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Allelic Discrimination of Vitamin D Gene Polymorphism in Children with Type 1 Diabetes

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Abstract

Background: *Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder characterized by the loss of insulin-secreting pancreatic cells due to immune system dysregulation, resulting in insulin insufficiency and hyperglycemia.*

Aim: *identify the prevalence of vitamin D deficiency with T1DM and evaluate the allelic discrimination of vit d gene polymorphism in children with diabetes type 1.*

Method: *The study included 192 participants, 96 patients of them with T1DM and 96 healthy participants. Data collection and genotyping involved collecting peripheral blood samples to assess the biochemical and hematological parameters. Molecular analysis for the VDR gene using RT-PCR was conducted as well.*

Results: *The study found a significant disparity in vitamin D levels between the control and diabetes cohorts. The control group had a mean vitamin D level of 39.14 ± 9.781, while the diabetes group had a lower level of 21.93 ± 8.222. (P-value 0.0001). Gender also played a role in ocular problems, with males having a higher prevalence than females (p-value 0.031). Elevated body mass index (BMI) was found to be a significant risk factor for ocular, neurological, diabetic nephropathy, and cardiovascular problems (P-value 0.001, 0.003) respectively. The rs7975232 gene had a very major link with nephropathy; however, no significant correlations were identified for ophthalmic, cardiac, or neurological disorders. The rs2228570 gene variations exhibit notable associations with particular diabetic problems, such as ocular difficulties, nephropathy, and cardiac issues. Eye complications exhibited no significant correlation with the rs2228570 polymorphism, although the TT genotype was the most prevalent among those with eye complications.*

Conclusion: *The rs2228570 gene variants are linked to specific diabetic issues like ocular difficulties, nephropathy, and cardiac problems. Eye complications have no significant correlation with the rs2228570 polymorphism, but the TT genotype is more prevalent among those with eye complications.*

Keywords: *Vitamin D, Diabetes Mellitus, Diabetic Complications, Body Mass Index (BMI), Vitamin D Receptor Polymorphism.*

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease-causing destruction of insulin-secreting pancreatic cells due to immune system dysregulation, leading to insulin deficiency and elevated blood glucose levels (Popoviciu et al., 2023). It impacts about 150 million individuals globally and is anticipated to rise to 439 million by 2030 (El-Mesallamy, H. O., et al., 2013). Treatment depends on exogenous insulin, which ensures survival but does not reverse the condition (Zhao et al., 2023). T1DM often manifests in children and adolescents, typically peaking between ages 10 and 14, with genetic and environmental factors contributing to its complex etiology (Trigg, 2022). Genetic predisposition is evident, with significant clustering in families and associations with other autoimmune diseases, primarily linked to the human leukocyte antigen (HLA) region on chromosome 6 (Harroud & Hafler, 2023).

Obesity is an escalating global health concern attributed to genetic predisposition, excessive caloric intake, and diminished physical exercise. This results in the excessive buildup of white adipose tissue, which stores surplus energy as fat. Obesity elevates the likelihood of developing insulin resistance, a primary feature of T2DM (Aboouf, M. A., et al., 2015).

Vitamin D deficiency is a common issue in healthy Egyptians. Insufficient vitamin D levels are associated with obesity, hypertension, hyperlipidemia, glucose intolerance, cardiovascular disease, and an elevated risk of metabolic syndrome (Mohammed, A. A., et al., 2023).

Candidate genes related to susceptibility include the vitamin D receptor (VDR) gene, recently associated with autoimmune diseases and T1DM susceptibility (Agliardi et al., 2023). Vitamin D3 influences immune responses by modulating monocytes and dendritic cells, inhibiting activated T-cells, and reducing Th1 cytokine production (Hafkamp et al., 2022). Vitamin D deficiency has emerged as a global epidemic, affecting health even in sun-exposed populations (Raymond-Lezman & Riskin, 2023). Its role extends beyond bone health to immune function, and VDR is expressed in various tissues, including pancreatic β-cells, prompting questions about its influence on T1DM (Eizirik et al., 2023).

Four significant single nucleotide polymorphisms (SNPs) in the VDR gene have been identified, linking VDR SNPs with T1DM in different populations. However, studies on VDR polymorphism and vitamin D status in Egyptian T1D children remain scarce, motivating this investigation into the significance of VDR gene polymorphisms and vitamin D levels in Egyptian type 1 diabetic children and their siblings.

Previous studies on Vitamin D receptor polymorphisms in T1DM demonstrated a protective role of the FokI A allele against T1DM, while the ApaL allele was found to be associated with T1DM susceptibility (Fteah et al., 2025). This suggests that different VDR SNPs may contribute differentially to the development of T1DM (Ferraz et al., 2022).

The association between FoKI and ApaI single nucleotide polymorphisms (SNPs) and type 1 diabetic mellitus (T1DM) is predicated on genetic variants within the vitamin D receptor (VDR) gene. FoKI is a start-codon mutation in the VDR gene, predominantly linked to type 2 diabetes and gestational diabetes (Ata, A., et al., 2024). ApaI is not linked to Type 1 Diabetes Mellitus or other kinds of diabetes. The variability in research findings may stem from sample sizes, ethnic diversity, and environmental factors (Apaydın, M., et al., 2019). This study aims to identify the prevalence of vitamin D deficiency in children and adolescents with T1DM and evaluate the allelic discrimination of vit d gene polymorphism in children with diabetes type.

METHOD

Study design

This study was a case–control study to identify the prevalence of vitamin D deficiency in children and adolescents with T1DM and evaluate the allelic discrimination of vit d gene polymorphism in children and adolescents with diabetes type 1.

Study setting

This study was conducted at National Nutrition Institute, General Organization for Teaching Hospitals and Institutes (GOTHI) at the period between July 2024 from November 2024.

Patients

One hundred ninety-two children and adolescents were participated in the study. They were categorized in the following manner: Group I comprised 96 patients diagnosed with type 1 diabetes. Group II comprised 96 healthy control cases.

Inclusion criteria

192 participants enrolled in this study with the following inclusion criteria

- T1DM diagnosis follows ADA or WHO criteria.

- Children aged 3 to 18 years with defined illness duration.
- Participants must not have significant diseases affecting vitamin D metabolism.
- Refrain from using drugs disrupting vitamin D metabolism or immune system.
- Written informed consent from parents or guardians and child is mandatory.
- Control group includes healthy, non-diabetic children.
- Absence of family history of T1DM or autoimmune disorders.

Exclusion criteria

- Children with alternative types of diabetes (e.g., type 2 diabetes, monogenic diabetes).
- patients with a history of any chronic inflammatory or infectious condition.
- Children who got vitamin D or calcium supplementation within a specified timeframe prior to the trial.
- Children with a history of skeletal diseases or rickets.
- Absence of adequate consent.

Sample size calculation

The sample size was determined using Quanto version 1.2.4, adhering to the parameters: $\alpha=0.05$, $\beta=0.10$, predicted OR=1.8, resulting in an estimated sample size of 100 children for both the case and control groups. The sample size was thus enough.

Data Collection and Genotyping

Vitamin D deficiency

Levels of 25(OH) D below 20 ng/mL are classified as vitamin D deficiency; concentrations ranging from ≥20-30 ng/mL are classified as vitamin D insufficiency; and levels of 30 ng/mL and above are classified as vitamin D sufficiency.

Routine Biochemistry

Blood samples was collecting from the patients after fasting for 6 to 8 hours before collecting 10 ml of whole blood. The blood divided between serum tubes and EDTA tubes. For assessing Hb% and WBCs were done by automated **Celltac Alpha (MEK -1301)** is an advanced hematology analyzer designed for high precision and accuracy in blood tests. In addition to routine biochemistry including fasting Blood sugar (FBS), Triglycerides (TG), total cholesterol (TC). The blood chemistry test levels were quantified utilizing automated chemistry analyzer Cobas c 311 analyzer (Roche Diagnostics, Rotkreuz, Switzerland) according to manufacture instructions.

Molecular Analysis for the VDR Gene

Genomic DNA was extracted from peripheral EDTA blood using a Qiagen DNA isolation kit. Red and white blood cell lysis, protein purification, and DNA extraction were completed in 35 minutes using centrifugation and incubation at 56°C for 10 minutes. 200 µL of genomic DNA was obtained from 150 µL of blood and stored at -80°C until analysis. DNA quantification was performed using a NanoDrop spectrophotometer, and the concentration was converted into 20 µg/mL for the amplification screening program for ApaL, and FokI SNPs in the VDR gene.

PCR (Polymerase Chain Reaction) is employed to amplify the specific segment of the Vitamin D gene that harbors the polymorphism of interest. A specific set of forward and reverse primers is designed to encompass the polymorphic region. A reaction mixture is formulated comprising the extracted DNA template, forward and reverse primers, Taq DNA polymerase, deoxynucleotide triphosphates (dNTPs), and a buffer solution containing magnesium chloride.

The reaction mixture is positioned in a thermal cycler, which undergoes temperature fluctuations to facilitate the PCR process. This cycle is replicated around 25-40 times, resulting in an exponential amplification of the target DNA sequence.

Real-time PCR (RT-PCR) is an effective method for allelic discrimination, facilitating concurrent amplification and detection of target DNA. A unique TaqMan probe is engineered to hybridize with the target DNA sequence located between the forward and reverse primers. The reaction is conducted in a RT-PCR apparatus capable of detecting various fluorescence signals. The allelic status of each individual is ascertained by the ratio of the two fluorescent signals at the conclusion of the reaction**.**

Ethical considerations

Informed consent was obtained from all participants following a comprehensive description of the study's objectives and procedures. Participants retained the right to withdraw from the study at any time without providing justification. The privacy and confidentiality of the acquired data were ensured for all

participants. The study was executed in compliance with the principles outlined in the Declaration of Helsinki and received clearance from the Ethics Committee of General Organization for Teaching Hospitals and Institutes (GOTHI) under the registration number IN000154.

Statistical analysis

The research employed Statistical Package for the Social Sciences version 26.0 software for data analysis. Descriptive statistics encompassed the mean, standard deviation, and internal rate of return (IRR). Analytical statistics comprised Kruskal-Wallis analysis of variance, ANOVA with repeated measures, Student's t-test for normally distributed data, and Mann-Whitney U test for non-normally distributed data. The Pearson method was employed for correlation analysis, while multiple linear regression was utilized to ascertain the relationships among predictors. The threshold for statistical significance was established at $P > 0.05$, whereas $P < 0.001$ denoted extremely significant results.

RESULTS

The study revealed no significant age disparity between the control and diabetes groups, with a mean age of 10.81±2.381 years. The gender distribution revealed a notable disparity, with 57% of the diabetes cohort being male and 43% female. The exercise habits exhibited a notable disparity, with 57% of the control group participating in regular physical activity, suggesting a possible correlation between insufficient exercise and the prevalence of diabetes. The average BMI of the diabetic cohort was elevated, signifying an increased risk factor for diabetes. The diabetic group exhibited a greater average waist circumference, signifying an increased prevalence of central obesity.

The familial history of diabetes markedly differed between the two cohorts, with 46% of the diabetic group possessing a familial history of the condition, indicating a genetic susceptibility to diabetes development. The data indicate that age, gender, exercise habits, and family history may influence the occurrence of diabetes.

Table 1: Demographic Data in Studied Groups

Parameter	GP 1 Diabetic (Patients)	GP 2 Control (Healthy)	P-value	Significance
Age	11.06 ± 2.698	10.85 ± 2.406	0.573	No
Sex (Gender)	Male= 52 (54.2%) Female = 44 (45.8%)	Male = 34 (35.4%) Female = 62 (64.6%)	0.009	Yes
Exercise	Yes = 26 (27.1%) No = 70 (72.9%)	Yes = 54 (56.3%) No = 42 (43.8%)	< 0.0001	Yes
BMI	24.86 ± 4.296	21.42 ± 2.096	< 0.0001	Yes
Waist	73.27 ± 11.668	60.96 ± 7.702	< 0.0001	Yes
Family History of Diabetes	Yes = 44 (45.8%) No = 52 (54.2%)	Yes = 18 (18.8%) No = 78 (81.3%)	< 0.0001	Yes

The research identified substantial disparities in dietary patterns between Group 1 (patients) and Group 2 (healthy individuals). Group 1 had a greater prevalence of moderate to high carbohydrate meals, whereas Group 2 primarily adhered to a high protein diet. A greater number of patients adhered to a high carbohydrate diet, although adherence to low to moderate carbohydrate diets was comparable.

Table 2: Comparison between the studied groups regarding to type of diet.

	Type of diet	Group 1 Diabetic	Group 2 Control	P-value
Diet	Low to moderate carb	18	23	0.001
	Moderate to high carb	49	27	
	High Carb	8	3	
	High protein	21	43	

The study suggests a possible correlation between dietary habits and health condition. The healthy group ingests higher protein and lower to moderate carbohydrates, whereas the ill group predominantly takes moderate to high carbohydrates. These eating patterns may influence the health outcomes of these people; however, causation cannot be shown.

Table 3: Comparison between the studied groups regarding to Laboratory Findings

Parameter	Diabetic (Patients)	Control (Healthy)	P-value	Significance
Cholesterol	195.36 ± 24.699	161.83 ± 25.170	0.000	Yes
Triglycerides	190.69 ± 35.065	155.34 ± 30.154	0.000	Yes

Parameter	Control (Healthy)	Diabetic (Patients)	P-value	Significance
Vitamin D Level	21.93 ± 8.222	39.14 ± 9.781	0.0001	Yes
Hb	12.20 ± 1.489	11.27 ± 1.790	0.000	Yes
WBCs	7.79 ± 1.981	7.29 ± 4.644	0.330	No
Fasting Blood Sugar	179.61 ± 48.682	94.61 ± 10.610	0.000	Yes
Creatinine	0.8074 ± 0.40151	0.974 ± 0.18987	0.000	Yes
GFR	80.22 ± 10.499	85.03 ± 5.996	0.000	Yes

The research identified a notable disparity in vitamin D levels between the control and diabetes cohorts. The control group exhibited a mean vitamin D level of 39.14 ± 9.781, whereas the diabetes group demonstrated a markedly lower level of 21.93 ± 8.222, signifying a substantial disparity in vitamin D levels between the two cohorts (Table 3)

Table 4: Correlation Between Gender and Complications

Complication	Gender	Yes (n, %)	No (n, %)	P-value	Significance
Eye Complications	Male	43 (55.1%)	34 (35.4%)	0.031	Yes
	Female	35 (44.9%)	62 (64.6%)		
Neurological Complications	Male	8 (44.4%)	78 (44.8%)	0.975	No
	Female	10 (55.6%)	96 (55.2%)		
Diabetic Nephropathy	Male	4 (44.4%)	82 (44.8%)	0.983	No
	Female	5 (55.6%)	101 (55.2%)		
Cardiac Complications	Male	9 (50.0%)	77 (44.3%)	0.641	
	Female	9 (50.0%)	97 (55.7%)		

The study identified a notable association between gender and ocular problems, with a higher prevalence in males (55.1%) compared to females (44.9%). Neurological problems exhibited no correlation with gender, as males constituted 44.4% and females 55.6%, resulting in nearly equivalent distributions. Diabetic nephropathy and cardiovascular complications shown no correlation, affecting 50% of both men and women.

Table 5: Correlation Between BMI and Complications

Complication	BMI (Mean ± SD)	P-value
Eye	27.22 ± 3.623 (Yes) 24.32 ± 4.275 (No)	0.009
Neurological	27.78 ± 3.191 (Yes) 24.19 ± 4.252 (No)	0.001
Nephropathy	29.11 ± 1.764 (Yes) 24.43 ± 4.244 (No)	0.002
Cardiac	27.50 ± 3.204 (Yes) 24.26 ± 4.302 (No)	0.003

The study identified a substantial association between body mass index (BMI) and many problems in diabetes individuals. Individuals with elevated BMI had a greater propensity for experiencing ocular, neurological, diabetic nephropathy, and cardiovascular problems, indicating that increased BMI may serve as a possible risk factor for these diabetes-related conditions. The findings presented in Table 5 demonstrate an absence of statistically significant correlation between Vitamin D levels and the assessed complications, which encompass ocular, neurological, nephropathic, and cardiac issues, as indicated by the elevated p-values, all exceeding the conventional significance threshold of 0.05.

Table 6: Correlation between Vitamin D and the complications

Complication	Vitamin D	p-value
Eye	22.39 ± 6.455 (Yes) 21.82 ± 8.611 (No)	0.793
Neurological	22.50 ± 6.573 (Yes) 21.79 ± 8.589 (No)	0.745
Nephropathy	20.44 ± 3.046 (Yes)	0.573

	22.08 ± 8.577 (No)	
Cardiac	22.06 ± 6.301 (Yes) 21.90 ± 8.639 (No)	0.942

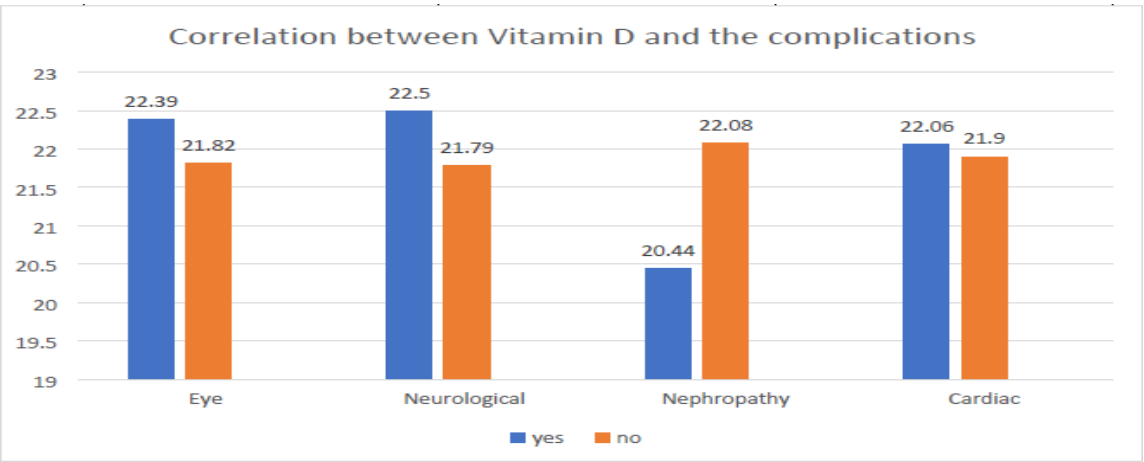

Figure 1: Correlation between Vitamin D and the complications

The rs7975232 gene exhibits a nearly substantial correlation with nephropathy, as patients with nephropathy demonstrate elevated frequencies of the GG and TT genotypes. Nonetheless, no substantial correlations were identified for ocular, cardiac, or neurological problems. The rs2228570 gene variations exhibit notable associations with particular diabetic problems, such as ocular difficulties, nephropathy, and cardiac issues. Eye complications exhibited no significant correlation with the rs2228570 polymorphism, although the TT genotype was the most prevalent among those with eye complications. Neurological issues had no significant correlation; however, the TT genotype was more prevalent among individuals with neurological complications. No significant correlation was observed between the rs2228570 gene and cardiac problems.

Table 7: Correlation Analysis between rs7975232 and rs2228570 genes and diabetic complications

Complications	**rs7975232**	**GG**	**TG**	**TT**	**P value**
Nephropathy	**Yes**	22.2% (2)	55.6% (5)	22.2% (2)	**0.058**
	No	5.7% (5)	86.2% (75)	8.0% (7)	
Eye	**Yes**	11.1% (2)	72.2% (13)	16.7% (3)	**0.363**
	No	**6.4% (5)**	**85.9% (67)**	**7.7% (6)**	
Cardiac	**Yes**	11.1% (2)	72.2% (13)	16.7% (3)	**0.363**
	No	6.4% (5)	85.9% (67)	7.7% (6)	
Neurological	**Yes**	11.1% (2)	72.2% (13)	16.7% (3)	**0.363**
	No	6.4% (5)	85.9% (67)	7.7% (6)	
Complications	**rs2228570**	**GG**	**TG**	**TT**	**P value**
Nephropathy	**Yes**	5.6% (1)	38.9% (7)	55.6% (10)	**0.505**
	No	12.8% (10)	44.9% (35)	42.3% (33)	
Eye	**Yes**	5.6% (1)	33.3% (6)	61.1% (11)	**0.281**
			46.2% (36)		
Cardiac	**Yes**	11.1% (1)	44.4% (4)	44.4% (4)	**0.999**
	No	11.5% (10)	43.7% (38)	44.8% (39)	
Neurological	**Yes**	5.6% (1)	38.9% (7)	55.6% (10)	**0.505**
	No	12.8% (10)	44.9% (35)	42.3% (33)	

The research indicated that allelic variation in the rs7975232 (ApaI) and rs2228570 (FokI) genes does not substantially influence the age distribution within the examined population. The average age for rs7975232 varies from 10.67 ± 2.45 years to 11.08 ± 2.75 years, with no significant variation among genotypes. The mean age for rs2228570 ranges from 9.50 ± 3.54 years to 12.00 ± 2.65 years. The Chi-Square test revealed a substantial correlation between rs7975232 genotypes and sex, with the CT genotype predominating in females (71.9%) and the TG genotype in males (57.5%).

Table 8: Correlation between allelic discrimination, age and sex.

	Genotype	Female (n) %	Male (n) %	Total	P-value	Genotype	Age	P-value
rs7975232 (ApaI)	**CC**	15 (50.0%)	15 (50.0%)	30		**GG**	10.67 ± 2.45	**0.819**
	CT	46 (71.9%)	18 (28.1%)	64		**CT**	10.89 ± 2.42	
	GG	3 (42.9%)	4 (57.1%)	7	0.006	**TG**	11.08 ± 2.75	
	TG	34 (42.5%)	46 (57.5%)	80		**TT**	10.73 ± 2.10	
	TT	8 (72.7%)	3 (27.3%)	11				
rs2228570 (FokI)	**CC**	5 (45.5%)	6 (54.5%)	11		**CC**	12.00 ± 2.65	**0.460**
	CT	17 (40.5%)	25 (59.5%)	42		**CT**	10.62 ± 2.56	
	GG	2 (100.0%)	0 (0.0%)	2	0.125	**GG**	9.50 ± 3.54	
	TG	50 (61.7%)	31 (38.3%)	81		**TG**	10.89 ± 2.34	
	TT	32 (57.1%)	24 (42.9%)	56		**TT**	11.16 ± 2.80	

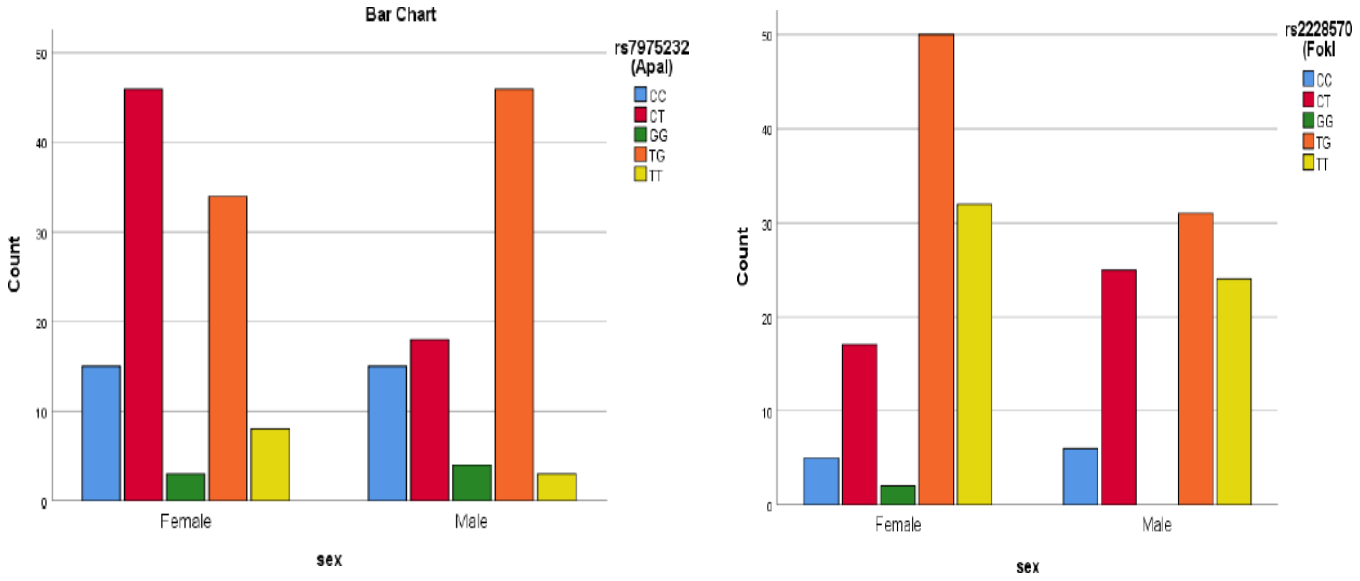

Figure 2: Correlation between rs7975232 (ApaI), Correlation between rs2228570 (FokI) and Sex.

DISCUSSION

This study aims to evaluate the allelic discrimination of vit d gene polymorphism in children with diabetes type 1. Our study found no significant age difference between control and diabetes groups, but a significant gender disparity.

Extensive analyses consistently demonstrate that age is a risk factor for type 2 diabetes. Older adults are at a heightened risk of developing the illness, while several studies suggest that early-onset cases exhibit a greater prevalence of microvascular problems. A study revealed no substantial disparity in diabetes risk between middle-aged and elderly individuals after controlling for confounding variables; nonetheless, the risk of prediabetes increases with age (Lee DC, et al., 2019).

On the other hand; other research indicates that age disparities may not significantly forecast diabetes incidence, particularly in specific populations, after other risk factors are accounted for. (Yan, Z., et al., 2023).

Global gender discrepancies in diabetes incidence are apparent, with males frequently exhibiting greater rates, and these differences may be intensified by sex-specific behaviors and socioeconomic factors (Sujata, Thakur, R. 2021).

In certain contexts, the disparity is less evident or fluctuates according to age, race, or socioeconomic status. Certain research indicate that women are less predisposed to diabetes until post-menopause, with risk factors influencing each sex differently (Kautzky-Willer, A., et al., 2023).

Our study showed that the diabetes cohort had elevated BMI indicating increased risk. Regular physical activity is strongly linked to a lower risk of diabetes and better control of blood sugar levels. Research supports our assertion that insufficient physical activity correlates with an increased risk of diabetes, whereas regular exercise facilitates both prevention and control by improving insulin sensitivity (Sriyono, G. H., et al., 2023).

A high BMI and central (abdominal) obesity are strong indicators of diabetes risk, often even stronger than genetic variables or family history (Alwash, S. M., McIntyre, H. D., & Mamun, A. (2021). A high BMI can raise the risk of diabetes by as much as eleven times. A larger waist circumference is a critical sign of central obesity, which is intimately associated to type 2 diabetes (Chandrasekaran, P., & Weiskirchen, R., 2024).

Some research indicates that those with a reduced BMI but elevated waist circumference (central obesity) has risks comparable to those who are overweight, highlighting the necessity of assessing both metrics rather than BMI in isolation (Feller, S., Boeing, H., & Pischon, T., 2010).

Our study showed that the familial history of diabetes was also significant, with 46% of the diabetic group having a genetic susceptibility. These factors may influence diabetes occurrence.

Genetic and shared environmental variables make it much more likely that someone will have diabetes if they have a family history of it. First-degree relatives have a threefold increased risk, while parental diabetes can elevate the lifetime risk by as much as 70% (Ali O., 2013). Some studies, on the other hand, say that non-genetic variables may also have a role (Tsenkova, V. K., et al., 2016).

Our results showed that majority of diabetic patients were on moderate to high carbohydrates while the majority of healthy patients in control group were on high protein diet. These results point to the fact that high carb diet may be a contributing factor to increased BMI and diabetic condition.

A study by Schmidt, S., et al., 2019 agree to our findings, the results of his study revealed elevate blood sugar levels during the periods of high carb intake.

Our study showed that individuals with diabetes have significantly lower levels of vitamin D compared to those without diabetes, and the prevalence of deficiency is markedly higher among diabetics. Insulin resistance, inadequate glycemic regulation, and beta-cell impairment are all believed to be exacerbated by a deficiency of vitamin D (Bayani, M. A., et al., 2014)

Vitamin D receptors exist in pancreatic beta cells, essential for insulin synthesis. A deficiency in vitamin D is believed to contribute to insulin resistance, impaired glycemic control, and potentially beta-cell malfunction and apoptosis (Abugoukh, T. M., et al., 2022).

Our study revealed a significant correlation between gender and ocular issues, showing a greater frequency in males (55.1%) than in girls (44.9%). Neurological issues demonstrated little connection with gender, with males comprising 44.4% and females 55.6%, yielding virtually similar distributions. Diabetic nephropathy and cardiovascular problems shown no association, impacting 50% of both males and females.

Numerous research indicated that men possess a somewhat elevated chance of acquiring diabetic retinopathy (DR). A significant study in Sardinia demonstrated a greater prevalence of diabetic retinopathy in males than in females among persons with type 2 diabetes. A clinical study revealed that male gender increased the risk of retinopathy in individuals with type 1 diabetes by 32% (Chen, Y., et al., 2024).

Recent studies, particularly concerning type 2 diabetes, indicate that women exhibit a higher or comparable prevalence of diabetic retinopathy to that of men. A comprehensive Chinese investigation revealed a markedly elevated prevalence of diabetic retinopathy in females, especially among individuals with a diabetes duration exceeding 10 years or of advanced age. Several research indicate that there is minimal disparity between men and women regarding retinopathy after controlling for other variables (Mokhtarpour, K., et al., 2024).

Regarding neurological complications, Studies show no significant gender difference in diabetic neuropathy frequency or onset, aligning with our results (Javed, A., et al., 2014). However, some reports show higher prevalence or more pronounced symptoms in females, particularly regarding pain or mood-related symptoms, depending on the population, diabetes type, and assessment method (Mubeen, M., et al., 2023).

Regarding diabetic nephropathy. Our study indicates no substantial gender disparity in the risk or prevalence of diabetic nephropathy. Recent studies indicate that women may have an elevated risk of acquiring nephropathy or experiencing a rapid loss in renal function following the onset of diabetes (Mokhtarpour, K., et al., 2024).

Men may have a higher prevalence of microalbuminuria, whilst women may demonstrate more advanced stages of the condition. Variations may arise from study design, demographic age, or duration of diabetes (Zhang, F., et al., 2024).

Regarding cardiac complications; Diabetes, in itself, does not exhibit notable gender disparities in cardiac consequences (M El Sayed, A., et al., 2024). Diabetic women exhibit a markedly elevated relative cardiovascular risk in comparison to their non-diabetic counterparts, with certain problems potentially manifesting more severely in women. This heightened risk may not indicate the absolute prevalence within the diabetic community but rather the extent to which diabetes elevates risk relative to each sex's baseline (Penno, et al., 2013).

The findings of our study indicate that increased BMI correlates with a greater prevalence of ocular, neurological, nephropathic, and cardiovascular complications in individuals with diabetes, whereas no significant relationship was observed between Vitamin D levels and these complications. These results are consistent with contemporary scientific literature and align with prevailing research trends.

A previous study indicates that elevated BMI augment the risk of diabetic retinopathy and associated microvascular problems (Huang, Y., et al., 2023). Both observational and Mendelian randomization analyses corroborate this causal link. Nonetheless, certain studies indicate that the association may be inverse or less definitive due to confounding factors such as inadequate glycemic control and sample characteristics (Sarrafan-Chaharsoughi, Z., et al., 2018).

Numerous meta-analyses and genetic investigations indicate that elevated BMI is a risk factor for diabetic nephropathy and negative renal outcomes in diabetic patients, including a causal relationship that is independent of glycemic regulation (Lu, J.et al., 2022).

Obesity, diabetes, and cardiovascular disease are interrelated, since elevated BMI heightens the risk of myocardial infarction, stroke, augmented arterial stiffness, and cardiovascular mortality in individuals with diabetes. The risk is notably elevated when obesity and diabetes are present simultaneously, exacerbating cardiovascular biomarkers and incidents (Brown, O. I., et al., 2023).

Our study showed that Vitamin D deficiency is prevalent among diabetics; nonetheless, most research reveal weak or inconsistent correlations with problems. Evidence is inconclusive regarding whether Vitamin D deficiency independently forecasts the onset or severity of diabetes problems. Certain studies with favorable outcomes are constrained by sample size, design, or insufficient control for confounding variables. The absence of a substantial connection between Vitamin D and complications indicates that Vitamin D levels may not be a principal factor influencing complication risk in individuals with established diabetes, in contrast to BMI and other metabolic variables (Bajaj, S., et al., 2014).

Our study found that the rs7975232 gene is linked to nephropathy, with patients showing higher frequencies of the GG and TT genotypes. However, no significant correlations were found for ocular, cardiac, or neurological problems. The rs2228570 gene has significant associations with specific diabetes problems, including ocular difficulties, nephropathy, and cardiac issues. Eye complications showed no significant correlation with the rs2228570 polymorphism, while neurological issues had no significant correlation.

Research indicates that SNPs in the VDR gene, such as rs7975232, elevate the risk of diabetic nephropathy. Individuals possessing the GG and TT genotypes exhibit a heightened predisposition to nephritis, indicating a possible genetic vulnerability (Elhuseiny, A. E., et al., 2024).

Nevertheless, the majority of analyses revealed no substantial correlation between rs7975232 and other problems in diabetes patients, with nephropathy being the most closely associated SNP. Alternative outcomes have yielded inconsistent or bad effects (Yang, L., et al., 2017).

Our study found that the rs2228570 polymorphism is associated with diabetes-related comorbidities, such as heightened risk of nephropathy, ophthalmic disorders, and cardiovascular problems in patients with diabetes. Specific genotypes, such as the GG or AA variation, exhibit increased susceptibility to these problems when associated with low vitamin D levels. Nevertheless, the data revealed no substantial association between rs2228570 and ocular or neurological problems, aligning with the inconsistent findings in the literature (Zhong, P., et al., 2023). On the other hand; Certain investigations fail to establish definitive correlations between rs2228570 (FokI) and ocular or neurological outcomes, despite the presence of links with nephropathy or cardiac events (Alfaqih, M. A., et al., 2022).

CONCLUSION

The research indicates that elevated BMI, central obesity, and a favorable familial history are substantial risk factors for diabetes and its primary consequences, which encompass ophthalmic, neurological,

nephropathic, and cardiovascular issues. Vitamin D deficiency is apparent in patients with diabetes, compared to patients in control group. Males exhibit a higher prevalence of ocular problems, but not of neurological, nephropathic, or cardiac issues. An elevated BMI is a persistent risk factor for several diabetes-related problems, underscoring the significance of metabolic health in diabetes management. Genetic variants such as the rs7975232 VDR polymorphism have a robust correlation with diabetic nephropathy and cardiac difficulties; however, no significant relationships were identified with ocular or neurological disorders.

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