Asian Journal of Biochemistry, Genetics and Molecular Biology

Volume 17, Issue 9, Page 56-64, 2025; Article no.AJBGMB.143320
ISSN: 2582-3698

Cross-sectional Analysis of VDBP Polymorphisms rs7041 and rs4588 and their Impact on Vitamin D Levels in Ivoran Hemodialysis Patients (Subsaharian Africa)

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ajbgmb/2025/v17i9492

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://pr.sdiarticle5.com/review-history/143320

Original Research Article

Received: 05/07/2025
Published: 06/09/2025

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Cite as: *Carine Mireille Yao Yapo, Yékayo Bénédicte Koné Dakouri, Morel Kouacou, Jean Louis Konan, Eric Sagou Yayo, Emmanuel Able, Adele Kakou N'Douba, and Marie-Laure Hauhouot Attoungbre. 2025. "Cross-Sectional Analysis of VDBP Polymorphisms rs7041 and rs4588 and Their Impact on Vitamin D Levels in Ivoran Hemodialysis Patients (Subsaharian Africa)". Asian Journal of Biochemistry, Genetics and Molecular Biology 17 (9):56–64. https://doi.org/10.9734/ajbgmb/2025/v17i9492.*

ABSTRACT

Introduction: Hypovitaminosis D is a real public health problem. Populations in sub-Saharan Africa, despite favorable sun exposure, are not immune to this scourge. Among the reasons mentioned are the inhibitory action of melanin on the cutaneous synthesis of vitamin D but also the involvement of genetic variants of the vitamin D binding protein. In a pathology such as chronic kidney disease already characterized by a deficit in the activation of vitamin D, knowing the polymorphisms of this binding protein is important because it could influence not only the status of vitamin D in the serum but also its bioavailability and the response to vitamin D supplementation. This study aimed to determine the genetic variants rs7041 and rs4588 of the vitamin D transporter protein and to correlate them with the vitamin D status of hemodialysis patients from Sub-Saharan Africa systematically supplemented orally with vitamin D.

Methods: This cross-sectional study involved 48 patients who gave their written consent. The genetic variants of the transporter protein were determined by PCR-RFLP and the dosage of 25(OH)D was done by ELFA technique. SNPStats software was used to estimate allele, genotype, and haplotype frequencies. Fisher's exact test was used to establish correlations between vitamin D concentrations and polymorphisms.

Results: The results showed a predominance of the Gc1f variant (rs7041-T and rs4588-C). Despite vitamin D supplementation, 40% of patients had hypovitaminosis D. We did not find a direct association between vitamin D transporter protein variants and vitamin D concentrations. As found in other Black populations, the Gc1f variant remains predominant.

Conclusion: Conducting this study on a larger population would allow us to better assess its association with 25(OH)D.

Keywords: GC gene polymorphisms; vitamine D deficiency; Chronic kidney disease; Ivorian population.

1. INTRODUCTION

Long known for its role in maintaining phosphocalcic homeostasis, vitamin D is now recognized for its involvement in numerous physiological processes such as modulation of the renin-angiotensin-aldosterone system, redox balance, infertility, innate and adaptive immunity, etc. (Tissandié et al., 2006).

The decrease in its concentration is at the center of concerns as a major public health problem because it is associated with several pathologies including chronic kidney disease. (Mogire et al., 2020; Moukayed & Grant, 2013).

Indeed, hypovitaminosis D is one of the most well-known complications in chronic kidney disease, causing bone complications. Thus, patients with kidney failure are regularly given vitamin D supplements to compensate for this deficiency. (Ernandez & StoermannChopard, 2012; Negrea, 2019).

In the body, the response to this vitamin D supplementation as well as the maintenance of the concentration of vitamin D at optimal levels are directly dependent on the enzymes involved in its synthesis or catabolism but also on the integrity of the transporter protein and the vitamin D receptors. (Tissandié et al., 2006).

Studies have shown that certain polymorphisms in these regulatory elements could be directly correlated with different concentrations of vitamin D and the response to vitamin D supplementation. (Shab-Bidar et al., 2014; Yao et al., 2016).

These include the rs7041 and rs4588 polymorphisms of the Gc gene encoding the protein that transports vitamin D and its metabolites into the bloodstream, also known as VDBP (Vitamin D-binding protein) (Bouillon, 2017; Kamboh & Ferrell, 1986). Located on chromosome 4q13, it exhibits several single nucleotide polymorphisms (SNPs), the two most studied of which are rs7041 (Asp416Glu) and rs4588 (Thr420Lys). These SNPs lead to three main protein isoforms: Gc1f (rs7041-T and rs4588-C), Gc1s (rs7041-G and rs4588-C), and Gc2 (rs7041-T and rs4588-A), which affect the structure and charge of VDBP.

These polymorphisms have repeatedly been shown to be linked to differences in 25OHD concentrations and are thought to influence not only serum vitamin D status but also the response to vitamin D supplementation (Al-Daghri et al., 2019; Bouillon, 2017; Malik et al., 2013).

Individuals carrying the Gc1f allele would have higher levels of 25(OH)D, while those carrying the Gc2 allele would have lower levels. This difference is attributed to the variation in the affinity of VDBP for vitamin D depending on the isoform expressed: Gc1f has the highest affinity, followed by Gc1s, and then Gc2 (Al-Daghri et al., 2019; Arnaud & Constans, 1993; Nissen et al., 2015).

Thus, the measured 25(OH)D concentration could vary independently of vitamin D intake or sun exposure, solely due to the Gc genotype.

This study therefore aims to evaluate the impact of the rs7041 and rs4588 variants of the vitamin D transporter protein on vitamin D status in Ivorian hemodialysis patients (sub-Saharan Africa).

2. MATERIALS AND METHODS

2.1 Study Type and Population

This is a descriptive cross-sectional study of Ivorian hemodialysis patients monitored at the National Center for the Prevention and Treatment of Renal Failure in Ivory Coast (CNPTIR) in collaboration with the Angré University Hospital Center. It took place during the month of June 2025. Of the 60 patients included in the study, 12 were excluded due to PCR failure.

2.2 Collection and Storage of Specimens

Blood samples were collected simultaneously in a purple-top (EDTA) tube and a redtop (dry) tube.

The EDTA tube was used initially to determine rs7041 and rs4588 polymorphisms of the VDBP Gc gene, and the dry tube was used to measure 25-OH vitamin D. Serum and whole blood were stored at -20°C to ensure sample integrity throughout the analytical process.

2.3 Determination of rs7041 and rs4588 Polymorphisms of the VDBP Gc Gene

DNA was extracted using the Gene Jet Whole blood kit (Thermofischer, Ref K0781) using the forward primers 5'-CAAGTCTTATCACCATCCTG-3' and reverse primers 5'GCCAAGTTACAATAACAC-3'. The extract was amplified using the thermocycler Light cycler® 480z (Roche diagnostic®, Germany). An 809bp fragment of the Gc gene was amplified by conventional PCR according to the following program (initial denaturation at 95°C for 5 minutes, 34 cycles of 95°C for 30 seconds, annealing at 58°C for 30 seconds and an elongation at 72°C for 10 minutes). Approximately 50ng of genomic DNA was used for each patient in a 25µl reaction. The volumes and concentrations of the elements of the reaction medium are specified in Table 1.

Amplicon size was verified on a 2% agarose gel against the 50bp molecular weight marker (Thermofisher®). Gel staining was performed using SYBR Safe DNA Gel Stain (Invitrogen®).The amplicons were digested with the appropriate restriction enzyme after PCR:

The HaeIII (GG/CC) enzyme was used to digest the 809-bp PCR product at 37°C for 2 hours, followed by enzyme inactivation at 80°C for 20 minutes. The Styl (C/CWWGG) enzyme was used to digest the 809-bp PCR product at 37°C for 2 hours, followed by enzyme inactivation at 65°C for 20 minutes. The digested products were separated by agarose gel electrophoresis. Determination of 25(OH)D 25(OH)D was measured in each patient's sera using the ELFA (Enzyme-linked fluorescent assay) method on the VIDAS PC. Quality controls and calibrations were performed according to the manufacturer's instructions.

Table 1. Volume and concentrations of the constituent elements of the reaction mix

Elements	Final concentration	Volume per sample	Volume for 50 samples
Tampon 10X	1X	2,5 µL	125 µL
Mélange dNTP 10mM	200µM	0,5 µL	25 µ
Amorces sens 100µM	0,5µM	0,125 µL	6,25 µL
Amorces antisens 100µM	0,5µM	0,125 µL	6,25 µL
Taq polymérase 500U	1,25U	0,0625 µL	3,125 µL
Eau biomol		16,69 µL	834 ,5 µL
DNA		5 µL	

2.4 Data Processing

SNPStats software was used to estimate allele, genotype, and haplotype frequencies. 25OH vitamin D concentrations were interpreted based on values determined in a presumed healthy Ivorian population by Cavalier et al. which were ≥25 pg/mL (Cavalier et al., 2019). Patients whose 25OH vitamin D concentrations were strictly less than 25 ng/mL were therefore considered to be subjects with hypovitaminosis D. Fisher's exact test was used to establish correlations between vitamin D concentrations and polymorphisms.

3. RESULTS

3.1 Epidemiological and Clinical Characteristics of the Study Population

The study population was predominantly young, with a mean age of 39 ± 16 years and a male/female sex ratio of 1.5. Most of these patients (58%) had been on dialysis for more than 3 years. Almost all of these patients suffered from high blood pressure (85%). Interviews and patient records revealed that 58% complained of minor bone complications such as bone pain (96%). Bone deformities and fractures were found in only 22% and 11% of cases, respectively. Almost all patients were receiving oral supplementation with pharmaceutical specialties containing both calcium and vitamin D3 (OROCAL D3®, CALGEN D3®).

3.2 Distribution of rs7041 and rs4588 Polymorphisms in the Vitamin D Transporter Protein Gc gene

Digestion of the 809-bp PCR products with the two restriction enzymes HaeIII (GG/CC) and StyI (C/CWWGG) allowed the identification of the alleles by analyzing the size of the different fragments of the digestion products. The rs7041 G allele introduces a HaeIII (GG/CC) restriction site generating fragments of 578 bp and 231 bp, while the rs4588 A allele introduces a StyI (C/CWWGG) restriction site and produces fragments of 585 bp and 224 bp. The migration of the digestion products by the HaeIII (GG/CC) restriction enzyme is shown in Fig. 1.

The numbers correspond to the individual patients, and the letter M represents the molecular weight marker. Patients 1, 3, 4, 5, 9, and 7 are homozygous T/T (a single 809-bp fragment), and patient 2 is homozygous G/G (two fragments, one 578-bp fragment and one 231-bp fragment).

Allele frequencies were then estimated using SNPstats software. Analysis of these alleles showed that the Gc1f variant (c.1296T, c.1307C) was the predominant variant (83%), followed by the Gc1s variant (c.1296G, c.1307C). The Gc2 variant (c.1296T and c.1307A) was not observed in our study population. Table 2.

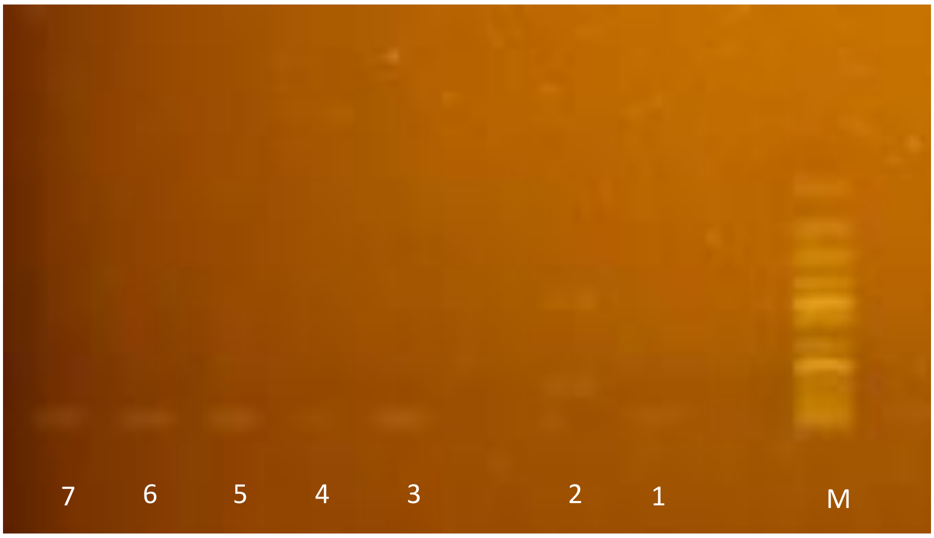

Fig. 1. Results of electrophoresis after the action of the restriction enzyme HaeIII (GG/CC)

Table 2. Distribution of Gc variants and haplotypes Gc

rs7041(c.1296T>G)	rs4588(c.1307C>A)	Variants	Number (n)	Frequency (%)
T	C	Gc1f	80	83%
G	C	Gc1s	16	17%
T	A	Gc2	0	0
		Haplotypes		
T/T	C/C	Gc1f-1f	40	83%
G/G	C/C	Gc1s-1s	8	17%
T/G	C/C	Gc1f-1s	0	0
T/T	A/A	Gc2-2	0	0
T/T	C/A	Gc1f-2	0	0
T/G	C/A	Gc1s-2	0	0

3.3 Vitamin D Status of the Study Population

The median 25(OH)D level was 25.6 pg/ml (95% CI 23.7-27.5). Based on the median values with 95% CI found by Cavalier et al. in a presumably healthy Ivorian population, 60% of patients had a concentration deemed sufficient in 25(OH)D in this population. Hypovitaminosis D was found in 40% of patients Table 3.

3.4 Correlation between Vitamin D Status and Gc Gene Variants of the Transporter Protein

Fisher's exact test did not show a significant association between the polymorphism phenotype (Gc1s/Gc1f) and vitamin D concentration at the α5% threshold. Table 4.

Similarly, analysis of 25(OH) vit D concentrations according to the Gc1f and Gc1s phenotypes using the Bartlett test reveals no significant difference between the two groups at the α5% threshold. Indeed, the means comparison test gives a p-value > 0.05, indicating that the observed difference can be attributed to chance. Fig. 2.

4. DISCUSSION

With a global prevalence estimated at over one billion people, hypovitaminosis D constitutes a real public health problem (Mogire et al., 2020). It is associated with numerous pathologies and affects both young and old people, as well as all types of populations, regardless of race.

Sub-Saharan African populations, despite favorable sun exposure, the main source of vitamin D, are not left out of this scourge (Mogire et al., 2020; Ntyonga-Pono, 2014). Several reasons have been suggested. The best known is skin pigmentation, with the inhibitory action of melanin on the cutaneous synthesis of vitamin D (Young et al., 2020).

However, authors have also highlighted the role of genetic variants of the vitamin D binding protein in the significant variability of systemic vitamin D levels and effects, but also in the response to vitamin D supplementation (Lauridsen et al., 2001; Powe et al., 2013).

Table 3. Vitamin D status of the study population

25(OH)D (pg/ml)	Number (n)	Percentage (%)	Status	
≥ 30	14	29	Sufficiency	Normal
[25-30[	15	31		
[20-25[	12	25	Insufficiency	Hypovitaminosis D
< 20	7	15	Deficiency	
Total	48	100		

Table 4. Vitamin D status according to Gc variants

Vit D/Variants Correlation	Gc1f	Gc1s	Total	p
25(OH)D normale	17	2	19	
Hypovitaminosis D	23	6	29	0,45 (NS)
Total	40	8	48	

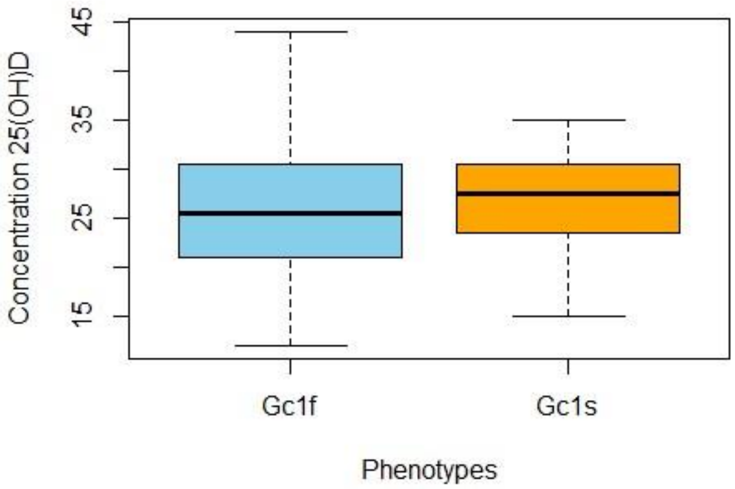

Fig. 2. Boxplot diagram of 25(OH)D concentration as a function of vitamin D transporter protein variants

In a pathology such as chronic kidney disease, already characterized by a deficit in vitamin D activation and almost systematic vitamin D supplementation of patients, it is important to ensure the functional integrity of its transporter protein, whose polymorphisms could influence not only the status of vitamin D in the serum but also the bioavailability of vitamin D and the response to vitamin D supplementation.

This study aimed to determine the genetic variants rs7041 and rs4588 of the vitamin D transporter protein and to correlate them with the vitamin D status of hemodialysis patients in sub-Saharan Africa (Côte d'Ivoire), systematically supplemented orally with vitamin D.

It showed, regarding the genetic variants of the vitamin D transporter protein, a predominance of the Gc1f variant (rs7041-T and rs4588-C), a variant related, according to the literature, to lower vitamin D levels but higher bioavailability. often preserved and a better response to vitamin D supplementation (Bouillon et al., 2019; Powe et al., 2013; Yao et al., 2017).

This predominance of the Gc1f variant has not only been found in other Central and subSaharan African countries but also in African Americans (Braithwaite et al., 2015; Mogire et al., 2021; Nesby-O'Dell et al., 2002; Powe et al., 2013).

On the other hand, in populations from North African countries, Caucasian countries, and white populations in America, a predominance of the Gc1s variant (rs7041-G and rs4588-C) was found (rs7041-G et rs4588-C) (Lefranc et al., 1981; Navas-Nazario et al., 2014; Powe et al., 2013).

In summary, black populations, characterized by a predominance of the Gc1f variant, would be more receptive to vitamin D supplementation and would present lower 25OH vitamin D concentrations without showing signs of functional deficiency due to the sufficiency of the bioavailable fraction (Bhan et al., 2012; Nielson et al., 2016). Whereas, white populations, characterized by a predominance of the Gc1s variant, would tend to have higher vitamin D levels with correct bioavailability but a moderate response (Langer-Gould et al., 2018).

Unfortunately, in hemodialysis patients, irreversible kidney damage further reduces the bioavailable fraction. Vitamin D supplementation is therefore the only option to compensate for this vitamin D deficiency.

These genetic variations and their consequences on vitamin D raise questions about the relevance of applying universal thresholds to define vitamin D deficiency.

In Côte d'Ivoire, a previous study by Cavalier et al. on vitamin D in healthy subjects showed a median 25(OH)D level of 25.9 ng/mL (95% CI 24.9–27.0) (Cavalier et al., 2019). Thus, in this study, the threshold value of 25 pg/mL was used to define hypovitaminosis D instead of 30 pg/mL.

Despite oral vitamin D supplementation, we noted a high proportion of patients with hypovitaminosis D (40%). This observation, which appears to contradict what was stated above, could be explained by possible poor treatment adherence. Indeed, many patients admitted during the interview that they were not properly following their treatment due to a lack of financial means. This non-compliance with treatment has contributed favorably to the high prevalence of hypovitaminosis D in this population.

However, in this study, we did not find a direct association between vitamin D transporter protein variants and vitamin D concentrations.

5. CONCLUSION

This showed that like all black populations, the Gc1f variant of the vitamin D transporter protein was predominant in Ivorian hemodialysis patients. The small sample size of our study was unable to demonstrate the association between the variants and vitamin D concentrations. Given the lack of resources available to us, obtaining financial support from the Ministry of Research in Côte d'Ivoire or partnerships with countries to obtain reagents, especially molecular biology reagents, will allow us to carry out this study on a larger population and thus make better observations.

6. LIMITATION OF THE STUDY

The main limitation of this study was the small sample size. Indeed, the small sample sizeconstitutes a major obstacle in the detection by statistical tests on the links between the differents variables. The association between variants and vitamin D concentrations would have been better assessed with a larger sample size. Similarly, the response to vitamin D supplementation would have been better assessed if the treatment had been offered free of charge to patients over a well-defined period.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

Each subject provided written consent before participating in the study. The study protocol was approved by the National Ethics and Research Committee (CNER) of the Ministry of Health and Public Hygiene of Côte d'Ivoire and the scientific authorities of the participating health centers.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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