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Association of Vitamin D Receptor Gene Single Nucleotide Polymorphism (BSMI) with COPD

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Abstract:
Background: *Vitamin D receptor gene (VDR) polymorphism and its association with various diseases have been previously investigated. But the association of vitamin D receptor gene polymorphism with COPD has not investigated yet.*
Objectives:*To assess the association of vitamin D receptor gene polymorphism (BsmI) and COPD.*
Methods: *This cross sectional study was carried out in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from March 2019 to February 2020. For this study, 15 (fifteen) pulmonologist diagnosed COPD patients with age 40 to 80 years (post-bronchodilator FEV1/FVC <0.70 and FEV1 <80% predicted) and 15 (fifteen) apparently healthy age matched individuals (for comparison), were selected. The single nucleotide polymorphism of vitamin D receptor gene (BsmI) of all subjects were assessed by PCR-RFLPs. Data were expressed as mean±SD and percentage. Statistical analysis was done by independent sample't' test and chi-square test. In the interpretation of results, ≤ 0.05 level of probability (p) was accepted as significant.*
Results: *The frequency distribution of BsmI genotype was 80% (BB), 20% (Bb), 0% (bb) and 60% (BB), 40% (Bb), 0% (bb) COPD patients and healthy subjects, respectively. However, difference of BsmI VDR genotype between two groups was statistically non-significant. Furthermore, the association of BsmI [BB (OR 0·26, 95% CI 0·52-13.65, p=0·23); Bb (OR 0.37, 95% CI 0·07-1.92, p=0·23)] VDR SNP with COPD was statistically non-significant.*
Conclusion: *The present study reveals that BsmI of VDR SNP is not associated with COPD.*
Keywords*: Vitamin D receptor gene, Single nucleotide polymorphism, BsmI*

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I. Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. It is a complex disease associated with multifactorial background of long-term exposure to noxious gases and particles, combined with a variety of host factors including genetics, airway hyper-responsiveness and poor lung growth during child hood[1]. It has been found that different genes are associated with COPD. Among them alpha1- antitrypsin (AAT) deficiency is one of the most common genetic cause of COPD. This enzyme deficiency occurs due to Taq-1 polymorphism of AAT, Z-isoform of AAT, and mutation of serpin family A member 1 (SERPINA1). In addition, Single nucleotide polymorphism (SNP) of matrix metalloproteinase 9 (MMP9), promoter region of tumor necrosis factor alpha (TNFα) gene and SERPINA3 were also associated with COPD[2-6].

As, COPD is a chronic inflammatory respiratory ailment, so, immunomodulation would be one of its major causative factor[7-9]. Recently the immunomodulatory role of vitamin D has been explored [10-14]. This immunomodulatory characteristic acts via vitamin D receptor (VDR), which alter genomic signaling[12,15-19]. So, the main regulator of vitamin D signaling is the VDR[20], which is present in numerous tissues, including kidney, heart, muscle, breast, colon, prostate, brain and immune cells, making itself as a natural target of modulation in disease pathogenesis including variety of cancers[21], metabolic syndrome[22,23], renal transplant[24] and dermal disorders[25]. In addition, polymorphisms of the VDR gene have been found to be associated with immune mediated diseases characterized by an imbalance in helper T- cell development[9], such as Cronhn's disease[26] and tuberculosis[27].

VDR gene is located on 12q13.11 possessing 11 exons with a length of 5.6 kb[28]. This VDR gene has more than 470 single nucleotide polymorphisms (SNPs), a number of which modulate the uptake of 1,

$25(OH)_2D_3$[29]. Among them, the common SNPs are ApaI[30], BsmI[31], TaqI[32] and FokI[33].

These SNPs have been found to be associated with efficacy of antiresorptive treatments in postmenopausal women (with BsmI)[34], essential hypertension (with FokI)[35], metabolic syndrome (with FokI)[23], prostate cancer (with ApaI)[36], Leprosy (with FokI and ApaI)[13], lumbar spine pathogenesis (with BsmI, ApaI and TaqI)[37] and familial multiple sclerosis (with TaqI)[38]. Moreover, in the perspective of respiratory ailments, both FokI and ApaI VDR SNPs were found to be associated with asthma[11,39,40]and FokI VDR SNP was found to be associated with tuberculosis[41,42]. In addition, ApaI was associated with osteoporosis[43] and FokI along with BsmI were associated with skeletal muscle strength in COPD patients[44]. To the best of our knowledge different diseases were found to be associated with VDR polymorphism. However, as far as we searched, no study was available on association of VDR SNP with COPD. Therefore this study aimed to investigate the association of one common VDR SNP (BsmI) with COPD.

II. Materials And Method

Data collection

This cross sectional study was conducted from March 2019 to February 2020 in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU) after getting protocol approval from the Institutional Review Board (IRB) of BSMMU. For this study, 15 male (age 40 to 80 years) COPD patients (Study group) diagnosed by Pulmonologist with spirometric evidence of COPD (presence of a post-bronchodilator FEV1/FVC <0.70 and FEV1 <80% predicted) and enrolled by purposive sampling from Out Patients Department (OPD) of the National Institute of the Diseases of Chest and Hospital (NIDCH). For comparison, 15 age, BMI and smoking status matched apparently healthy male (Comparison group) were selected by personal contacts. A written informed consent was taken from all the participants after detailing of study procedure. With all aseptic precautions 5 ml venous blood was drawn from ante-cubital vein.

DNA extraction

DNA extraction was done by ReliaPrep™ Blood gDNA isolation kit (Promega, Wisconsin, USA) and assayed for purity and concentration by spectrophotometry (absorbance at 260 nm and 280 nm).

BsmI polymorphism

PCR amplification of VDR gene was done in 25 µl reaction mixtures containing primers for BsmI polymorphism[45]. The PCR amplification conditions were initial denaturation at 95°C for 5 minutes followed by 35 cycles at 94oC for 30 sec, 52°C for 1 min, 72°C for 1 min and final extension at 72°C for 5 minutes. The primers for BsmI polymorphism were 5□-CGGGGAGTATGAAGGACAAA-3□ and 5□-CCATCTCTCAGGCTCCAAAG -3□[45]. The PCR product (628 bp) was digested with 1.0 unit BsmI restriction enzyme (New England BiolabsInc, USA) in a heat block at 65°C for 20 minutes. The products of restriction enzyme cleavage were analyzed on 1% agarose gels and were visualized under UV light after staining with ethidium bromide (Figure 1, Table 1). BsmI VDR SNP was resulted in fragments of 348bp, 242 bp and 106 bp.Therefore, BsmI, BB resulted in one fragment of 348 bp, Bb exhibited all three fragments (348 bp, 242 bp, 106 bp).

Table no 1: Primer sequence and PCR conditions for genotyping of BsmI VDR

Location	Locus	Alleles	PCR primer	PCR product (bp)	Restriction enzyme	RFLP products (bp)
Intron 8	rs1544410	G/A	F: CGGGGAGTATGAAGGACAAA R: CCATCTCTCAGGCTCCAAAG **Initial denaturation:* 95 °C for 5 min; *35 cycles:* 94 °C for 30 s, 52 °C for 1 min, and 72 °C for 1 min; and *final extension*: 72 °C for 5 min	348	BsmI	348 242 106

PCR-Polymerase chain reaction; RFLP-Restriction fragment length polymorphism; bp-Base pair

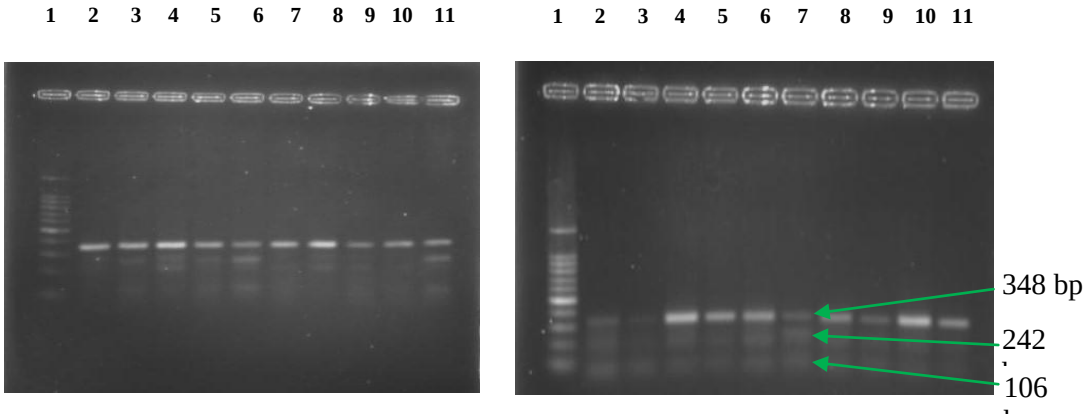

Figure 1: Restriction fragment length polymorphism digestion of *BsmI*in 1% agarose gel stained with ethidium bromide with 100 bp ladder in the first Lane, in lanes 2, 4, 6, 8, 10 shows PCR products; in lanes 3, 5, 7, 9, 11 shows digested products in gel picture. BsmI digestion – BB/348 (major homozygous), Bb/348, 242, 106 (heterozygous), bb/242, 106 (minor homozygous).

Statistical analysis

The data were expressed as mean with standard deviation (mean±SD) and frequency distribution in percentage. The data were statistically analyzed by SPSS statistical package, version 22.0 (IBM, SPSS Inc., Chicago, IL) using Chi-square test. Allelic frequencies of VDR gene polymorphisms were determined by Hardy-Weinberg equilibrium. In the interpretation of results, ≤0.05 level of probability (p) was accepted as significant.

III. Results

The baseline characteristics of all our study subjects are presented in Table 2. The distribution of BsmI VDR genotype and allele frequency is shown in Table 3.The frequency distribution of BsmI genotype was 80% (BB), 20% (Bb), 0% (bb) and 60% (BB), 40% (Bb), 0% (bb) COPD patients and healthy subjects, respectively. However, difference of BsmI VDR genotype between two groups was statistically non-significant. Furthermore, the association of BsmI [BB (OR 0·26, 95% CI 0·52-13.65, p=0·23); Bb (OR 0.37, 95% CI 0·07-1.92, p = 0·23)] VDR SNP with COPD was statistically non-significant.

Table no 2: Baseline characteristics of COPD patients and healthy subjects (N=30)

Characteristics	COPD patients (n=15)	Healthy subjects (n=15)	p value
Age (years)	60.46 ± 6.31 (40 - 80)	56.00 ± 7.80 (40 - 80)	0.096^{ns}
Body mass index (BMI) (kg/m^2)	22.76 ± 4.26 (16.90 - 33.70)	21.96± 2.30 (18.80 - 25.91)	0.531^{ns}
Duration of smoking (pack year)	14.07 ± 5.41 (4 - 30)	17.16 ± 5.17 (4 - 30)	0.121^{ns}
FEV1/FVC (%)	57.60 ± 10.61 (39 - 68)	80.60 ± 6.38 (72 - 92)	0.000***
FEV1(% of predicted value)	44.88 ± 10.98 (28.30 - 63.60)	83.26 ± 10.51 (70 - 100)	0.000***

Data were expressed as mean ± SD; Figures in parentheses indicate ranges; Statistical analysis was done by Independent sample't' test; N = Total number of subjects; n = number of subjects in each group; Pack year = (number of cigarette smoked per day/20) X no. of years smoked; FEV_1 = Forced expiratory volume in first second; FVC = Forced vital capacity; ns = non-significant; *** = statistically significant (p<0.001)

Table no 3: Genotype and allele distribution of BsmI VDR SNP in study subjects (N=30)

SNP	COPD patients (n=15)		Healthy subjects (n=15)		OR (95%CI)	χ^2 value (p value)
	no	%	no	%		
BsmI						
BB	12	80	9	60	0.26 (0.52-13.65)	χ^2=1.42, p= 0.23
Bb	3	20	6	40	0.37 (0.07-1.92)	χ^2=1.42, p= 0.23
bb	0	0	0	0	-	
B	27	90	24	80	0.44 (0.10-1.97)	χ^2=1.17, p= 0.27
b	3	10	6	20	2.25 (0.50-9.99)	χ^2=1.17, p= 0.27

VDR=Vitamin D receptor; SNP=Single Nucleotide polymorphism; OR=odds ratio; CI=confidence interval

IV. Discussions

It is well known that VDR gene is located on chromosome 12q13.11[28,46]encoding the VDR protein by exon II to IX. Among the four common VDR SNPs, BsmI is located in intron 8 (between exon VIII and IX)[10,47,48,49] near the 3 UTR. However, it has been reported that exon VII to IX involves the binding of VDR to vitamin D[47]. In addition, it has also been observed that, variations in the 3 UTR sequence often affect mRNA stability and the efficiency of protein translation[32] and altered protein levels[13,50,51]. Therefore, this BsmI polymorphism may affect the activity of VDR and subsequent downstream effects of vitamin D[52] including its immunomodulatory role[50,51]. In addition, it was found that 3UTR is associated with tuberculosis in Asian populations[53]. However, in our study, neither the genotype nor the allele of BsmI VDR single nucleotide polymorphism was associated with COPD. Similar observation was reported in a group of British people, where, this VDR SNP was found not associated with exacerbation frequency in COPD patients[54].Furthermore, investigations from Africa,India,andKorea were found no association between BsmIpolymorphism of VDR gene and pulmonary tuberculosis (PTB)[53,55,56,57]. In contrast, significant association was found between BsmI genotype and PTB in Indonesia and Turky[58,59].

V. Conclusion

The results of the present study elucidates that, BsmI VDR SNP is not associated with COPD. There were few limitations in our study. First, intake of vitamin D and environmental exposure to ultraviolet radiation of our study population could not be assessed. Second, as a genetic association study, the results were based on a small number of samples. For further researches, similar type of study should be done including information of vitamin D intake and environmental exposure to ultraviolet radiation in a large number of COPD patients to confirm this result.

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