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The Association of Vitamin D Receptor Gene Variants (*FokI* and *ApaI*) with Gastric Cancer Susceptibility.

Hind Mahmood Jumaah *, Israa Ayoub Alwan and Halah Kamal Al-Qazzaz

Department of Biotechnology, College of Science, University of Baghdad, Baghdad, Iraq.

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Abstract

Background: Gastric Cancer is the fourth leading cancer worldwide and remains an important health burden due to high morbidity and mortality. The association of vitamin D receptor (VDR) with various cancer types had been investigated. Nevertheless, there are controversial results concerning the association of certain VDR gene polymorphisms with gastric cancer.

Objectives: The present study sought to assess the levels of Vitamin D in patients with gastric cancer as compared with healthy individuals and to investigate the association of VDR gene polymorphisms (*ApaI rs7975232* and *Fok1 rs2228570*) with risk of gastric cancer in Iraqi population of Baghdad city.

Methodology: This case-control investigation involved 128 individuals, from them 64 patients with gastric cancer as well as 64 apparently healthy individuals. The VIDAS total (VITD) has been utilized to measure the concentrations of Vitamin D. The PCR-RFLP technique has been applied to detect the studied genetic variants.

Results: The results of statistical analysis showed a significant (p=0.001) decrease of vitamin D in patients with Gastric cancer as compared with control group. The genetic analysis of studied variants showed that only the genotypes and alleles frequencies of *FokI* (*rs2228570*) variant demonstrated a significant difference between patients and healthy individuals, where this variant reveals a significant association with gastric cancer susceptibility, while no significant associations were found regarding *ApaI* (*rs7975232*) variant. Furthermore, the present investigation also explored the association between VDR variants and serum levels of vitamin D, the distribution of serum concentrations of vitamin D according to genotypes of *FokI* revealed a significant increase in vitamin D levels in both patients and controls have the genotype CC as compared with those have CT and TT; while there are no significant differences among serum levels of vitamin D distributed according to *ApaI* genotypes in both patients and controls.

Conclusion: Vitamin D levels were significantly reduced in gastric cancer patients relative to healthy individuals. *FokI* (*rs2228570*) variant was linked with both vitamin D status and gastric cancer risks.

Keywords: Gastric Cancer; PCR-RFLP; vitamin D; VDR; *ApaI rs7975232*; *Fok1 rs2228570*

1. Introduction

In terminology context, gastric cancer or gastric carcinoma is referring to adenocarcinoma in stomach that is responsible for nearly 90% of all stomach malignant cancers cases. Other malignant lesions in stomach include gastric lymphomas (lymphoma of mucosa-linked lymphoid tissues), gastric stromal cancers (sarcomas) along with carcinoid tumor [1] .It is the fourth leading cancer worldwide remains an important health burden due to high morbidity and mortality (2). According to GLOBOCAN 2020 assessments, Gastric cancer led to nearly 800 000 deaths, thus accounting

* Corresponding author: Hind Mahmood Jumaah

for 7·7% of the global tumor-attributable mortality (3). Gastric cancer exhibits notable geographic variability, whether regionally or across the countries; its great incidence regions involve East Asia (Japan, Korea and China), Western Latin America, and some countries in Europe and Middle East (4, 5). During duration of life, its risk is roughly 1 from 112, with a somewhat greater risk in males than females (6). Even though the incidence of Gastric cancer is slightly lower in Iraq as compared to some neighboring high-risk countries such as Iran, Gastric cancer in Iraq seems to present in more advanced stages and in relatively younger ages (7). In the Iraqi population, the clinicopathological pattern shows a predominance of intestinal-type adenocarcinoma, suggesting that certain genetic variants influence the transition from chronic inflammation to cancer (8).

The development of Gastric cancer has a complex development with multifactorial etiology, which may be attributable to genetic changes or environmental impacts (9). Chronic infection with Helicobacter pylori is the main risk factor for this type of cancer (10). Many factors such as alcoholic consumption, Epstein Barr virus infection, older age, hyperlipidemia, unhealthy diet, tobacco use, history of stomach surgery, and pernicious anemia have been associated with etiology of gastric cancer. Additionally, it is known that genetic predisposition may play a role in the pathogenesis of gastric cancer (11). One of the most exciting fields of molecular research in oncology is impact of Vitamin D pathway. In addition to its classical roles in bone homeostasis, Vitamin D biologically active form ($1,25(OH)_2D_3$) exerts vigorous antitumor impacts by regulation cell proliferation, apoptosis, alongside the angiogenesis (12). These impacts are mediated via the Vitamin D Receptor (VDR), a ligand-dependent nuclear transcription factor coded in the genome on chromosome 12q13. 1 (13). Certain single nucleotide polymorphisms (SNPs) present in the VDR gene alter expression or function of the protein, which can compromise the protective signaling of Vitamin D and increase the risk of diverse neoplasms such as gastrointestinal cancers (11). Whilst several genetic SNPs were uncovered in VDR gene, *ApaI* (r*s7975232 G>T*) and *FokI* (*rs2228570 C>T*) regard the most prevalent SNPs, which can change vitamin D ability for binding to its receptor by affecting the expression of VDR. *ApaI* has been positioned in 3' end region of VDR gene, while *FokI* has been present in translation start codon (12, 14). Previous investigations had demonstrated that these variants of VDR have been associated with the susceptibility to various kinds of malignancies such as gastric, lung, and colorectal cancers (15,16,17). However, the effects of VDR gene alterations on gastric cancer susceptibility still debatable; accordingly, the current investigation sought to investigate the association VDR Variants (*ApaI* and *FokI*) with gastric cancer susceptibility.

2. Materials and Methods

2.1. The studied population, study design and samples collection

The current investigation involved 128 individuals, from them 64 patients with gastric cancer (32 males and females 32) their ages ranged between 43-65 years as well as 64 apparently healthy individuals (32 males and females 32) their ages ranged between 40-60 years. This case-control study has received ethical approval from our College Ethics Committee. To conduct the required tests, 5 ml of peripheral blood was collected from each participant, part of which was separated into tubes coated with anticoagulant Ethylenediaminetetraacetic acid(EDTA) and preserved at (−20°C) to achieve the genetic analysis. Another part of blood put in gel tube that centrifuged to get sera and preserved at (−20°C) until evaluating concentrations of vitamin D for both patients and controls.

2.2. Evaluation the concentrations of Vitamin D

The VIDAS total (VITD) has been utilized to measure the concentrations of Vitamin D. This automated quantitative technique estimates the 25-Hydroxyvitamin D Total in serum employing enzyme-linked fluorescent approach.

2.3. The genetic analysis of study of *FokI rs2228570* and *ApaI rs7975232* genotypes.

The PCR-RFLP technique has been applied to detect Vitamin D Receptor *ApaI rs7975232* as well as Vitamin D Receptor gene *FokI rs2228570* for patients with gastric cancer and healthy individuals. Specific primers were utilized from Bioneer/Korea, their sequences and origin were displayed in Table (1). The genomic DNA samples were extracted employing the AccuPrep®Genomic DNA Extraction Kit from Bioneer/Korea. Then these samples have been amplified by PCR, where typical thermal cycling conditions were including the following steps: initial denaturation (95°C) for 5 mins, (30)cycles of (95°C) for 45 sec in proper denaturation, (63°C) for 45 sec in annealing steps, and(72°C) for 45sec in extension step, the final extension at(72°C) for 10 mins. The products from PCR technique were processed by restriction endonuclease from Biolabs Inc./ England in an incubator at (37 ◦ C) for 30 mins with fast digest with Apa-I restriction endonuclease for *Apa-I* polymorphic site in VDR gene and Fok-I restriction endonuclease for *Fok-I* polymorphic site in VDR gene. Subsequent to these steps, the products were electrophoresed to digest them on 2% agarose gel for two hours and using the DNA ladder (50-1500bp), and then visualized using UV-illuminator after adding ethidium bromide dye to detect the genotypes of SNPs of *ApaI* (*rs7975232)* and *Fok1* (*rs2228570*). The genotypes of

(*ApaI rs7975232)* were detected: the homozygote genotype (GG) possesses one band for (630bp) fragment, heterozygote genotype (GT) had three bands for fragments were 630bp, 484bp, and 146bp, finally homozygote genotype (TT) possesses two bands were 484bp and 146bp. As for *Fok1* (*rs2228570*) homozygote genotype (CC) possesses one band (267bp) fragment, (CT) genotype had three bands for fragments were 267bp, 198bp, and 69bp, the (TT) genotype possesses two bands were 198bp and 69bp.

Table 1 The primers utilized in present study

Primers name	Sequences	Origin
ApaI	F: 5- GGATCCTAAATGCACGGAGA-3	(18)
	R: 5- ACGTCTGCAGTGTGTTGGAC-3	
FokI	F: 5-AGCTGGCCCTGGCACTGACTCtGGCTCT-3	(19)
	R: 5-ATGGAAACACCTTGCTTCTTCTCCCTC-3	

2.4. The statistical analysis

Data had been analyzed using SPSS statistical software (version-26). The Z-test was utilized to compare the levels of vitamin D between gastric patients and healthy individuals. The association between the studied SNPs and the risk of gastric cancer was estimated by calculating Odds Ratio at 95% Confidence Interval. Vitamin D levels distributed according to the genotypes of patients and controls were compared using ANOVA analysis. The P-value of<0.05 was deemed statistically significant to decide the strength and direction of the relationship between genotypes and alleles and clinical outcomes.

3. Results and discussion

3.1. Evaluation of Serum Vitamin D concentrations

Figure (1) displays the levels of vitamin D in studied population, where the results of statistical analysis showed a significant (p=0.001) decrease of vitamin D in patients with Gastric cancer as compared with control group.

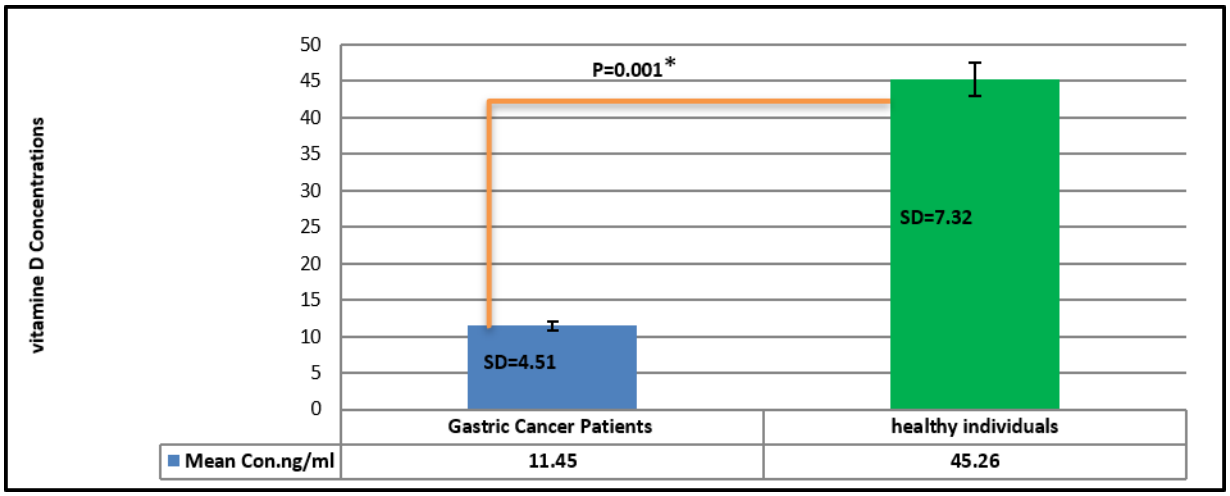

Figure 1 Serum vitamin D concentrations for Gastric patients and healthy individuals as evaluated by VIDAS total (VITD); (Results presented as mean ± standard deviation (SD): 11.45 ± 4.51 vs. 45.26 ± 7.32, P = 0.001*, Z-test).

3.2. Vitamin D Receptor *FokI rs2228570* genotypes and allele frequency in study population

Table (2) displays the genotypes and alleles frequencies of *FokI* (*rs2228570*) variant; this table demonstrates a significant difference between patients and healthy individuals. The CC genotype was found in 31.25% of patients versus 62.5% of controls, while CT genotype was notably more frequent among patients (59.38%) than controls (25%). The TT genotype is present in 9.37% of patients and in 12.5% of controls. The outcomes of statistical analysis showed that these differences being highly significant (p = 0.0005), with an odds ratio (OR) of 0.2727 and a confidence interval

(CI) of 0.1312 to 0.5669, indicates that CC genotype may provide a protective impact against gastric cancer. Moreover, when we analyzed the alleles frequencies, it is demonstrated that variant allele was significantly linked with gastric cancer risk (p= 0.0166), with OR of 0.5200 and CI of 0.3046 to 0.8878, revealing that carriers of this *FokI* polymorphism had a lower risk.

Table 2 Genotype and allele frequency of Vitamin D Receptor *FokI rs2228570* in Gastric cancer patients and control

Genotypes	**Gastric cancer Patient N=64**		**Healthy individuals N=64**		**Odds ratio**	**CI 95 %**	**P value Significance levels**
	No.	%	No.	%	0.2727	0.1312 to 0.5669	0.0005*
CC	20	31.25%	40	62.5%			
CT	38	59.38%	16	25%			
TT	6	9.37%	8	12.5%			
Total	64	100%	64	100%			
Alleles frequency							
C	78	60.94%	96	75%	0.5200	0.3046 to 0.8878	0.0166*
T	50	39.06%	32	25%			
Total	128	100%	128	100%			

Table(3) shows the association between *FokI* polymorphism and the danger of gastric cancer according to four genotype forms are found employing different genetic models. Under co-dominant model, CT was significantly more frequent among gastric cancer patients than in healthy individuals (with OR of 0.2105; CI: 0.0952 - 0.4654, p= 0.0001), suggests a potent protective impact relative to the reference genotype (CC). In contrast, TT genotype did not reveal a statistically significant association. The dominant model (CT-TT vs. CC) assured this protective impact, where carriers of variant alleles exhibited a notably lessened risk for gastric cancer (OR= 0.2727; CI=0.1312 to 0.5669, p= 0.0005). On the other hand, recessive model (TT vs. CC-CT) showed non-significant association. Interestingly, model of over-dominant (CT vs. CC-TT) showed a highly significant association (OR=0.2281; CI=0.1073 to 0.4849; p=0.0001), suggesting that carriers have heterozygous genotype may benefit from a decreased susceptibility to gastric cancer relative to those who have homozygous.

Table 3 Forms of Vitamin D Receptor *FokI rs2228570* gene Gastric patients and control

Model	**Genotypes**	**Gastric cancer Patient N=64**		**Healthy individuals N=64**		**Odd ratio (95% CI)**	**P. Value Significance levels**
		No.	%	No.	%		
Co-Dominant	CC	20	31.25%	40	62.5%	References (OR=1)	-
	CT	38	59.38%	16	25%	0.2105 (0.0952 to 0.4654)	0.0001*
	TT	6	9.37%	8	12.5%	0.6667 (0.2035 to 2.1845)	0.5031 NS
Dominant	CC	20	31.25%	40	62.5%	References (OR=1)	-
	CT-TT	44	68.75%	24	37.5%	0.2727 (0.1312 to 0.5669)	0.0005*
Recessive	CC-CT	58	90.63%	56	87.5%	References (OR=1)	-

	TT	6	9.37%	8	12.5%	1.3810 (0.4504 to 4.2341)	0.5723 NS
Over Dominant	CC-TT	26	40.62%	48	75%	References (OR=1)	-
	CT	38	59.38%	16	25%	0.2281 (0.1073 to 0.4849)	0.0001*

3.3. Vitamin D Receptor *ApaI rs7975232* genotypes and allele frequency in study population

Table (4) shows the genotypes and alleles frequencies of *ApaI* (*rs7975232*) variant; where the results of statistical analysis revealed non-significant association between this SNP and risk of gastric cancer.

Table 4 Genotypes and alleles frequency of Vitamin D Receptor *ApaI rs7975232* in Gastric cancer patients and control

Genotypes	**Gastric cancer Patient N=64**		**Healthy individuals N=64**		**Odds ratio**	**CI 95 %**	**P value Significance levels**
	No.	%	No.	%	0.8171	0.3978 to 1.6786	0.5825 NS
GG	22	34.38%	25	39.06%			
GT	31	48.44%	27	42.19%			
TT	11	17.18%	12	18.75%			
Total	64	100%	64	100%			
Alleles frequency							
G	75	58.59%	77	60.16%	0.9373	0.5691 to 1.5436	0.7991 NS
T	53	41.41	51	39.84%			
Total	128	100%	128	100%			

Table (5) shows the association between *ApaI rs7975232* polymorphism and the danger of gastric cancer according to four genotype forms that are found employing different genetic models. Also, the results of statistical analysis demonstrated non-significant association between these forms of genotypes and gastric cancer susceptibility.

Table 5 Forms of Vitamin D Receptor *ApaI rs7975232* Gastric cancer patients and control

Model	**Genotypes**	**Gastric cancer Patient N=64**		**Healthy individuals N=64**		**Odd ratio (95% CI)**	**P. Value Significance levels**
		No.	%	No.	%		
Co-Dominant	GG	22	34.38%	25	39.06%	References (OR=1)	-
	GT	31	48.44%	27	42.19%	0.7665 (0.3545 to 1.6571)	0.4989 NS
	TT	11	17.18%	12	18.75%	0.9573 (0.3762 to 2.4358)	0.9270 NS
Dominant	GG	22	34.38%	25	39.06%	References (OR=1)	-
	GT-TT	42	65.62%	39	60.94%	0.7800 (0.3808 to 1.5977)	0.4970 NS
Recessive	GG-GT	53	82.82%	52	81.25%	References (OR=1)	-
	TT	11	17.18%	12	18.75%	1.1119	0.8180 NS

						(0.4506 to 2.7435)	
Over Dominant	GG-TT	33	51.56%	37	57.81%	References (OR=1)	-
	GT	31	48.44%	27	42.19%	0.7768 (0.3867 to 1.5603)	0.4779 NS

3.4. The association between Studied SNPs *(FokI rs2228570 and ApaI rs7975232)* of Vitamin D Receptor gene and serum concentration vitamin D

Table (6) exhibited the distribution of serum concentrations of vitamin D according to genotypes of *FokI rs2228570* polymorphism, where the results of statistical analysis revealed a significant increase in vitamin D levels in both patients and controls have the genotype CC as compared with those have CT and TT.

Table 6 The association between genotypes of *FokI rs2228570* and serum concentration vitamin D

Genotypes	**Gastric cancer Patient**	**Healthy individuals**
	Concentration (Mean± SD)	
CC	16.24±4.71	47.67±5.31
CT	11.68±2.42	42.21±4.22
TT	9.22±3.66	30.97±6.48
P. Value Significance levels	0.010*	0.023*

Table (7) shows the distribution of serum concentrations of vitamin D according to genotypes of *ApaI rs7975232* polymorphism, where the results of statistical analysis indicated non-significant differences in vitamin D levels in both patients and controls.

Table 7 The association between genotypes of *ApaI rs7975232* and serum concentration vitamin D

Genotypes	**Gastric cancer Patient**	**Healthy individuals**
	Concentration (Mean± SD)	
GG	11.3±5.78	44.13±5.32
GT	10.67±3.42	45.9±6.48
TT	10.02±4.21	38.11±3.26
P. Value Significance levels	0.753 NS	0.432 NS

4. Discussion

The significant decrease in vitamin D concentrations that recorded in our study on gastric cancer cohort emphasized an increasing consensus in nutritional oncology concerning the protecting role of vitamin D. The present finding aligns with the outcomes of a retrospective chart analysis by Vyas *et al*. (20) which revealed that those with gastric adenocarcinoma had notably high vitamin D deficiency as compared with healthy individuals (20). Likewise, the meta-analysis by Liu et al. established that sera levels of 25(OH)D are consistently lower in gastric cancer patients, and they suggested that depressed vitamin D levels may be a considerable risk factor for this disease (21). The prospective clinical relevance of our findings is further emphasized by the study of Ren *et al.* (22) which showed that vitamin D deficiency serves as an independent predictive factor for poor survival opportunities in patients with gastric cancer (22). On the other hand, some literatures, like Khayatzadeh *et al*., reported that data can be conflicting across populations (23). In addition, some large-scale pooled studies like Stomach Cancer Pooling Project had revealed more nuanced outcomes, revealing that dietary vitamin D intake may exhibit some negative association with gastric cancer risk, but evidence still conflicting across different populations (24).

In the context of genetic analysis, the current study investigates the association of two VDR polymorphisms, *FokI (rs2228570)* and *ApaI (rs7975232)* with susceptibility of gastric cancer in affected patients. Regarding *FokI (rs2228570)* SNP, it was found a significant association with risk of gastric cancer; CC genotype is less frequent among patients, while CT was markedly higher in patients. Allelic analysis further emphasized this association; the low OR value for genotype distribution reveals that CC genotype may confer a degree of protection against gastric oncogenesis, while the presence of T allele (especially in heterozygous CT form) is associated with high risk. The results in Table (3) suggest a contribution for the *FokI* polymorphism in gastric cancer risk which may be accomplished by a heterozygous advantage mechanism. The strong associations noted in the co-dominant, dominant and over-dominant models are consistent with the proposed role of the variant allele in modifying VDR activity to enhance the protective effects of vitamin D against carcinogenesis. The absence of association in the recessive model is also consistent with the beneficial effect of heterozygosity versus homozygosity for the variant allele.

FokI is situated at the 5' end of the VDR gene (25), this SNP involved nucleotide substitution of T to C at the first codon of exon 2 eliminating the first translation initiation site and leading to a shorter peptide than wild type by 3 amino acids and resulting in a new transcriptionally more active form of VDR (26).

The current finding aligns with the study of Hoseinkhani et al., who demonstrated significant associations of *FokI* variant with risk of gastric cancer in Iranian population (12). Also, our finding agrees with Qadir *et al*., who revealed that SNPs of VDR, including *FokI*, were significantly affected gastric cancer risk in Kashmiri population, emphasized the significance of ethnic and geographic variations in genetic predisposition (17). The Meta-analysis studies provide further support for this association; where the Guan and Wang (11) collected data from 9 studies and demonstrated that common VDR polymorphisms, including *ApaI* and *FokI* have a significant association with gastric cancer risk, despite the intensity of the association diversified across populations (11). Similarly, our findings are in line with an earlier study of Cong *et al*., which also revealed that *FokI* polymorphism was associated with escalated susceptibility to gastric cancer (27). The correspondence across different populations indicates that VDR polymorphisms may change receptor functions, thus affecting vitamin D-mediated pathway in cells proliferation, apoptosis, along with immune regulation. The protective association seen with the *ApaI* polymorphism is even suggestive of an increase in either VDR activity or stability for some variants, possibly increasing the anti-tumor effects of vitamin D in gastric tissue. Clinically these results suggest that VDR polymorphism could be used to identify those at higher or lower risk of gastric cancer, and eventually contribute to personalized prevention. In addition, the findings are consistent with the notion that the vitamin D deficiency and impaired VDR signaling are mutually reinforcing in the context of gastric cancer. As for *ApaI (rs7975232)* variant, it presents within exon 9 neighboring to 3' untranslated region (3' UTR), at this SNP, G is substitute by T, it was established that it inversely control expression of VDR gene (28, 29). The polymorphism *ApaI* (*rs7975232*) of VDR gene had not shown any significant association with gastric cancer risk in present study. The importance of this result lies with the effects of VDR polymorphisms being heterogeneous in different populations and different cancers. Although other SNPs like *FokI* (*rs2228570*) have been consistently associated with gastric cancer susceptibility, this SNP appeared to have little or no impact on our cohort. This non-significant association in current study in line with previous findings of several studies (11,12,17), which also demonstrated non-significant associations of *ApaI (rs7975232)* variant with risk of gastric cancer in Iranian population. Furthermore, the present investigation also explored the association between VDR variants and serum levels of vitamin D, showing recognizable patterns for *FokI* and *ApaI* SNPs. With respect to *FokI* (*rs2228570*) SNP, participants have CC genotype evinced significantly increased vitamin D levels in both patients and controls compared to those have other genotypes, this finding agrees with previous studies that have documented functional implications of this variant (12, 17, 27).

5. Conclusion

Our investigation reveals that serum levels of vitamin D significantly diminished in cases with gastric cancer as compared with healthy subjects, reinforcing the hypothesis that deficiency of vitamin D may engage with gastric carcinogenesis. Genetic analysis of VDR gene demonstrated that *FokI (rs2228570)* SNP was notably associated with both vitamin D levels and gastric cancer danger, especially under co-dominant, dominant, and over-dominant genetic models. Conversely, *ApaI (rs7975232)* SNP exhibited non-significant association with either vitamin D status or gastric cancer risk. Collectively, our outcomes underscore the dual importance of vitamin D deficiency and genetic variations in the VDR gene as prospective contributors to gastric cancer susceptibility.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interests.

Statement of informed consent

The Research Ethical Committees of the College of Sciences/University of Baghdad accepted this study protocol (Ref. CSEC/0426/0035).

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