]
Selection	
Representativeness of the case exposed cohort	*
Selection of the non-exposed cohort	*
Ascertainment of exposure	*
Demonstration that outcome of interest was not present at start of study	*
Comparability	
Comparability of cohorts on the basis of the design or analysis	**
Outcome	
Assessment of outcome	*
Was follow-up long enough for outcomes to occur	*
Adequacy of follow up of cohorts	*
Score	8

Subtitle: (*) = 1 star = 1 point; (**) = 2 stars = 2 points

Table 4. Summary of studies evaluated by type of methodological design.

Case-control				
Authors/Country/Year	Age Group (y)	SN	Other variables	Outcomes
Swapna <i>et al.</i> [26]/India/2011	35-60	CS=280; CT=200	-Duration of disease, BMI, cigarettes, alcohol, diabetes and lipid profile.	-Association between Fok I and HP risk.
Vaidya <i>et al.</i> [27]/United States/2012	29-56	CS= 375; CT=146	-PRA and 25 (OH) D.	-Fok I was associated with lower PRA.
Glocke <i>et al.</i> [28]/Germany/2013	>90 and <90	CS=101; CT=208	-Weight, height and BMI.	-Potential influence of Fok I on DBP in men.
Cottone <i>et al.</i> [29]/Italy/2014	18-75	CS=71; CT=72	-25 (OH) D, PRA, BMI, PTH, Ca ²⁺ , phosphorus, estimated glomerular filtration rate.	-Higher DBP values in patients with ff genotype.
Jia <i>et al.</i> [30]/China/2014	47-72	CS=2.409; CT=3.063	-History of hypertension, diabetes, cigarettes, BMI, lipid profile and glucose.	-Association between Fok I and AH in men.
Errouagui <i>et al.</i> [31]/Morocco/2014	35-68	CS=177; CT=176	-FGP, lipid profile and 25 (OH) D.	-Correlation between Fok I and AH susceptibility.
Gussago <i>et al.</i> [32]/Italy/2016	72-102	CS=102; CT=163	-Glucose, total cholesterol and uric acid.	-Association between Fok I and AH polymorphism.
Cross-sectional				
Authors/Country/Year	Age Group (y)	SN	Other variables	Outcomes
Ndiaye <i>et al.</i> [33]/ France, Greece, Ireland, Portugal/2013	32-61	P1=1,912; P2=1,755	-BMI.	-Association with systolic and diastolic pressure.
Wang <i>et al.</i> [34]/United States/2014	47-62	W=23,294; I=69,395	-Pulse pressure.	- No association between Fok I and AH.
Cohort				
Authors/Country/Year	Age Group (y)	SN	Other variables	Outcomes
Wang <i>et al.</i> [35]/United States/2013	49-66	885	-Cigarette, alcohol, exercise, multivitamin, BMI, diabetes and hypercholesterolemia. -25 (OH) D and 1,25 (OH) ₂ D ₃ .	-Association between Fok I and AH risk.

Subtitle: SN, sample number; CS, case; CT, control; BMI, body mass index; PRA, plasma renin activity; DBP, diastolic blood pressure; PTH, parathyroid hormone; AH, arterial hypertension; FGP, fasting glucose plasma; P, phase; W, women's genome health study; I, international consortium of blood pressure; (y), years.

DISCUSSION

In this systematic literature review, studies examining the relationship between *Fok I* polymorphism and AH were identified and analyzed. In the study by Swapna and coauthors [26], the association between *Fok I* polymorphism and AH was assessed in Indian individuals of both sexes, ranging in age from 35 to 60 years, and grouped into hypertensive patients (N = 280, systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg) and control subjects (N = 200, systolic blood pressure of 120 mmHg or diastolic blood pressure of 80 mmHg). The association was found to be statistically significant (P < 0.05). They also observed a significant difference in the frequencies of genotypes and alleles at the VDR locus. The FF, Ff, and ff genotypes exhibited frequencies of 53.6%, 35.7%, and 10.7%, respectively, in hypertensive individuals, and 34%, 51%, and 15%, respectively, in healthy normotensive subjects.

The risk for hypertension was calculated from the odds ratio (OR). The FF genotype showed a 2.25-fold and 2.20-fold higher risk for hypertension than the Ff and ff genotypes, respectively. Notably, the risk for hypertension was high in both men and women with the FF genotype (OR: 2.020 and 95% CI: 1.228–3.322 in men, OR: 2.467 and 95% CI: 1.246–4.4881 in women) and in individuals with a positive family history of hypertension (OR: 2.011 and 95% CI: 1.119–3.616), smoking (OR: 3.686 and 95% CI: 1.414–9.611), and alcohol consumption (OR: 2.239 and 95% CI: 0.983–5.096) [26].

In another study, Vaidya and coauthors [27] sought to understand the role of polymorphisms in plasma renin (RP) activity using the data of the subjects studied in the International Hypertensive Pathotype (HyperPATH) Consortium for investigating the pathophysiological and genotypic mechanisms involved in hypertension and cardiovascular diseases. In this study, 375 hypertensive (aged 40.1 to 56.5 years) and 146 normotensive (aged 29.0 to 50.8 years) Caucasian Americans of both sexes were investigated to determine whether the genetic variation of VDR was associated with RP activity and whether this interaction was independent of 25 (OH) D levels. The study subjects received a high (≥ 200 mmol Na/24 h) or low (≤ 10 mmol Na/24 h) Na dose for 5–7 days. At the end of the experiment, the F allele was associated with low RP activity in hypertensive patients (P < 0.05). An association between *Fok I* polymorphism and 25 (OH) D concentrations was not observed, suggesting that the frequency of the F allele and high concentrations of 25 (OH) D may have additive rather than mutual associations with respect to RP activity in hypertensive and normotensive individuals. These results indicate that the negative regulation of renin by 1,25 (OH)₂ D₃ is mediated in part by VDR.

Another study was conducted by Glocke and coauthors [28] to compare the prevalence of *Fok I* polymorphism in 101 elderly (> 90 years of age) and 208 young (< 90 years old) subjects of both sexes (Caucasians of German descent). A negative effect of *Fok I* polymorphism on diastolic blood pressure was observed in the elderly group (P < 0.05), especially in those with the ff genotype because they had a lower mean blood pressure of 70.00 ± 2.12 mmHg than those with the FF genotype (82.9 ± 3.10 mmHg) and Ff genotype (76.17 ± 2.69 mmHg). The prevalence of hypertension was lower in subjects with ff and Ff genotypes than in those with FF genotype; however, the difference was not statistically significant. The lifespan of subjects can also be affected by this polymorphism.

Cottone and coauthors [29] conducted a study in 71 patients with essential hypertension and 72 control subjects, of both sexes, aged 18–75 years, in Italy. The frequencies of FF, Ff, and ff genotypes in hypertensive patients were 50.7%, 42.3%, and 7.0%, respectively, and in control subjects were 40.3%, 50.0%, and 9.7%, respectively. The allelic frequencies of F and f were 71.8% and 28.2%, respectively, in hypertensive patients, and 65.3% and 34.7%, respectively in normotensive individuals. The diastolic blood pressure was different for all three genotypes of *Fok I* polymorphism (P = 0.018). Patients with the ff genotype had a higher diastolic blood pressure than those with the Ff genotype (P = 0.002). A negative correlation was observed between 25 (OH) D levels and pulse blood pressure, and this correlation was statistically significant in patients with the Ff genotype (r = -0.474, P = 0.035). There was no association between a specific genotype or allele and hypertension. An association between *Fok I* polymorphism and RP activity was also not observed.

Jia and coauthors [30] conducted a study in 2,409 hypertensive and 3,063 normotensive sexagenarian and septuagenarian Han Chinese subjects of both sexes. The correlation of *Fok I* polymorphism with decreased risk for hypertension after adjusting for confounding factors (sex, age, body mass index, total cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein cholesterol, and smoking) in men was significant. The OR and 95% CI for the additive, dominant, and recessive models were 0.828 (0.74–0.927; P = 0.001), 0.75 (0.631–0.89; P = 0.001), and 0.816 (0.67–0.995; P = 0.044), respectively. Subjects with the Ff/ff genotype had a lower blood pressure than those with the FF genotype (p = 0.002). The

frequencies of F and f alleles were 55.9% and 44.1%, respectively, in the hypertensive patients, and 54.3% and 44.7%, respectively in control subjects.

In another study, Errouagui and coauthors [31] analyzed 177 hypertensive (aged 45.47 to 68.41 years) and 222 normotensive (aged 34.67 to 64.59) subjects of both sexes in Morocco, and found a strong association between *Fok I* polymorphism and AH in codominant, dominant, and recessive genetic models. The frequency of the ff genotype in hypertensive patients was significantly lower than that in the control subjects (OR = 0.24, 95% CI = 0.10–0.58, P = 0.002). The mean concentrations of vitamin D in subjects with the FF, Ff, and ff genotypes were 28.06 ± 10.57 , 29.04 ± 11.97 , and 26.40 ± 19.15 ng/mL, respectively. However, the differences in the concentration of vitamin D were not statistically significant between subjects with FF and Ff (P = 0.6463) and those with FF and ff (P = 0.0767) genotypes.

Gussago and coauthors [32] conducted a study in 70-year-old subjects and centenarians of both sexes in northern Italy. The frequencies of the FF, Ff, and ff genotypes in centenarians were 47.4%, 42.1%, and 10.5%, respectively, with F being the most frequent allele (68.4%). In the control group comprising septuagenarians, the frequencies of the FF, Ff, and ff genotypes were 48.4%, 38.7%, and 12.9%, respectively, with F being the most frequent allele (67.8%). Moreover, the prevalence of hypertension was higher in subjects with the FF genotype than in those with the Ff and ff genotypes (P = 0.015).

Ndiaye and coauthors [33] conducted a study in two phases. In the first phase, 1,912 French Caucasian adult subjects with a mean age of 51.13 ± 10.02 years were included; the subjects were predominantly women (51.3%). Normotensive and hypertensive patients not on drug therapy were included in this group. In the second phase, 1,755 healthy Europeans from Greece, Ireland, and Portugal, with a mean age of 42.06 ± 9.89 years were included; the subjects were predominantly men (67%). The *Fok I*-f polymorphism of the *VDR* gene was significantly associated with diastolic ($P_{\text{adjusted}} \leq 4.93 \times 10^{-4}$) and systolic ($P_{\text{adjusted}} \leq 9.48 \times 10^{-4}$) blood pressure.

Two surveys were conducted during the Women's Genome Health Study (WGHS) to obtain blood pressure data and genotyping information for *Fok I* SNP in 23,294 women of European ancestry with a mean age of 54.7 ± 7.1 who participated in the International Consortium of Blood Pressure (ICBP). Wang and coauthors [34] did not find a correlation between *Fok I*-f polymorphism and hypertension, with beta (SE) = 0.055 ± 0.19 and P = 0.77 for systolic blood pressure, beta (SE) = 0.00096 ± 0.13 and P = 0.99 for diastolic blood pressure, and beta (SE) = 0.054 ± 0.11 and P = 0.63 for pulse pressure.

Wang and coauthors [35] conducted a prospective study in 1,211 Caucasian American men with a minimum and maximum follow-up periods of 15.2 and 27.4 years, respectively. In this study, 695 subjects were diagnosed with hypertension. The prevalence of *Fok I* polymorphism was investigated in 885 subjects and the majority of hypertensive patients had a polymorphism of the *VDR* gene. The association of *Fok I* polymorphism with the risk for hypertension was found only in the recessive model. The ff genotype in model 2 had a multivariate hazard ratio (HR) of 1.32 (95% CI: 1.03–1.70) for the incidence of hypertension. The correlation between 25 (OH) D concentrations and the risk for hypertension was higher in subjects with the ff genotype than in those with the Ff and FF genotypes.

Fok I polymorphism affects the length and function of the VDR protein. The reduced activity of VDR is caused by the deficiency or excess of vitamin D and inactivation of its biologically active form [28]. It is worth noting that the results of the studies by Swapna and coauthors [26], Glocke and coauthors [28], Jia and coauthors [30], Errouagui and coauthors [31], Gussago and coauthors [32], and Wang and coauthors [35] corroborate the hypothesis that *Fok I* polymorphism causes AH. Vaidya and coauthors [27] have shown that the regulation of RP activity is important to preventing AH. In their study, they observed the effect of *Fok I* polymorphism on the regulation of RP activity. In order to understand this process, it is important to identify gene-gene or gene-environment interactions [34] as well as epistatic interactions that may be useful for the identification of undetected genetic markers by analyzing individual markers or assessing the combinatorial effect of the locus by other alternatives. The absence of comprehensive analysis may be the reason for the differences in the results of the cited studies [33].

It was noticed that the analyzed publications employed a variety of protocols and population groups, which can also cause differences in the results. Moreover, age and ethnicity of an individual are important factors for studying hypertension. The inhibition of renin activity and the subsequent increase in the levels of angiotensin II, a potent vasoconstrictor, can contribute to elevated blood pressure. Interestingly, the levels of $1,25(\text{OH})_2\text{D}_3$ affect renin expression. $1,25(\text{OH})_2\text{D}_3$ downregulates renin expression by suppressing, at least in part, CRE-mediated transcriptional activity that is activated by cAMP-PKA signaling and subsequent CREB phosphorylation. The recruitment of CBP / p300 to VDR blocks the binding of CREB to CRE, and inhibits transcription of the renin gene [36]. Figure 2.

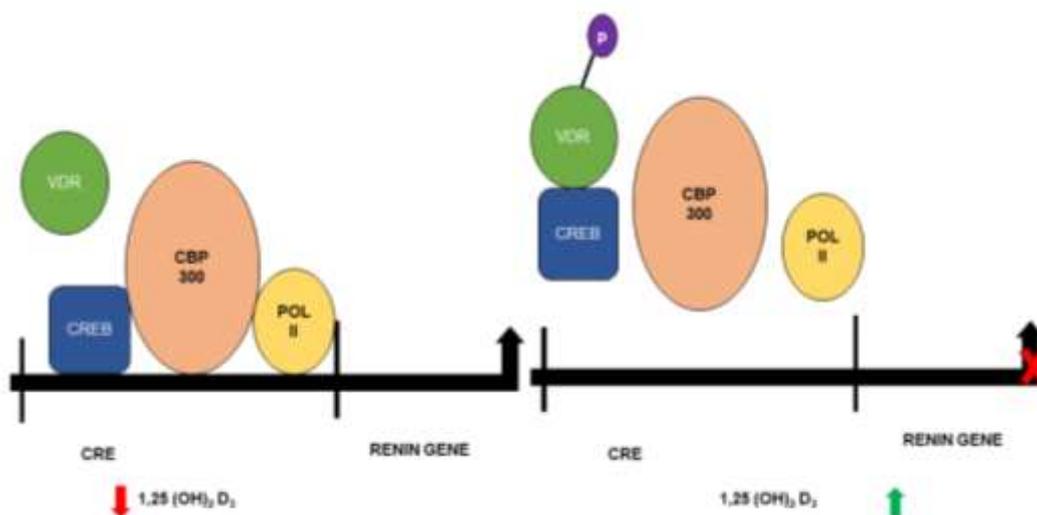


Figure 2. Mechanism proposed for action of vitamin D on the expression of renin. Adaptation [36].

The following points must be addressed in future studies:

- Determine the need for early blood pressure monitoring in individuals with *Fok I* polymorphism of the VDR gene to prevent the onset of AH.
- Determine the efficacy of vitamin D supplementation to reduce the risk and delay the development of hypertension in individuals with *Fok I* polymorphism.
- Determine the optimal dose to achieve this effect.

CONCLUSION

Based on the data analysis of the selected studies, most of the publications showed an association between *Fok I* polymorphism and AH. Although this result is promising, there are several limitations of these studies. The results of these studies cannot be expanded to other population groups because they did not consistently include representative samples with ethnic diversity. Additionally, all of the study participants were either adults or elderly, and one study was conducted on only one of the sexes.

These studies do not provide unanimous results regarding the risk for hypertension and its association with the frequency of *Fok I* genotypes. A correlation was found between AH and two different genotypes, ff and FF. It is unclear whether 25 (OH) D levels are associated with *Fok I* polymorphism and hypertension because the results were inconclusive in a few studies investigating this association.

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