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Association of Vitamin D Receptor (VDR) Gene BSMI polymorphism with inflammatory bowel disease in Iraqi Patients: A Case-Control Study

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Abstract

Background: The inflammatory bowel disease (IBD) that includes ulcerative colitis (UC) and Crohn disease (CD) is associated with complex interactions between genetic, environmental and immunological factors. Emerging evidence highlights an important role of vitamin D signaling in the regulation of intestinal immune homeostasis, with the Polymorphisms in the Vitamin D Receptor (VDR) gene having the potential to alter the disease susceptibility. This case-control study investigated the relationship between VDR *Smi* (rs1544410) polymorphism and IBD in an Iraqi population, and evaluated corresponding biochemical markers such as serum vitamin D_3 and C-reactive protein (CRP).

Methods: Eighty participants were enrolled, consisting of 40 clinically confirmed IBD patients (28 UC and 12 CD) and 40 healthy, age-matched controls. Genetic DNA was obtained via peripheral blood and 265 bp fragment of VDR gene was amplified through PCR, and restriction fragment length polymorphism was performed through data digestion using *Smi* enzyme to identify genotypes. Biochemical profiling was done by measuring serum vitamin D_3, CRP, glucose, hemoglobin, and calcium. Statistical analyses included chi-square tests, t -tests, Hardy-Weinberg analysis, and ROC curve analysis.

Results: Genotype distribution of the *Smi* polymorphism differed significantly between groups. Bb and bb genotypes had a significant relationship with increased IBD as compared to the BB genotype, giving odds ratios of 7.28 and 26.71 respectively. The frequency of minor b allele was higher in the patient (33.7%), compared to the control (8.8%). The level of serum vitamin D_3 was significantly lower in patients, with significantly higher CRP and glucose. The ROC analysis showed superior diagnostic performance for vitamin D_3 (AUC 0.912, Sensitivity 87.5%, specificity 85.0%) compared to CRP (AUC 0.710).

Conclusion: The findings of the study indicate that VDR *Smi* polymorphism is a genetic predisposing factor to IBD in the Iraqi population and it is associated with significant biochemical changes, which substantiates the importance of vitamin D mechanisms in the pathogenesis of the disease and possible clinical monitoring.

Keywords: VDR; BSMI; Inflammatory Bowel Disease; Vitamin D3; Iraqi Patients

1. Introduction

Inflammatory bowel disease (IBD) is a chronic and multifactorial ulcerative bowel inflammatory disease of both adults and children leading mostly to ulcerative colitis (UC) and Crohn disease (CD). The primary difference between these two forms is in the way they are involved in the bowel wall. UC normally starts in the rectum and may spread proximally

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to include the sigmoid colon, but CD may result in trans-mural ulceration along any part of the gastrointestinal tract (GI) [1, 2].

IBD has gained popularity in the world, and in the past, developing countries had higher rates of ulcerative colitis than those of Crohn's disease. However, the recent reports show that there is an increase in cases of CD in these areas. Even though social, microbial, immunological, genetic, and environmental factors have been suggested as possible disease risk factors, the mechanism involved is still not well understood [3, 4].

The high number of independent SNPs and genetic locus SNPs in 231 disease-associated SNPs in extensive genome wide association studies (GWAS) have revealed a total of 200 genetic loci [5] in large international IBD cohorts. Most of these variants are assumed to have control effects on the expression of genes (regulatory effect) and not on the amino-acid sequence of coded proteins. It is 1,25(OH) 2D3 (calcitriol), the biologically active metabolite of vitamin D 3, which is one of the most important regulators of the intestinal mucosal barrier integrity. The action of this molecule is associated with the binding to the vitamin D receptor (VDR), which is a phosphoprotein that is a member of the nuclear hormone receptor superfamily [6]. The immune system is multifaceted with VDR signaling having anti-inflammatory, immunomodulatory, antimitotic, pro-differentiation, and pro-apoptotic effects. Calcitriol/VDR binding facilitates the heterodimerization with retinoid X receptor and binding to vitamin D response elements and thus controls the expression of downstream target genes [6].

VDR gene is on chromosome 12q1214 having over 100 kb and consists of eight coding and six non-coding exons covering about 75 kb. The gene has high polymorphism, and the FokI, APAI, BSMI and TAQI restriction fragment length polymorphism (RFLPs) are the most frequently studied in inflammatory and immune-mediated diseases [7].

The objective of this study was to evaluate the relationship between the BSMI polymorphism of the Vitamin D Receptor (VDR) gene and inflammatory bowel disease susceptibility in an Iraqi population and to assess the relationships between this polymorphism, serum vitamin D3 levels and other biochemical indicators.

2. Materials and Methods

2.1. Study Population

A total of 80 participants were selected to take part in this case-control study: 40 patients with IBD and 40 healthy controls. The IBD group consisted of 28 ulcerative colitis (UC) and 12 Crohn's disease (CD) patients.

- The diagnosis of UC cases was made in accordance with standard clinical, endoscopic and histopathological features.
- Confirmation of CD cases was performed through laparoscopy and/or endoscopy with assistance of histopathology.

Recruitment of all patients was done at the Gastroenterology and Liver Teaching Hospital in Baghdad, between October 2023 and December 2023. The patients were aged between 17 and 65 years and the sex proportion was one-to-one. The control group was a sample of 40 healthy persons of the same age (24 men and 16 women, 17-65 years old) who did not have gastrointestinal disorder history or abnormal bowel screening. Direct interviews were used to collect demographic and clinical data. Venous blood (5 mL each) was taken out of each participant in EDTA tubes to do genomic DNA extraction and biochemical analyses.

2.2. Genetic Analysis

The whole blood was used to extract genomic DNA utilizing a commercial DNA extraction kit (Gene aid, Korea) following the instructions of the manufacturer.

2.3. Polymerase Chain Reaction (PCR)

The following primers were used to amplify A 265 bp fragment of the vitamin D receptor (VDR) gene which contained the Smi (rs1544410) polymorphism

- Forward: 5′-AGC TGG CCC TGG CAC TGA CTC TGC TCT-3′
- Reverse: 5′-ATG GAA ACA CCT TGC TTC TCC CTC-3′

The specificity of primers was verified using the BLASTN tool (NCBI). Primer was prepared in nuclease-free water in a final concentration of 100 PM/ML and stored at −20°C until use. PCR was performed in a final volume of 25 ML using genomic DNA, primers, dNTPs, Taq DNA polymerase, and reaction buffer.

The amplification protocol was as follows

Initial denaturation at 95°C for 5 minutes

35 cycles of

- Denaturation at 95°C for 1 minute
- Annealing at 60.8°C for 45 seconds
- Extension at 72°C for 54 seconds
- Final extension at 72°C for 5 minutes

The electrophoresis was done for PCR products on a 1.5% agarose gel in 1XTAE buffer, with a 50 bp DNA ladder as size marker. The presence of a clear band at 265 bp was an indication that there was successful amplification.

2.4. Restriction Fragment Length Polymorphism (RFLP)

Amplified PCR products were digested with the BSMI restriction enzyme (Thermon Scientific, USA) at 37°C for 2 hours to genotype the rs1544410 polymorphism.

- The B allele (G at rs1544410; no restriction site) remained uncut at 265 bp.
- The b allele (A at rs1544410; restriction site present) was cleaved into fragments of 196 bp and 69 bp.

Digested products were separated on a 2% agarose gel, stained with ethidium bromide, and visualized using a gel documentation system. The BSMI recognition sequence was 5′-G↓GATCC-3′.

2.5. Statistical Analysis

The SAS (2018) and Medal software were used to analyze data. Continuous variables (age, BMI, and vitamin D3) were compared using independent t-tests whereas the difference in genotype and allele frequency was assessed using chi-square tests. The control group was evaluated in by Hardy-Weinberg equilibrium. Furthermore, Receiver Operating Characteristic (ROC) curves were constructed to identify the diagnostic ability of CRP and vitamin D3 and the area under the curve (AUC) used for comparison. The p-value of < 0.05 was regarded to be statistically significant.

3. Results

3.1. Demographic and Clinical Characteristics of Study Population

Eighty blood samples were used in the analysis, 40 of which were patients with IBD and 40 healthy controls. The patient population consisted of those who were diagnosed with ulcerative colitis (n=28) and the Crohns disease (n=12). Every sample underwent the PCR and restriction digestion of the BSMI (rs1544410) VDR gene polymorphism. The unique features of the two groups are presented in Table 1. Mean body mass index and age were both found to be significantly lower in-patient group than controls ($P<0.0001$). There were no significant differences between groups in terms of sex distribution or residence. The patient cohort consisted of 70% ulcerative colitis and 30% Crohn's disease cases.

Table 1 Demographic and Clinical Characteristics of Study Groups

Parameter	Controls (n=40)	Patients (n=40)	P-value	Test
Age (years), mean ± SD	43.60 ± 10.71	32.05 ± 11.43	<0.0001	t-test
BMI (kg/m^2), mean ± SD	28.03 ± 4.17	24.06 ± 5.45	<0.0001	t-test
Residence – Rural, n (%)	5 (12.5%)	5 (12.5%)	1.00	Chi-square
Residence – Urban, n (%)	35 (87.5%)	35 (87.5%)	–	–
Sex – Male, n (%)	20 (50%)	24 (60%)	0.36	Chi-square
Sex – Female, n (%)	20 (50%)	16 (40%)	0.36	Chi-square
Ulcerative colitis, n (%)	–	28 (70%)	–	–
Crohn's disease, n (%)	–	12 (30%)	–	–

3.2. Genomic DNA Extraction

Genomic DNA was successfully extracted from all samples. Agarose gel electrophoresis (1%, 90 V, 30 min) demonstrated the intact, high-molecular-weight DNA in both groups as patients (lanes 1–8) and controls (lanes 9–16). The reference DNA ladder was also included and standardized gel staining and imaging processes were applied (Figure 1).

Figure 1 Agarose Gel Electrophoresis of Extracted Genomic DNA

3.3. PCR Amplification of VDR Gene

A fragment of 265 bp, corresponding to the target region of the VDR BSMI locus, was successfully amplified in all samples. Electrophoresis on a 1.5% agarose gel (90 V, 1 h) revealed clear, consistent bands in every examined lane. A 50-bp DNA ladder and a negative control were included for reference (Figure 2).

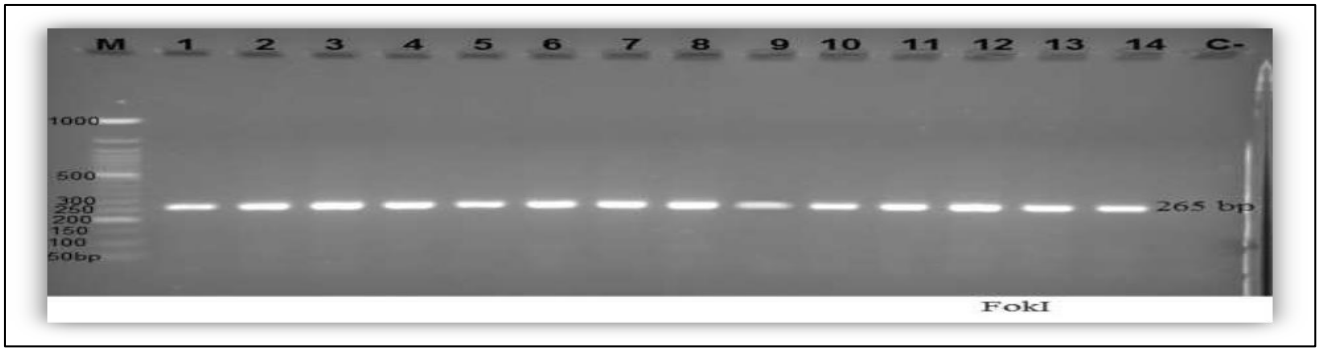

Figure 2 PCR Amplification of VDR (BSML) Fragment

3.4. Restriction Fragment Length Polymorphism Analysis

Restriction enzyme digestion identified three genotypes based on fragment size:

- BB (wild type): undigested 265 bp fragment.
- Bb (heterozygous): 265 bp, 196 bp, and 69 bp fragments.
- BB (variant): 196 bp and 69 bp fragments."

Electrophoresis on 2% agarose gel confirmed these digestion patterns in all samples. All sample lanes, reference ladder, and control lanes were clearly labeled. Fragments at 70 bp or below were detectable within the gel resolution limits (Figure 3).

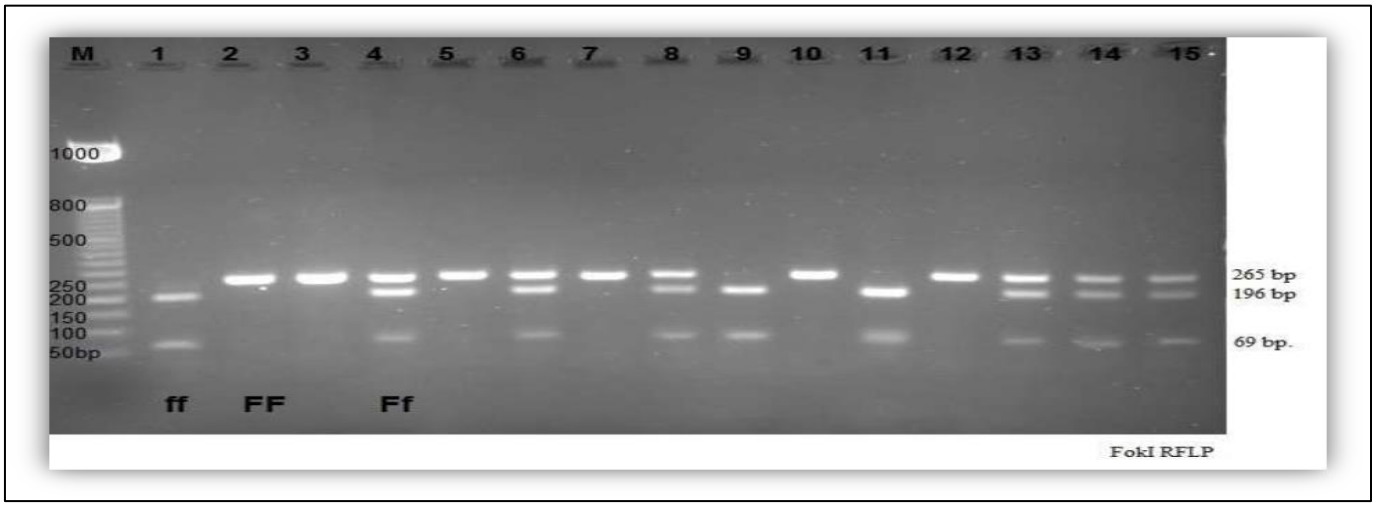

Figure 3 RFLP Analyses of Digested PCR Products

3.5. Genotype and Allele Distribution

Table 2 displays the genotype and allele frequencies of VDR Bsml polymorphism. The test of Hardy - Weinberg equilibrium did not indicate any deviation in either the patient groups (P=0.12) or the controls (P=0.17). All the three genotypes had significant differences in their genotype frequencies between the patients and the controls. Distribution of alleles also showed disparity among groups, and the total allele counts were done in accordance to the diploid number of chromosome (2 × sample size). P-value of chi-square of whole genotype distribution was p<0.0001. This large confidence interval of the bb genotype may be explained by its extremely low frequency in the control group (n=1), which is a limitation related to the sample size.

Table 2 Distribution of VDR (BSML) Genotypes and Alleles in Study Groups

Genotype	Patients (n=40)	Controls (n=40)	X^2	P-value	OR (95% CI)
BB	14 (35%)	34 (85%)	20.83	<0.0001	Reference
Bb	15 (37.5%)	5 (12.5%)	6.67	0.009	7.28 (2.22–23.90)
bb	11 (27.5%)	1 (2.5%)	9.80	0.001	26.71 (3.14–226.98)
HWE P-value	0.12	0.17	–	–	–
Allele	Patients (n=80)	Controls (n=80)			
B allele	53 (66.3%)	73 (91.3%)			
b allele	27 (33.7%)	7 (8.8%)			

3.6. Diagnostic Performance of CRP and Vitamin D3

Tables 3 and 4 summaries the diagnostic accuracy of CRP and Vitamin D3 levels. CRP showed sensitivity and specificity of 72.50 and 67.50, respectively with Vitamin D3 showing sensitivity and specificity of 87.50 and 85.00, respectively with the cutoff values identified. CRP and Vitamin D3 had AUC of 0.710 and 0.912 respectively according to ROC analysis. An integrated ROC plot demonstrates the values of diagnostic across thresholds (Figure 4).

Table 3 Diagnostic Performance of CRP and Vitamin D3 Levels

Marker	Cut-off Value	Units	Sensitivity (%)	Specificity (%)
C-reactive protein (CRP)	>3.2	mg/L	72.50	67.50
Vitamin D3	≤19.32	ng/mL	87.50	85.00

Table 4 Area Under ROC Curve for CRP and Vitamin D3

Variable	AUC	Standard Error	95% CI			
CRP	0.710	0.0586	0.597–0.806			
Vitamin D3	0.912	0.0325	0.827–0.964			
Comparison	Difference in AUC		Standard Error	95% CI	z	P-value
CRP vs. D3	0.202		0.0629	0.0789–0.326	3.213	0.0013

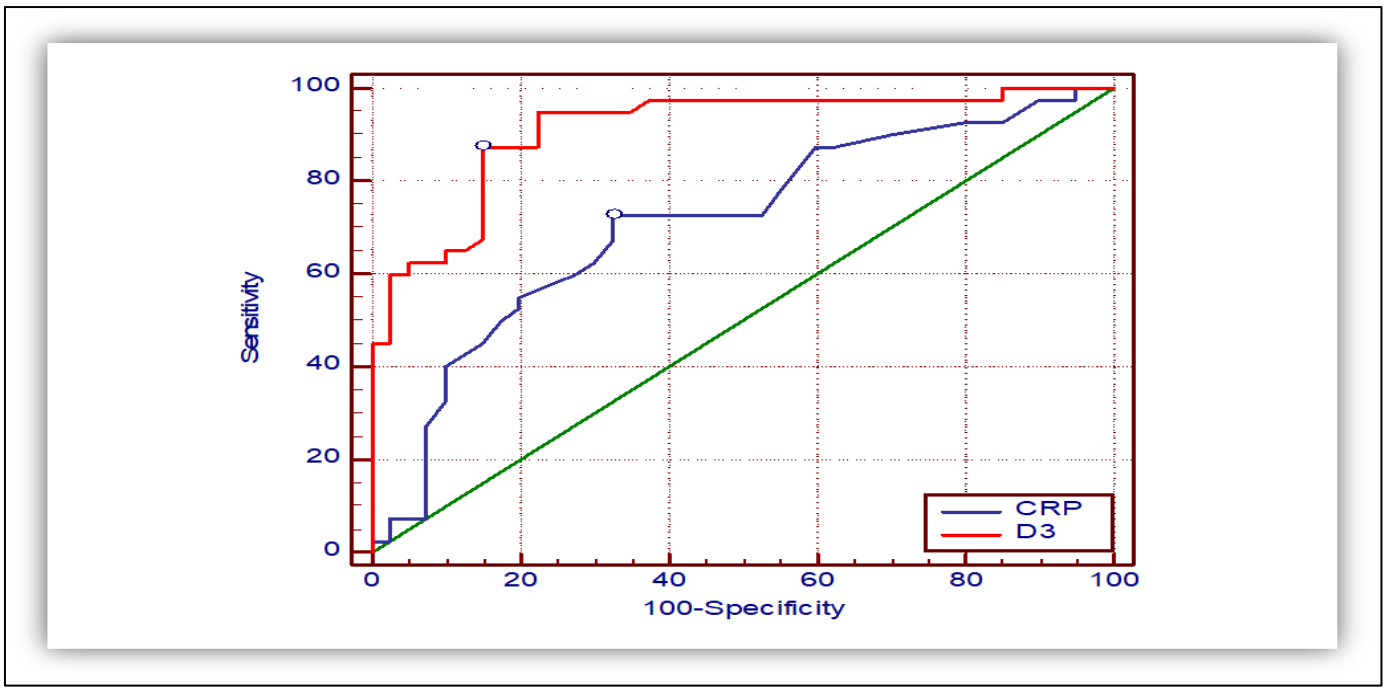

Figure 4 Receiver Operating Characteristic Curve

3.7. Comparison of Biochemical Parameters

Table 5 shows differences in biochemical parameters between groups. There was a significant difference in the level of vitamin D3 and CRP between patients and controls (P = 0.0001 and P = 0.02 respectively). Patients also had a significant higher level of glucose (P = 0.002). There were no statistically significant differences between hemoglobin or calcium levels.

Table 5 Biochemical Parameters in Patients and Controls

Parameter	Controls (n=40) Mean ± SD	Patients (n=40) Mean ± SD	Units	P-value	Test
Calcium	9.80 ± 4.17	10.29 ± 4.11	mg/dL	0.59	t-test
Vitamin D3	25.14 ± 6.32	13.28 ± 6.21	ng/mL	<0.0001	t-test
CRP	3.73 ± 2.36	5.15 ± 3.00	mg/L	0.02	t-test
Hemoglobin	12.54 ± 1.55	12.44 ± 1.74	g/dL	0.80	t-test
Glucose	97.93 ± 16.79	124.93 ± 51.91	mg/dL	0.002	t-test

4. Discussion

This was a case-control study aimed at investigating the association between Vitamin D Receptor (VDR) gene Smi (rs1544410) polymorphism and the susceptibility to IBD in an Iraqi population. Our principal findings reveal that there is a significant association between BsmI polymorphism and the risk of IBD. In particular, the heterozygous (Bb) and the homozygous variant (bb) genotypes were associated with a significantly increased risk of IBD development as compared to the homozygous wild-type (BB) genotype. Moreover, we found that the mean serum Vitamin D3 concentration and mean CRP concentration were significantly lower in the group of patients than in healthy controls, which supported the link between vitamin D condition, inflammation, and the pathogenesis of IBD.

The distribution of BsmI genotypes in our case control sample was in a Hardy-Weinberg equilibrium which showed the representative sample. The most interesting genetic findings of the research are the close association of the minor allele b with IBD susceptibility. The bb genotype was associated with an extremely high risk (OR: 26.71; 95% CI: 3.14-226.98), and the Bb genotype was also associated with a significant risk (OR: 7.28; 95% CI: 2.22–23.90). These findings are consistent with an accumulating body of evidence implicating VDR polymorphisms in the dysregulated immune response characteristic of IBD. VDR plays a vital role in regulator integrity of intestinal barrier, antimicrobial defense and T-cell differentiation [8]. Such polymorphisms as BsmI, which are located in the 3' untranslated region, can have an impact on VDR mRNA stability and expression levels, thereby modulating the entire vitamin D signaling pathway and its anti-inflammatory effects [9].

With our findings, several other studies internationally confirm these findings but with significant population-specific differences. A meta-analysis study by Xue et al. (2013) has found that the BsmI B allele was a protective factor of IBD in Asians which validates our result of the b allele as a risk allele in our Iraqi cohort [10]. On the same note, a past study conducted on the Iraqi population revealed that the BsmI bb genotype was strongly associated with higher vulnerability to ulcerative colitis [11]. Nevertheless, a European cohort study did not detect a significant association and this may indicate the strength of ethnic and geographical dissimilarity in genetic susceptibility, perhaps because of diversity in the patterns of linkage disequilibria with the other causal variants or disparities in other environmental influences such as sun exposure [12]. Such ethnic heterogeneity makes it clear that genetic association studies must be carried out in a heterogeneous population, including the Iraqi cohort offered here.

Beyond genetics, our biochemical findings provide a strong functional correlate to the genetic susceptibility. The levels of serum Vitamin D3 were significantly low in patients with IBD (13.28 ± 6.21 ng/mL) than those of controls (25.14 ± 6.32 ng/mL), which is well- documented in the literature [13]. IBD patients have a high likelihood of vitamin D deficiency which can be attributed to a number of factors such as malabsorption, low sunlight exposure and perhaps, increased catabolism [14]. More importantly, our ROC analysis showed that Vitamin D3 level was a better diagnostic criterion to identify patients and controls (AUC = 0.912) than CRP (AUC = 0.710). The sensitivity of 87.50% and specificity of 85.0% at the cut-off of ≤19.32 ng/mL indicate that Vitamin D3 may be a great value biochemical test in clinical diagnosis of IBD in this group at a low cost. Here, it is notable that Myint et al. (2020) also stated that an insufficient amount of vitamin D also was an independent predictor of disease activity in UC patients [15].

The elevated CRP in our patients group proves the presence of a state of systemic inflammation, which is a symptom of active IBD. Low vitamin D together with high inflammation forms a vicious circle; low vitamin D may have insufficient power to restore pro-inflammatory cytokines such as TNF-a and IL-6 and consequently leading to an everlasting disease [16]. We observed no significant correlation between BsmI genotypes and the levels of Vitamin D3 in the patients group indicating that the observed hypovitaminosis D could be rather a result of the disease process itself, rather than a direct

consequence of this specific polymorphism. This is consistent with the fact that the levels of serum vitamin D are largely determined by dietary intake, sun exposure and disease activity, whereas VDR polymorphisms primarily affect the cellular response to the vitamin [17].

There are certain limitations of the present research that should be considered. The sample size used is adequate to identify the strong relationships identified, although it is relatively small, especially when dividing into subgroups of UC and CD. This limitation is reflected by the wide confidence interval of the odds ratio of the bb genotype and means that one should be cautious about determining the exact extent of risk. In addition, cross-sectional design can only be used to determine association rather than causation. The findings need to be replicated in future longitudinal studies of larger cohorts to verify and test the interactions that may occur between the BsmI polymorphism, vitamin D status, and clinical outcomes, including disease severity, phenotype, and response to therapy.

5. Conclusion

This study presents compelling evidence that the BsmI of the VDR gene is a significant risk factor of IBD amongst Iraqis, where the bb and Bb genotypes are associated with significantly higher risk. This genetic predisposition is added to that the prevalence of vitamin D deficiency and high levels of inflammatory markers in patients. These results emphasize the critical contribution of the vitamin D pathway to the pathogenesis of IBD and suggest the possible clinical benefits of genetic screening of VDR polymorphisms as well as regular monitoring of serum Vitamin D3 levels in the management of Iraqi patients with IBD.

Compliance with ethical standards

Acknowledgments

We appreciate the support and consent of the participants, the Gastroenterology and Liver Teaching Hospital staff, and the Ibn Sina University IRB.

Disclosure of conflict of interest

No conflict of interest to be declared.

Statement of ethical approval

The ethical review committee of the Ibn Sina University of medical and pharmaceutical sciences and in partnership with the Gastroenterology and liver teaching hospital approved the study. All subjects were recruited through written informed consent

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