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Research Article

GENETIC INSIGHTS INTO METABOLIC SYNDROME: VITAMIN D RECEPTOR BSMI POLYMORPHISM AMONG THE INDIGENOUS PEOPLE OF MANIPUR

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ABSTRACT

Objectives: The objectives of this study were to determine the association between the BsmI (rs1544410) polymorphism in the Vitamin D receptor (*VDR*) gene and metabolic syndrome (MetS) among the Indigenous population of Manipur.

Methods: A cross-sectional study total of 200 participants were genotyped for the BsmI polymorphism using polymerase chain reaction-restriction fragment length polymorphism analysis. Clinical parameters such as fasting blood sugar (FBS), lipid profile, blood pressure (BP), and Vitamin D were assessed.

Results: Statistical analysis revealed a significant association between the BsmI polymorphism and FBS levels, suggesting a potential genetic predisposition to impaired glucose metabolism. BB genotype is associated with higher FBS, cholesterol, triglycerides, and BP, which are risk factors for MetS. BB genotype also has significantly lower Vitamin D levels, which may play a role in these metabolic disturbances.

Conclusion: Individuals with the heterozygous (Bb) and homozygous recessive (bb) genotypes exhibit more favorable metabolic parameters compared to those with the homozygous dominant (BB) genotype. These findings highlight the role of *VDR* gene variants in MetS and underscore the need for further studies to validate these results in larger populations. Understanding genetic risk factors can contribute to personalized prevention and therapeutic strategies for MetS, particularly in genetically distinct ethnic groups like Manipur.

Keywords: Metabolic syndrome, Single nucleotide polymorphism, Vitamin D receptor gene, Type 2 diabetes, Cardiovascular disease.

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INTRODUCTION

Metabolic syndrome (MetS)

The MetS also known as syndrome X has been defined as a condition with interrelated metabolic risk factors of obesity, hypertension, type 2 diabetes mellitus (T2DM), and atherogenic dyslipidemia. The MetS has been also accompanied by insulin resistance, chronic inflammatory, and other prothrombotic states [1-3]. The MetS refers to the classification of common risk factors for cardiovascular disease (CVD). This condition is commonly referred to as "insulin resistance syndrome" due to its strong association with reduced insulin sensitivity. An important part of its pathophysiology depends on the resistance to the metabolic effects of insulin [4]. The prevalence of this disorder has been increasing in recent years and stands at about 25% globally; it is therefore among the main health problems in the world [5,6]. The incidence of MetS varies globally, ranging from 28 to over 70 cases/1,000 person-years in different regions [7]. If the current trend in obesity and type 2 diabetes continues unchanged, the incidence of MetS will be expected to increase, especially in developing countries [5,7]. Those who are in risk of having MetS have a higher probability about 30–40% of developing diabetes and/or CVD within 20 years [8]. According to epidemiological studies, the incidence of MetS is higher in women than men [9]. The prevalence of MetS among adolescents in India is also increasing relatively, primarily concentrated in urban areas and wealthier households. To prevent MetS from emerging as a major public health concern, early intervention strategies promoting healthy lifestyles are essential, particularly in high-prevalence regions [10].

Vitamin D is asteroid hormone that plays a crucial role in bone health, immune function, and metabolic homeostasis. Beyond its traditional role in calcium and phosphate metabolism, growing evidence suggests that vitamin D is involved in glucose and lipid metabolism, inflammation, and insulin sensitivity, all of which are key factors in MetS [11,12]. It was found out that hypovitaminosis D is associated with impaired glucosehomeostasis that make a particular interest for further study. Yadavelli *et al.* study revealed that the prevalence of vitamin D deficiency and insufficiency is not limited to type 2 diabetes but also among T1 diabetes children was very high [13]. A meta-analysis of 28 studies demonstrated that higher serum 25(OH)D levels were associated with a 55% reduction in diabetes, a 51% decreased risk of the MetS and a 33% lower risk of CVD [14]. The biological effects of vitamin dare mediated through the vitamin D receptor (VDR), a nuclear receptor widely expressed in tissues such as adipose tissue, pancreatic β-cells, liver, and skeletal muscle. Upon activation by 1,25-dihydroxy Vitamin D (the active form of vitamin D), VDR regulates the transcription of several genes involved inglucose and lipid metabolism, insulin secretion, and inflammation. Disruptions in vitamin D signaling due to genetic variations in the *VDR* gene may contribute to the development of metabolic disorders, including MetS, obesity, and type 2 diabetes [15]. As type 2 diabetes also arises from the cumulative effects of various cellular and biochemical abnormalities, leading to elevated blood glucose levels beyond the normal physiological range. It was associated with a 5% increase in premature mortality and ranked as the ninth leading cause of death, accounting for approximately 1.5 million fatalities [16].

Genetic variations in the *VDR* gene, known as single nucleotide polymorphisms, can influence the expression and function of the receptor, potentially affecting metabolic pathways. Several VDR polymorphisms, including BsmI (rs1544410), FokI (rs2228570), ApaI (rs7975232), and TaqI (rs731236), have been extensively studied for their association with glucose metabolism, insulin resistance, lipid profiles, and obesity. Among these, the BsmI polymorphism (rs1544410), located in the 3' untranslated region of the *VDR* gene, has been implicated in mRNA stability and receptor expression levels.

Some studies suggest that specific BsmI genotypes (BB, Bb, or bb) may influence insulin sensitivity and glucose metabolism, thereby increasing susceptibility to MetS and type 2 diabetes [17]. However, the association between BsmI polymorphism and MetS remains inconsistent, with some studies reporting a significant link, whereas others find no association, indicating that genetic-environmental interactions and population differences may play a role. Therefore, the present study is undertaken to highlight the association between BsmI polymorphism and MetS among indigenous people of Manipur.

METHODS

Study design

This analytical cross-sectional study was conducted in a cohort of 200 participants who belong to an indigenous population of Manipur during the period from August 2022 to March 2024. The participants were Manipuri between 18 years and 80 years of age with no evident physical disability or severe diseases, attending Jawaharlal Nehru Institute of Medical Sciences (JNIMS) hospital, Manipur.

Ethical clearance

Prior approval from the Institutional Ethics Committee (IEC), JNIMS, Imphal Manipur was obtained bearing registration No.Ac/03/IEC/JNIMS/2018 (PhD) dated November 14th, 2022.

Inclusion criteria

Eligible participants in the age group 18–80 years attending the medicine outpatient department who are willing to give consent were included in the study.

Exclusion criteria

Patients under 18 years, or with chronic illnesses such as liver diseases, kidney diseases that could potentially alter Vitamin D metabolism, use of medications that affect bone metabolism, pregnant or breastfeeding women, or taking Vitamin D supplements, etc., will be excluded from the study.

Sample collection and bioassays

After the collection of demographic data, fasting blood samples were taken in ethylenediaminetetraacetic acid -coated vacutainers. Assessment of fasting blood sugar (FBS) (fasting blood glucose) was done by glucose oxidase peroxidase (POD)-4 aminoantipyrine, enzymatic photometric test (Diasys 200 pro), 25-OH Vitamin D was estimated by Chemiluminescent immunoassay Maglumi and lipid profile for cholesterol and high-density lipoprotein (HDL) by cholesterol oxidase POD method, triglycerides (TGs) by glycerol phosphate POD method (Medsource Ozone Biomedicals Pvt. Ltd) as per manufacturer's guidelines using Semi-autoanalyzer (MeriliyzerCliniQuant).

Anthropometric measurement

Waist circumference (WC) was measured, whereas the subjects were standing up, with a tape placed at the midpoint level between the lower intercostal border and the anterior superior iliac supine, whereas the subject was gently exhaling. Blood pressure (BP) was obtained using an automatic BP monitor (Omron, Omron Health Care, Inc., USA) reading of which has been standardized to that of a mercury sphygmomanometer. Three measures were taken at rest in a sitting position, with intervals of 5 min between the measurements. The average from the measurements was taken for analysis.

Table 1: PCR thermal cycling condition

Steps	Temp (°C)	Time	No. of cycles
Initial denaturation	95°C	3 min	1
Denaturation	95°C	30 s	33
Annealing	57°C	30 s	
Extension	72°C	45 s	
Final extension	72°C	10 min	1

PCR: Polymerase chain reaction

Genotyping

Genomic DNA was extracted from the collected blood by using Purelink genomic DNA kit according to the manufacturer's instructions. After genomic DNA extraction, the quantity and quality of DNA were assessed by Eppendorf BioPhotometer. The purity of the DNA was assessed by measuring the ratio of optical density (OD) at 260 and 280 nm (OD_{260}/OD_{280}). BsmI (1544410) polymorphisms were identified using polymerase chain reaction (PCR) restriction fragment length polymorphism analysis (Bio-Rad T100 Thermal cycler). Experimental conditions including primer sequences, reaction conditions, restriction enzymes used, and length of resulting PCR products are shown (Tables 1 and 2). Digested PCR products were determined on 2% agarose gel imaging and documentation (Bio-Rad Gel Doc XR+Gel Documentation System).

Statistical analysis

The results were expressed as mean±standard deviation. Numerical data were analyzed using paired student's *t*-test, whereas one-way analysis of variance was used to evaluate the significance of biochemical and molecular results. Genotype frequencies were calculated and the Chi-square test was used to determine their associations with MetSparticipants (BsmI). The results were considered statistically significant when $p<0.05$ using the Statistical Package for the Social Sciences (version 20.0).

RESULTS

Characteristic of the study population

This study includes a cohort of 200 indigenous people - 94 female (47%) and 106 male (53%). The frequency distribution of the study population is shown in Table 3.

Genotype frequencies and distributions of VDR polymorphism (BsmI)

After genotyping, we identified 63 (31.5%) were bb, 97 (48.5%) were Bb and 40 (20.0%) belonged to BB genotypes. Participants genotype and frequencies of VDR polymorphism are presented in Table 4.

Comparison of variables in relation to BsmI polymorphism of participants studied and are presented in Table 5

The BsmI polymorphism in the *VDR* gene showed significant associations with several metabolic parameters. Individuals with the BB genotype had notably higher FBS (157.38 mg/dL, $p<0.001$), systolic BP (SBP) (132.75 mmHg, $p=0.045$), total cholesterol (211.33 mg/dL, $p<0.001$), and TGs (211.9 mg/dL, $p<0.001$). Interestingly, the BB genotype also exhibited the highest HDL levels (46.73 mg/dL, $p=0.008$), which is generally considered protective; however, this did not offset the adverse lipid profile. Moreover, individuals with the BB genotype had significantly lower vitamin D levels (17.06 ng/mL, $p<0.001$), indicating a potential link between this genotype and vitamin D deficiency. However, some parameters did not show any significant association with the BsmI polymorphism. Age ($p=0.432$), WC ($p=0.276$), and diastolic BP ($p=0.166$) were similar across different genotypes, indicating that the BsmI variation in the *VDR* gene does not have a measurable impact on these specific factors.

Table 2: Experimental condition with primers, PCR product with restriction enzyme

SNPid	Primers	PCR product size	Restriction enzyme	Recognition site
rs1544410	Fwd: CGGGGAGTATGAAGGACAAA Rev: CCATCTCTCAGGCTCCAAAG [18]	348 bp (243+105 bp)	Mva1269I (BsmI)	5'..GAATGCN*...3' 3'..CTTAC*GN...5'

PCR: Polymerase chain reaction. *Indicates cutting site of the restriction enzymes for its specific recognition sequences of nucleotides

DISCUSSION

Obesity together with two of the three additional diagnostic criteria (elevated BP, elevated blood sugar, or elevated TGs) is referred to as MetS. The development of obesity and MetS components significantly increases the risk of cardiovascular events [19]. This study investigated the association between the BsmI (rs1544410) polymorphism in the *VDR* gene and MetS risk factor among the indigenous population of Manipur. Regarding the *VDR* gene polymorphism BsmI, this study found that 97 participants had the Bb genotype and 40 participants had the BB genotype indicating that alleles "b" are more prevalent among the MetS. And also the results indicate a significant relationship between the BB genotype and elevated FBS levels, suggesting a potential genetic predisposition to MetS. Individuals carrying the B allele exhibited higher FBS levels compared to those with the bb genotype, supporting the role of *VDR* gene variation in glucose metabolism.

Al-Shahwan *et al*. state that vitamin D deficiency could lead to many troubling diseases such as depression, Osteoporosis, obesity, diabetes, heart diseases, MetSs, immunity-related diseases (sclerosis, erythematosis), and cancer [20]. The active form of vitamin D 1,25-Dihydroxyvitamin D [1,25$(OH)_2$D], plays a crucial role in regulating various metabolic pathways through its receptor, the VDR. VDR is widely expressed in multiple tissues; β-cells of the pancreas (Langerhans islets), muscle cells, liver cells, and adipocytes. Due to its broad expression, VDR-mediated signaling plays a crucial role in maintaining metabolic homeostasis. Consequently, polymorphisms in the *VDR* gene, such as BsmI, can influence susceptibility to MetS [21]. Our findings align with the study done by Gholami *et al.* 2024 suggesting that *VDR* gene polymorphisms influence glucose homeostasis and insulin sensitivity [4]. Rahmadhani *et al.* 2017 showed a significant difference between the carriers of the A allele of BsmI and non-carriers and the risk of insulin resistance in patients with concurrent vitamin D deficiency [22]. Israni *et al*. suggested a potential role of BsmI polymorphisms [23]. Wang *et al.* studied a significant association of BsmI polymorphism with T2DM onset, supporting the hypothesis that VDR plays a role in metabolic regulation [9]. While Dilmec *et al.* did not found significant association with VDR polymorphism to T2DM onset [24]. Zakaria *et al*. study also states that *VDR* gene BsmI and FokI polymorphisms were not significantly associated with T2DM [18]. However, Fatma and Abdul 2019 study found that the BsmI may be related to susceptibility to T2DM subjects but the genetic contribution of *VDR* gene polymorphism for the development or existing diabetic complications is not clear, which may be due to differences in population genetics, environmental factors, or study design [25]. The *VDR* gene encodes the Vitamin D receptor, which plays a critical role in glucose metabolism by modulating insulin secretion and sensitivity [26]. Variations in the *VDR* gene, such as BsmI polymorphism, could alter receptor function, potentially affecting insulin response and increasing susceptibility to MetS [27]. Jin *et al.* studies that VDR polymorphisms show no association with the MetS risk like TGs, FBS, WC. However, VDR ApaI polymorphism is associated with hypertriglyceridemia and predisposed to developing MetS, whereas the variants of BsmI and TaqI seem to affect HDL-cholesterol (HDL-C). Nevertheless, the effect of FokI variants with SBP is obscure [17].

Dyslipidemia, a key component of MetS, includes elevated TG levels and Low HDL-C. Research indicates that specific VDR polymorphisms are linked to elevated TG and cholesterol levels in certain populations [28-30]. Vitamin D is thought to influence lipid metabolism, and several epidemiological studies have examined its relationship with dyslipidemia. A systematic review of 22 cross-sectional studies found a positive association between vitamin D levels and HDL-C and a negative association with TGs [17]. Our study supports the idea that genetic screening for BsmI polymorphism may help to identify individuals at higher risk of developing MetS, particularly in genetically distinct populations like the one studied here.

A major strength of this study is the focus on an indigenous population, which provides novel insights into genetic predispositions that may differ from other ethnic groups. In addition, the study design included a well-characterized sample and robust statistical analyses. However, several limitations should be acknowledged. First, the sample size, while sufficient for statistical analysis, may not fully represent the broader population. More research with a larger sample size is needed after removing confounding factors to determine whether *VDR* gene polymorphism is a protective factors for future diagnostic purposes. The second limitations, such as the individuals included in the study are of various age, their food habits, and exposure to sunlight. These studies do not yield consistent findings regarding the risk of hypertension and its association with the frequency of BsmI genotypes. The third limitation is investigating other VDR polymorphisms (e.g., FokI, ApaI, and TaqI) to understand their combined impact on MetS. Heterogeneity in different populations and limited knowledge of underlying mechanisms may be responsible for these discrepancies. Lastly, this study could have utilized direct sequencing to confirm the genotypes of the BsmI polymorphism. However, due to time constraints and financial limitations, this was not feasible.

Table 3: Gender frequency distribution of participant

Gender	No. of participant	Percentage
Female	94	47.0
Male	106	53.0
Total	200	100

Table 4: BsmI polymorphism -frequency distribution of participants studied

BsmI	No. of participant	Percentage
bb	63	31.5
Bb	97	48.5
BB	40	20.0
Total	200	100

Table 5: Comparison of clinical variables in relation to gene polymorphism (BsmI)

Variables	Gene (*BsmI*)			Total	p-value
	bb	Bb	BB		
Age (in years)	49.1±13.8	46.9±14.6	45.8±10.2	47.4±13.6	0.432
FBS (mg/dL)	119.1±36.9	120.7±24.2	157.4±43.6	127.5±36.1	<0.001**
WC (cm)	99.6±8.81	100.5±7.5	102.2±8.8	100.5±8.2	0.276
SBP (mmHg)	128.5±10.1	130.7±7.3	132.7±8.7	130.4±8.6	0.045*
DBP (mmHg)	87.1±6.7	88.6±5.1	88.9±4.5	88.2±5.6	0.166
Cholesterol (mg/dL)	172.2±41.2	182.2±36.25	211.3±43.1	184.9±41.5	<0.001**
Triglycerides (mg/dL)	156.6±55.4	161.8±45.0	211.9±73.3	170.2±58.6	<0.001**
HDL (mg/dL)	41.5±8.2	44.5±8.0	46.73±9.5	44.0±8.6	0.008*
Vitamin D (ng/mL)	24.3±9.3	23.98±8.4	17.1±5.9	22.7±8.7	<0.001**

FBS: Fasting blood sugar, WC: Waist circumference, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HDL: High-density lipoprotein. *All values are mean±SD of the clinical variables. SD: Standard deviation, **Highly significant

CONCLUSION

In Manipur, MetS factors have consistently been one of the leading causes of various CVDs like myocardial infarction, stroke, etc. Many studies have linked *VDR* gene polymorphism with essential factors such as BP, TGs, HDL, and FBS however some studies have focused on the relationship of vitamin D and *VDR* gene polymorphism, but the results of our studies show a significant relationship between Vitamin D and *VDR* gene polymorphism. Individuals with the BB genotype could be considered for early screening and intervention strategies for MetS. Since lower Vitamin D levels are observed in BB individuals, supplementation might help improve metabolic outcomes, but further studies are needed. Genetic screening for VDR polymorphisms could help in tailoring lifestyle or pharmacological interventions for at risk populations. Given the high burden of MetS, especially in indigenous populations, understanding genetic predispositions may aid in developing targeted prevention programs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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CONTRIBUTION OF AUTHORS

A. Sapna Devi involved in collection of articles, data acquisition, statistical analysis, manuscript writing, and final editing of manuscript. Dr. Narmada Thongam involved in manuscript writing, interpretation and technical support and proof reading. Dr Suchitra Chongtham involved in the critical revision of the manuscript, final screening of articles editing, and proofreading.

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