ISSN: 2457-0400

Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

www.wjahr.com

Volume: 9, Issue: 12

Page N. 75-82

Year: 2025

Original Article

Coden USA: WJAMA3

VDR GENE VARIANTS AND GUT MICROBIOME DIVERSITY IN RELATION TO VITAMIN D DEFICIENCY AND METABOLIC SYNDROME IN IRAQI ADULTS

***[1]Asmaa Ghafer, [2]Duaa Mohammed Al-Atta, [3]Sura Talal Kadhim**

[1]Department of Microbiology, College of Medicine, Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq.

[2]Senior Lecturer and Family Medicine Specialist, Department of Family and Community Medicine, College of Medicine, Ibn Sina University for Medical and Pharmaceutical Sciences, Baghdad, Iraq.

[3]Senior Lecturer, Family Medicine Specialist, Department of Family and Community Medicine, College of Medicine, Ibn Sina University for Medical and Pharmaceutical Sciences, Baghdad, Iraq.

Article Received: 03 November 2025 **Article Revised:** 24 November 2025 **Article Published:** 01 December 2025

***Corresponding Author: Asmaa Ghafer**

Department of Microbiology, College of Medicine, Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq.

DOI: https://doi.org/10.5281/zenodo.17748559

How to cite this Article: *1Asmaa Ghafer, 2Duaa Mohammed Al-Atta, 3Sura Talal Kadhim (2025). Vdr Gene Variants And Gut Microbiome Diversity In Relation To Vitamin D Deficiency And Metabolic Syndrome In Iraqi Adults. World Journal of Advance Healthcare Research, 9(12), 75–82.

ABSTRACT

Background: Metabolic syndrome (MetS) prevalence is increasing all over the world, with the Middle Eastern communities being no exception. Although metabolic disorders have been attributed to vitamin D deficiency and vitamin D receptor (VDR) gene polymorphisms, their interaction with gut microbiome modifications among Iraqi adults is insufficiently described. **Objective:** To investigate associations between VDR gene polymorphisms, gut microbiome diversity, and vitamin D status in relation to MetS among Iraqi adults. **Methods:** This case-control study enrolled 200 participants (100 MetS patients, 100 healthy controls) at Baghdad Teaching Hospital from January-August 2025. Serum 25-hydroxyvitamin D levels were measured by ELISA. Four VDR polymorphisms (FokI, BsmI, TaqI, ApaI) were genotyped using PCR-RFLP. Gut microbiome diversity was assessed through 16S rRNA sequencing, calculating Shannon diversity index and Prevotella/Bacteroides ratio. Multivariable logistic regression identified independent MetS predictors. **Results:** Vitamin D deficiency affected 70% of MetS patients versus 35% of controls ($p<0.001$). Mean serum 25(OH)D was significantly lower in MetS patients (17.2±6.8 vs 25.4±7.5 ng/mL, $p<0.001$). VDR FokI ff, BsmI bb, and ApaI aa genotypes were more prevalent in MetS patients. Gut microbiome diversity was significantly reduced in MetS patients (Shannon index: 3.2±0.6 vs 3.8±0.5, $p<0.001$). Independent MetS predictors included VDR FokI ff genotype (OR=1.9, 95%CI:1.1-3.4, $p=0.02$), vitamin D deficiency (OR=2.7, 95%CI:1.6-4.5, $p<0.001$), and low microbiome diversity (OR=2.2, 95%CI:1.3-3.7, $p=0.003$). **Conclusion:** Vitamin D deficiency, specific VDR polymorphisms, and reduced gut microbiome diversity are independently associated with MetS in Iraqi adults. These findings indicate the presence of multifactorial pathophysiology and indicate the importance of population-wide screening of vitamin D, genetic testing, and microbiome-specific interventions in this high-risk group.

KEYWORDS: Gut microbiome; Metabolic syndrome; Vitamin D deficiency; VDR polymorphisms.

INTRODUCTION

Metabolic syndrome (MetS) is a collection of cardiometabolic risk factors such as abdominal obesity, dyslipidemia, hypertension and insulin resistance that significantly predispose type 2 diabetes and cardiovascular disease.[1] MetS is an epidemic among people throughout the world, and especially, among the Middle Eastern population and Iraq is not the exception.[2] Deficiency in vitamin D is a condition in which serum levels of 25(OH)D [25-hydroxyvitamin D] have a level of less than 20 ng/mL and is known to affect over a billion people across the globe and has become a possible cause of MetS pathogenesis.[3]

In addition to its classical functions in calcium homeostasis and bone metabolism, vitamin D has pleiotropic effects on glucose metabolism, lipid regulation and inflammatory mechanisms in response to vitamin D receptor (VDR) binding.[4] VDR is a gene expressed on chromosome 12q13 which has a number of common single nucleotide polymorphisms, such as FokI (rs2228570), BsmI (rs1544410), TaqI (rs731236) and ApaI (rs7975232) which can modify the activity of the receptor and affect the responses of individuals to vitamin D.[5] Several findings have reported correlations between VDR gene variants and metabolic disturbances, but the results were not consistent in various ethnic groups.[6, 7]

Recent data reveal that the gut microbiome is an important part of the host metabolism via the processes of nutrient uptake, energy gains, immune regulation, and bioactive metabolic generation.[8] Obesity, insulin resistance and MetS have been associated with changes in the gut microbial diversity and composition.[9] Interestingly, new data indicate that there are two-way processes between vitamin D status, VDR signaling, and the gut microbiome and VDR polymorphisms may impact microbial composition and diversity.[10]

Although vitamin D deficiency and MetS are of high burden in Iraq, especially in adults visiting tertiary care units in Baghdad, little studies have been conducted to investigate the joint impacts of VDR genetic variants and modulation of gut microbiome in the population. Past literature of the adjacent Middle East nations has reported correlations between VDR SNP polymorphisms and metabolic phenotypes[11,12], although the precise genetic and microbial environment of the Iraqi adults has not been well established. The knowledge of these relationships may help carefully design individual preventive and management strategies towards vitamin D deficiency and MetS.

This study addresses a major gap since it will assess the VDR gene polymorphisms, gut microbiome diversity, and vitamin D status simultaneously in relation to MetS among Iraqi adults. The results can be of significant value in the identification of high-risk persons and the creation of specific interventions that are related to genetic and environmental background of this cohort.

OBJECTIVES

- To determine the prevalence of vitamin D deficiency and examine its association with VDR gene polymorphisms (FokI, BsmI, TaqI, ApaI) among Iraqi adults with and without MetS.
- To evaluate gut microbiome composition and diversity in relation to vitamin D status and VDR gene variants.
- To identify independent predictors of MetS, including the combined effects of VDR polymorphisms and gut microbiome diversity.

METHODS

Study Design, Setting, and Timing

This case-control study was conducted at Baghdad Teaching Hospital, a major Healthcare facility in Baghdad, Iraq, between January and August 2025. The hospital serves as a major healthcare center in the Baghdad, providing comprehensive Healthcare services.

Participants

A total of 200 adult participants aged 18-65 years were enrolled, comprising 100 patients diagnosed with MetS and 100 age- and sex-matched healthy controls. MetS was diagnosed according to the International Diabetes Federation criteria, requiring central obesity plus any two of the following: elevated triglycerides (≥150 mg/dL), reduced HDL cholesterol (<40 mg/dL in men, <50 mg/dL in women), elevated blood pressure (≥130/85 mmHg or on antihypertensive treatment), or elevated fasting glucose (≥100 mg/dL or previously diagnosed type 2 diabetes).

Inclusion criteria required adults aged 18-65 years attending the hospital for routine check-ups or management of chronic conditions, with willingness to provide written informed consent. Exclusion criteria included known chronic gastrointestinal disorders, recent antibiotic or probiotic use within the past month, pregnancy, or lactation.

Data Collection

Demographic and clinical data including age, sex, residence, educational level, employment status, smoking habits, physical activity levels, medical history, dietary patterns, and medication use were collected through structured interviews and review of medical records. Sun exposure duration was estimated through self-report of average daily outdoor time.

Biochemical Assessments

Fasting venous blood samples were collected after an overnight fast of at least 8 hours. Enzyme-linked immunosorbent assay (ELISA) was used to measure serum 25-hydroxyvitamin D with deficient (<20 ng/mL), insufficient (20-29 ng/mL) or sufficient (≥30 ng/mL) levels. The levels of parathyroid hormone (PTH), calcium, and phosphorus were measured by using standard laboratory tests. Automated chemistry analyzers were used to assess the metabolic parameters such as fasting glucose, lipid profile (Total cholesterol, HDL, LDL, triglycerides). Standardized sphygmomanometer was used to measure blood pressure triply after 5 minutes of rest. Anthropometric data such as body mass index (BMI) and waist circumference were taken according to the standard procedures.

Genetic Analysis

Leukocytes with peripheral blood were used as source of genomic DNA which was extracted using commercially available genomic DNA extraction kits. The genotyping of VDR gene polymorphisms (FokI, BsmI, TaqI and

ApaI) was done via polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP). PCR products were digested using corresponding restriction enzymes and fragments were separated using gel electrophoresis. Patterns of fragments were used to assign genotypes and random replicate samples were used with 10% of the total. They tested Hardy-Weinberg equilibrium in each polymorphism of the control group.

Gut Microbiome Analysis

The samples of the stool were collected in sterile containers and kept at -80°C awaiting analysis. The DNA extraction of the microbes was carried out through the commercial kits that are optimized with fecal samples. The bacterial 16S rRNA gene V3-V4 was a hypervariable region that was amplified and sequenced in high-throughput sequencing platforms. Bioinformatic analysis involved quality screening, operation taxonomic unit (OTU) clustering and taxonomic assignment. Alpha metrics of diversity such as Shannon diversity index and observed counts of OTU were estimated. Prevotella/Bacteroides ratio was used as an indicator of enterotype composition.

Statistical Analysis

The analysis of data was conducted by using SPSS version 26.0. Demographic and clinical characteristics were summarized using descriptive statistics that gave the mean ± standard deviation and interquartile range of continuous variables on the basis of the distribution normality as measured by Shapiro-Wilk test. Frequencies and percentages were the means of illustrating categorical variables. The chi-square tests were used to assess the association between categorical variables, and the independent t-tests or Mann-Whitney U tests were used to assess the association between continuous variables. Multivariate logistic regression models were used to generate independent predictors of MetS, controlling the possible confounders such as age, sex, lifestyle, and clinical factors. Confidence ratios of 95% odds ratios were computed. The statistical significance was determined as $p<0.05$ (two-tailed).

Ethical Considerations

The study was approved of by Institutional Review Board of Ibn Sina University of Medical and Pharmaceutical Sciences. Written informed consent was given by all the participants, following full information about the study procedures. The Confidentiality was ensured through the use of coded identifiers, participants were allowed to exit the study any time without interfering with their medical treatment.

RESULTS

Demographic and Clinical Characteristics

Two hundred adults were enrolled including 100 patients with MetS and 100 apparently healthy controls. MetS patients were on average much older than controls (52.4 ± 8.1 vs 47.9 ± 9.6 years, p=0.002). There was 60% and 50% Males in MetS and control group respectively (p=0.180). Patients with MetS (72%) were more likely to be urban residence than the controls (63.0%, p=0.091). Educational attainment differed significantly between groups (p=0.014), with 42.0% of MetS patients having primary education or below compared to 26.0% of controls, whereas 36.0% of controls held university degrees compared to 25.0% of MetS participants. Employment rates were lower among the MetS group (40.0%) relative to controls (58.0%, p=0.035). Current smoking was more prevalent among MetS patients (41.0%) than controls (28.0%, p=0.048). A sedentary lifestyle with low physical activity was reported by 63.0% of MetS participants versus 38.0% of controls (p=0.005). (Table 1)

Table 1: Demographic and clinical characteristics of study participants.

Variable	MetS (n=100)	Control (n=100)	p-value
Age (years, mean ± SD)	52.4 ± 8.1	47.9 ± 9.6	0.002
Male sex, n (%)	60 (60.0)	50 (50.0)	0.180
Urban residence, n (%)	72 (72.0)	63 (63.0)	0.091
Primary education or below, n (%)	42 (42.0)	26 (26.0)	0.014
Currently employed, n (%)	40 (40.0)	58 (58.0)	0.035
Current smoker, n (%)	41 (41.0)	28 (28.0)	0.048
Low physical activity, n (%)	63 (63.0)	38 (38.0)	0.005

Vitamin D Status and Biochemical Parameters

Mean serum 25-hydroxyvitamin D concentration was markedly lower in MetS patients compared to controls (17.2 ± 6.8 vs 25.4 ± 7.5 ng/mL, p<0.001). Vitamin D deficiency (<20 ng/mL) was detected in 70.0% of MetS patients and 35.0% of controls, whereas sufficiency (≥30 ng/mL) was found in only 10.0% of MetS individuals compared with 25.0% of controls (p<0.001). Serum parathyroid hormone levels were significantly elevated in MetS participants (58.3 ± 21.6 vs 45.7 ± 18.4 pg/mL, p=0.002). Phosphorus levels were lower in MetS patients (3.3 ± 0.7 vs 3.5 ± 0.6 mg/dL, p=0.040), while calcium differences approached but did not reach statistical significance (p=0.052). Daily sun exposure was substantially reduced among MetS individuals (0.9 ± 0.6 vs 1.6 ± 0.7 hours, p<0.001). Only 14.0% of MetS participants reported vitamin D supplement use compared to 28.0% of controls (p=0.018). (Table 2)

Table 2: Vitamin D status and biochemical parameters.

Variable	MetS (n=100)	Control (n=100)	p-value
Serum 25(OH)D (ng/mL, mean ± SD)	17.2 ± 6.8	25.4 ± 7.5	<0.001
Deficient (<20 ng/mL), n (%)	70 (70.0)	35 (35.0)	<0.001
Insufficient (20-29 ng/mL), n (%)	20 (20.0)	40 (40.0)	
Sufficient (≥30 ng/mL), n (%)	10 (10.0)	25 (25.0)	
Parathyroid hormone (pg/mL, mean ± SD)	58.3 ± 21.6	45.7 ± 18.4	0.002
Calcium (mg/dL, mean ± SD)	9.1 ± 0.6	9.3 ± 0.5	0.052
Phosphorus (mg/dL, mean ± SD)	3.3 ± 0.7	3.5 ± 0.6	0.040
Sun exposure (hours/day, mean ± SD)	0.9 ± 0.6	1.6 ± 0.7	<0.001
Vitamin D supplement use, n (%)	14 (14.0)	28 (28.0)	0.018

VDR Gene Polymorphisms

Genotype distributions for four VDR polymorphisms revealed significant differences for FokI, BsmI, and ApaI variants, while TaqI showed no significant difference between groups. For FokI, the ff genotype was more frequent among MetS patients (20.0%) than controls (15.0%, p=0.036). The BsmI bb genotype was observed in 27.0% of MetS subjects versus 15.0% of controls (p=0.019). The ApaI aa genotype occurred in 25.0% of MetS patients and 15.0% of controls (p=0.030). All polymorphisms were in Hardy-Weinberg equilibrium among controls (p>0.05), confirming genotyping accuracy. (Table 3)

Table 3: Distribution of VDR Gene polymorphisms.

VDR Variant	Genotype	MetS (n=100)	Control (n=100)	p-value	HWE (Control)
FokI				0.036	0.74
	FF	30 (30.0)	45 (45.0)		
	Ff	50 (50.0)	40 (40.0)		
	ff	20 (20.0)	15 (15.0)		
BsmI				0.019	0.62
	BB	25 (25.0)	41 (41.0)		
	Bb	48 (48.0)	44 (44.0)		
	bb	27 (27.0)	15 (15.0)		
TaqI				0.208	0.59
	TT	29 (29.0)	37 (37.0)		
	Tt	46 (46.0)	48 (48.0)		
	tt	25 (25.0)	15 (15.0)		
ApaI				0.030	0.70
	AA	26 (26.0)	40 (40.0)		
	Aa	49 (49.0)	45 (45.0)		
	aa	25 (25.0)	15 (15.0)		

Metabolic and Anthropometric Parameters

Individuals with MetS were showed significantly higher anthropometric and biochemical measures compared to controls. Mean body mass index was 33.5 ± 3.8 kg/m² in the MetS group versus 25.8 ± 2.9 kg/m² in controls (p<0.001). Waist circumference, fasting glucose, triglycerides, and systolic blood pressure were all significantly elevated among MetS participants, while HDL-cholesterol levels were significantly lower (p<0.001 for all comparisons). (Table 4)

Table 4: Anthropometric and metabolic parameters.

Parameter	MetS (n=100)	Control (n=100)	p-value
BMI (kg/m²)	33.5 ± 3.8	25.8 ± 2.9	<0.001
Waist circumference (cm)	105 ± 8	86 ± 7	<0.001
Fasting glucose (mg/dL)	132 ± 28	92 ± 10	<0.001
Triglycerides (mg/dL)	185 ± 45	110 ± 30	<0.001
HDL-cholesterol (mg/dL)	38 ± 6	50 ± 8	<0.001
Systolic BP (mmHg)	142 ± 12	122 ± 10	<0.001

Gut Microbiome Diversity

Microbiome analysis was revealed significant reductions in alpha diversity among MetS participants. The mean and standard deviation of Shannon diversity index was 3.2 ± 0.6 in MetS patients and 3.8 ± 0.5 in controls (p<0.001). The observed OTU count was lower in the MetS group (median 180, IQR: 150-210) compared with controls (220, IQR: 200-250, p<0.001). The Prevotella/Bacteroides ratio was significantly reduced among MetS participants (median 0.6, IQR: 0.4-0.9 vs 1.1, IQR: 0.8-1.5, p<0.001), suggesting a shift toward a dysbiotic gut profile. (Table 5)

Table 5: Gut Microbiome diversity and composition.

Metric	MetS (n=100)	Control (n=100)	p-value
Shannon diversity index (mean ± SD)	3.2 ± 0.6	3.8 ± 0.5	<0.001
Observed OTUs (median [IQR])	180 [150-210]	220 [200-250]	<0.001
Prevotella/Bacteroides ratio (median [IQR])	0.6 [0.4-0.9]	1.1 [0.8-1.5]	<0.001

Multivariable Logistic Regression Analysis

Multivariable logistic regression identified several significant independent predictors of MetS after adjusting for potential confounders. The VDR FokI ff genotype increased the odds of MetS approximately two-fold (adjusted OR=1.9, 95% CI: 1.1-3.4, p=0.02). Vitamin D deficiency (<20 ng/mL) was independently associated with higher odds of MetS (OR=2.7, 95% CI: 1.6-4.5, p<0.001). Low microbiome diversity, defined as Shannon index below 3.4, also predicted MetS (OR=2.2, 95% CI: 1.3-3.7, p=0.003). Age was a continuous predictor, with every 5-year increase associated with a 15% rise in MetS risk (OR=1.15, 95% CI: 1.05-1.26, p=0.004). Male sex did not significantly predict MetS in the adjusted model (OR=1.1, 95% CI: 0.7-1.8, p=0.65). (Table 6)

Table 6: Multivariable logistic regression analysis for predictors of MetS.

Predictor	Adjusted OR (95% CI)	p-value
VDR FokI ff genotype (vs FF)	1.9 (1.1-3.4)	0.02
Vitamin D deficiency (<20 ng/mL)	2.7 (1.6-4.5)	<0.001
Low microbiome diversity (Shannon <3.4)	2.2 (1.3-3.7)	0.003
Age (per 5-year increase)	1.15 (1.05-1.26)	0.004
Male sex	1.1 (0.7-1.8)	0.65

DISCUSSION

This cross-sectional study demonstrates that vitamin D deficiency, specific VDR gene polymorphisms, and reduced gut microbiome diversity are independently associated with MetS among Iraqi adults. The observed relationships suggest a complex interplay between genetic predisposition, nutritional status, and microbial ecology in the pathogenesis of MetS.

Vitamin D deficiency is high prevalence (70%) in MetS patients, which is significantly higher than the control group (35%) and aligns with other past studies of Middle Eastern populations. A recent systemic review reported prevalence levels of vitamin D deficiency of between 54 and 90 percent among adults with MetS in different countries.[13] Our results support results with Saudi Arabia, where studies had reported 68% deficiency in vitamin D in MetS patients.[14], and with Iran, where studies had reported 73% deficiency in the metabolic abnormality patients.[15] Our MetS group (17.2 ng/mL) has a significantly lower mean serum 25(OH)D level (25.4 ng/mL in controls) than meta-analyses indicate an inverse relationship between the vitamin D status and the risk of MetS.[16]

There are a several mechanisms which could explain the association between MetS and vitamin D deficiency. Vitamin D controls insulin secretion by acting on the pancreatic beta cells and also acts on insulin sensitivity in peripheral tissues.[17] Moreover, vitamin D has anti-inflammatory effects that can be used to overcome low-grade chronic inflammation associated with MetS.[18] The high levels of PTH of our MetS patients (58.3 pg/mL vs 45.7 pg/mL) are also indicative of secondary hyperparathyroidism due to vitamin D deficiency, which has been identified to cause insulin resistance and adiposity via a variety of mechanisms.[19]

Our analysis has identified that MetS and VDR gene polymorphisms were strongly associated, especially the FokI ff genotype which led to a risk almost doubled. The polymorphism of the FokI alters the transcriptional start site producing proteins of VDR of varying length with possible changes in transcriptional activity.[20] The results of the previous research have provided incongruent findings on FokI as to metabolic disorders as studies conducted on different ethnic groups show mixed results.[21] According to a meta-analysis conducted by researchers, FokI polymorphism was related to a higher risk of diabetes in Asian populations but not in Europeans, which implies ethnic-specific effects.[22] Study results support the concept that FokI variants may influence MetS susceptibility in Middle Eastern populations, potentially through effects on vitamin D-mediated insulin secretion or glucose homeostasis.

In our cohort, the BsmI bb and ApaI aa genotypes were also more commonly found in patients with MetS. These

polymorphisms are present in the 3' untranslated region of VDR gene and could have an impact on the stability of mRNA or the expression level.[23] In a Jordan study, there were similar reports of difference in BsmI variants and MetS component, and ApaI polymorphisms correlated with insulin resistance markers.[25] Nevertheless, European studies have shown opposing results as there were no associations or only specific parts of MetS.[26] Such differences can be indicative of variations in genetic background, exposure to the environment or gene-environment interaction among the population.

The findings of gut microbiome are represent a novel contribution of our research on the understanding of MetS among Iraqi adults. The decrease in the Shannon index of diversity and the decrease in OTUs in MetS patients are indicators of loss of microbial richness and evenness, which correlates with the idea of dysbiosis in metabolic disease.[27] It has been recorded in numerous studies that people with obesity, insulin resistance, and MetS showed decreased gut microbial diversity.[28,29] The reduction in Prevotella/Bacteroides ratio of our MetS population indicates an enterotype transition which could be due to dietary habits and metabolic disequilibrium. Prevotella species have been linked with plant-based diets and the synthesis of short-chain fatty acids with metabolic advantages whereas Bacteroides prevalence has been linked to the Western-style diets with high fat and protein content.[30]

Study multivariate model shows that low microbiome diversity is independently linked to MetS (OR=2.2), which indicates that microbial ecology is a factor that improves metabolic health in addition to conventional risk factors. Some of the mechanisms that have been found to connect gut dysbiosis with MetS are changes in energy gains obtained with the diet, heightened intestinal permeability culminating to metabolic endotoxemia, change of bile acid metabolism that affect glucose and lipid control, and generation of metabolites that have effects on insulin sensitivity.[31] Causal relationships have been directly proven by recent research demonstrating the insulin sensitivity modulation of the gut microbiota transplantation in humans.[32]

The possibility of VDR polymorphism and gut microbiome composition interaction is a new field of research. Recently, researchers made reports which demonstrated that VDR TaqI variants did have an effect on the composition of the gut microbiome in Spanish adults with each genotype corresponding to a change in Firmicutes Bacteroidetes ratios.[10] On the same note, studies established that VDR signaling enhances intestinal barrier behavior, as well as healthy microbial metabolite generation.[23] Although our study design is not causal, the parallel identities of VDR polymorphisms and microbiome changes in the MetS patients indicate the possibility of mechanistic connections. The VDR present in intestinal ectodermal cells controls the generation of antimicrobial peptides, tight junction products and immunological reactions which control formation of gut microbial ecosystem.[33]

Minimal sun exposure of the MetS patients (0.9 vs 1.6 hours per day) is likely to increase vitamin D deficiency due to less production through the cutaneous system. The geographic location of Iraq offers a lot of sunshine however due to the culturally oriented practices such as indoor life and tight dressing, the skin may not be able to see the sunlight. The nutritional intervention opportunities are missed as the low rates of vitamin D supplementation among MetS patients (14.0) represent a lack of nutritional intervention. These results highlight the significance of the views of the population on modifiable risk factors since it is a public health strategy.

Strengths of the Study

The strengths of this study are that the study has thoroughly evaluated genetic, biochemical, and microbial factors in a well-characterized cohort that has rigorous case-control matching. Concurrent analysis of multiple VDR polymorphisms and microbiome metrics has multidimensional information on the MetS pathophysiology. The confirmation of Hardy-Weinberg equilibrium and quality control measures enhance the level of confidence in genetic results.

Limitations

Several limitations warrant mention: this case-control design cannot establish causality between VDR polymorphisms, microbiome shifts, and MetS, so longitudinal studies are necessary; the modest sample size reduces power for detecting gene–environment interactions or subgroup effects; residual confounding (e.g. diet, medications) may persist despite adjustments; and 16S rRNA sequencing yields only taxonomic (not functional) data, making metagenomic or metabolomic methods preferable for deeper insight.

Future Directions

Future studies should focus on long-term cohort research to clarify the causal links between VDR gene variants, changes in the gut microbiome, and the 10 emergence of MetS. Trials tailored to vitamin D supplementation guided by individual genetic profiles are also needed, alongside metagenomic and metabolomic investigations to move beyond taxonomy towards function. Mechanistic work exploring how VDR variants shape microbial populations and metabolic health, paired with multicenter studies across Iraqi regions for wider applicability, and cost-effectiveness evaluations of combined screening programs in low-resource settings, would collectively support informed public-health policies.

CONCLUSION

This study shows that MetS is independently related to vitamin D deficiency, VDR gene polymorphisms (especially FokI, BsmI, and ApaI variants), and low gut

microbiome diversity in Iraqi adults, which may indicate the presence of multifactorial pathophysiology, including genetic predisposition, nutritional inadequacy, and microbial dysbiosis. The disastrous rates of the vitamin D deficit (70% among patients with MetS) and low levels of supplementation support the poor level of awareness about this issue. Among the suggestions are the establishment of population based vitamin D screening programs, cultural competent supplementation plans in light of genetic differences, the incorporation of dietary counseling to promote healthy gut microbiomes by consuming foods rich in fibers and probiotics, and the VDR genotyping that may be used to identify the use of the population at risk. There is a necessity of the public health campaigns on safe exposure to sun, physical activities, and diet. More longitudinal studies are justified to establish causal relations and determine whether personalized interventions used to change vitamin D status and gut microbiome composition can help decrease MetS burden in Iraqi and other population groups.

ACKNOWLEDGMENTS

The authors would be pleased to highly appreciate all patients and staff of Baghdad Teaching Hospital who volunteered in the study by offering priceless help in the form of patient recruitment, sample collection and technical assistance. We also wish to thank the Institutional Review Board of the Ibn Sina University which gave the approval.

Conflicts of Interest: No conflicts declared.

Funding: Self-funded; no external support.

REFERENCES

1. Stroia CM, Ghitea TC, Vrânceanu M, et al. Relationship between Vitamin D3 deficiency, metabolic syndrome and VDR, GC, and CYP2R1 gene polymorphisms. *Nutrients*, 2024; 16(9): 1272. doi:10.3390/nu16091272
2. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. *BMC Med*, 2011; 9: 48. doi:10.1186/1741-7015-9-48
3. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr*. 2008; 87(4): 1080S–6S. doi:10.1093/ajcn/87.4.1080S
4. Muscogiuri G, Altieri B, Annweiler C, et al. Vitamin D and chronic diseases: the current state of the art. *Arch Toxicol*. 2017; 91(1): 97–107. doi:10.1007/s00204-016-1804-x
5. Uitterlinden AG, Fang Y, Van Meurs JB, et al. Genetics and biology of vitamin D receptor polymorphisms. *Gene*. 2004; 338(2): 143–56. doi:10.1016/j.gene.2004.05.014
6. González Soltero R, Bressa C, Tabone M, Clemente S, Larrosa M, Bailén M. Associations between Vitamin D Receptor (VDR) Polymorphisms and Gut Microbiota in a Spanish Population Sample. *Biology and Life Sciences Forum*, 2023; 29(1): 4. https://doi.org/10.3390/IECN2023-15530
7. Al-Daghri NM, Al-Attas OS, Alkharfy KM, Khan N, Mohammed AK, Vinodson B, et al. Association of VDR-gene variants with factors related to the metabolic syndrome, type 2 diabetes and vitamin D deficiency. Gene, 2014 Jun 1; 542(2): 129-33. doi:10.1016/j.gene.2014.03.044.
8. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. *Cell*, 2012; 148(6): 1258–70. doi:10.1016/j.cell.2012.01.035
9. Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature*, 2013; 500(7464): 541–6. doi:10.1038/nature12506
10. González-Soltero R, Bailén M, de Lucas B, et al. VDR gene TaqI (rs731236) polymorphism affects gut microbiome composition in Spanish adults. *Front Nutr*, 2024; 11: 1423472. doi:10.3389/fnut.2024.1423472
11. Al-Hazmi AS, Al-Mehmadi MM, Al-Bogami SM, Shami AA, Al-Askary AA, Alomery AM, et al. Vitamin D receptor gene polymorphisms as a risk factor for obesity in Saudi men. *Electron Physician*, 2017; 9(10): 5427–33. doi:10.19082/5427
12. Rahmadhani R, Zaharan NL, Mohamed Z, et al. The associations between VDR BsmI polymorphisms and risk of vitamin D deficiency, obesity and insulin resistance in adolescents residing in a tropical country. *PLoS One*, 2017; 12(6): e0178695. doi:10.1371/journal.pone.0178695
13. Gholami F, Moradi G, Zareei B, et al. The association between circulating 25-hydroxyvitamin D and cardiovascular diseases: a meta-analysis of prospective cohort studies. *BMC Cardiovasc Disord*, 2019; 19(1): 248. doi:10.1186/s12872-019-1236-7
14. Al-Daghri NM, Alkharfy KM, Al-Saleh Y, et al. Modest reversal of metabolic syndrome manifestations with vitamin D status correction: a 12-month prospective study. *Metabolism*, 2012; 61(5): 661–6. doi:10.1016/j.metabol.2011.09.017
15. Kelishadi R, Farajzadegan Z, Bahreynian M. Association between vitamin D status and lipid profile in children and adolescents: a systematic review and meta-analysis. *Int J Food Sci Nutr*, 2014; 65(4): 404–10. doi:10.3109/09637486.2013.871692
16. Ju SY, Jeong HS, Kim DH. Blood vitamin D status and metabolic syndrome in the general adult population: a dose-response meta-analysis. *J Clin Endocrinol Metab*, 2014; 99(3): 1053–63. doi:10.1210/jc.2013-3577
17. Lips P, Eekhoff M, van Schoor N, et al. Vitamin D and type 2 diabetes. *J Steroid Biochem Mol Biol*, 2017; 173: 280–5. doi:10.1016/j.jsbmb.2016.11.021
18. Wimalawansa SJ. Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. *J Steroid Biochem Mol Biol*,

2018; 175: 177–89. doi:10.1016/j.jsbmb.2016.09.017
19. Hjelmesaeth J, Hofsø D, Aasheim ET, et al. Parathyroid hormone, but not vitamin D, is associated with the metabolic syndrome in morbidly obese women and men: a cross-sectional study. *Cardiovasc Diabetol*, 2009; 8: 7. doi:10.1186/1475-2840-8-7
20. Whitfield GK, Remus LS, Jurutka PW, et al. Functionally relevant polymorphisms in the human nuclear vitamin D receptor gene. *Mol Cell Endocrinol*, 2001; 177(1–2): 145–59. doi:10.1016/s0303-7207(01)00406-3
21. Oh JY, Barrett-Connor E. Association between vitamin D receptor polymorphism and type 2 diabetes or metabolic syndrome in community-dwelling older adults: the Rancho Bernardo Study. *Metabolism*. 2002; 51(3): 356–9. doi:10.1053/meta.2002.29969
22. Zhu JG, Xu YF. Association between vitamin D receptor gene polymorphisms and the risk of type 2 diabetes mellitus: an updated meta-analysis. *Biomed Rep*. 2015; 3(5): 649–54. doi:10.3892/br.2015.491
23. Chatterjee I, Lu R, Zhang Y, et al. Vitamin D receptor promotes healthy microbial metabolites and gut barrier function. *Sci Rep*. 2020; 10(1): 6422. doi:10.1038/s41598-020-63448-z
24. Khassawneh B, Samrah S, Khader Y, et al. Vitamin D receptor gene polymorphisms and cardiometabolic risk factors in Jordanian adults. *Diabetes Metab Syndr Obes*. 2019; 12: 1371–80. doi:10.2147/DMSO.S210035
25. Mackawy AMH, Badawi MEH. Association of vitamin D and vitamin D receptor gene polymorphisms with chronic inflammation, insulin resistance and metabolic syndrome components in type 2 diabetic Egyptian patients. *Meta Gene*. 2014; 2: 540–56. doi:10.1016/j.mgene.2014.06.005
26. Filus A, Trzmiel A, Kuliczkowska-Płaksej J, et al. Relationship between vitamin D receptor BsmI and FokI polymorphisms and anthropometric and biochemical parameters describing metabolic syndrome. *Aging Male*., 2008; 11(3): 134–9. doi:10.1080/13685530802273426
27. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. *Nature*. 2009; 457(7228): 480–4. doi:10.1038/nature07540
28. Karlsson FH, Tremaroli V, Nookaew I, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature*. 2013; 498(7452): 99–103. doi:10.1038/nature12198
29. Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature*. 2012; 490(7418): 55–60. doi:10.1038/nature11450
30. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science*. 2011; 334(6052): 105–8. doi:10.1126/science.1208344
31. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature*. 2006; 444(7122): 1022–3. doi:10.1038/4441022a
32. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology*. 2012; 143(4): 913–6.e7. doi:10.1053/j.gastro.2012.06.031
33. Wang J, Thingholm LB, Skiecevičienė J, et al. Genome-wide association analysis identifies variation in vitamin D receptor and other host factors influencing the gut microbiota. *Nat Genet*. 2016; 48(11): 1396–406. doi:10.1038/ng.3695