Research Article

Association of Vitamin D Receptor *FokI* Polymorphism and Some Clinical Parameters with Diabetes Mellitus (Type 1 and Type 2) in Iraqi Patients

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Abstract | In this study, the researchers seek to compare the pattern of vitamin D level and vitamin D receptor polymorphisms *FokI* in diabetes mellitus, type1 and type2 (T1DM and T2DM), as cases vs healthy population as control in Iraqi patients. The hypothesis of the study is that the "*VDR* gene polymorphism *FokI* rs2228570" and vitamin D level are associated with T1DM and T2DM of diabetes mellitus. The cases-control study was carried on 75 cases 45 T2DM, 30 T1DM and 25 controls. The sample were collected in Al-Yarmouk Teaching Hospital (T2DM and control) and from Pediatric Central Teaching Hospital (T1 DM and control) during January 2016 through April 2016. Vitamin D level of both cases and controls were measured by using Enzyme Linked Immunosorbent Assay (ELISA). Blood glucose was measured by enzyme method and also Glycated Hemoglobin was detected by same method. Genotyping was performed by Restriction Fragment Length Polymorphism (RFLP)– PCR method after DNA amplification, and the data were analyzed statistically with IBM-SPSS v.24 and Winpepi, compare program. The PCR product was sent to sequencing. Logistic regression test revealed insignificant association between TT and CC genotypes with T1DM (OR=1.36, 95%CI=0.42-4.43, *P*=0.425 and OR=1.00, 95%CI=0.35-2.90, *P*=0.608 respectively) and also showed T allele as etiological factor (OR=1.45, 95%CI= 0.68-3.12). For T2DM genotypes TT and CC was insignificantly with (OR=1.59, 95%CI= 0.39-6.45, *P*=0.394 and OR= 1.43 95%CI = 0.54-3.80, *P*=0.322 respectively) and showed C allele as etiological factor (OR = 1.07 95%CI = 0.52-2.19, *P*=0.455). Serum level of glucose and Glycated Hemoglobin and Vitamin D showed higher significantly elevations in patients group compared with controls group ($P \leq 0.05$). The study showed relation between Vitamin D deficiency and high level of glucose with DM patient. There was no association between (*FokI*) polymorphism and diabetes mellitus, but this study showed which allele distribution and genotype were as preventive factor and which was as etiological factor in both types. The samples of patients have sequencing ID LC342080.1 and LC342081.1, and 99% identities, score 219 with reference at NCBI.

Keywords | Diabetes mellitus, Vitamin D, FokI polymorphism rs2228570, Vitamin D receptor

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INTRODUCTION

Diabetes mellitus performs a group of metabolic diseases results from hyperglycemia which is produced by a disorder in pancreatic insulin secretion and the activity of insulin. Long-range harm, dysfunction, failure of various organs, like kidneys, heart, blood vessels and eyes, usually accompanied with chronic hyperglycemia of diabetes. T2DM distinguished by integration of reduced insulin secretion and progressing of insulin resistance (IR) in

peripheral target tissues, especially muscle and liver with progressing absence of β-cell secretory capacity (Karuna *et al*., 2013). Insulin receptor is considered to be a major participant in the imperfect response of body tissues to insulin (Benedict *et al*., 2004).About 80% to 90% of pancreatic beta cells no longer owns their normal function in type I onset occurrence under pathological conditions, β cells response and sense are both changeable in the levels of blood glucose by generating insulin, which works on other tissues to enhance glucose uptake from the blood and thus lower blood glucose levels. Moreover, when blood glucose is high, patient with type 1 who usually young and scraggy is susceptible to progress ketoacidosis (Evans *et al*., 2002).

Other specific kinds of diabetes are resulted by specific disorder off beta cell function, or insulin activity, the pancreas diseases and drug or chemical stimulated diabetes mellitus. Vitamin D has been recognized as the anti-rickets factor or sunshine vitamin. Nowadays, vitamin D insufficiency is believed to be the universal health problem. In 2008, it was evaluated that one billion individuals have vitamin D deficiency (25 OH vitamin D) (Chagas *et al*., 2012). Vitamin D classified as fat soluble vitamin. There are two types of it: D2 which is also known as ergocalciferol manufactured by plants, and D3 or cholecalciferol, manufactured by mammals (Holick, 2004). D2 is synthesized artificially by ultraviolet exposure of foods and utilized as vitamin D supplementation, while D3 was at first gained from cod liver oil (Vieth, 1999). Also, it's synthesized in human skin with the aid of ultraviolet B (UVB) radiation (Holick, 2011).

Clinical studies have shown a positive correlation between insulin sensitivity and circulating vitamin D levels, It points out that vitamin D insufficiency may predispose to change secretion of insulin in diabetes (Pittas *et al*., 2010). The VDR is encoded by a gene located in chromosome 12q12, which contain 9 exons and several polymorphisms (Zmuda *et al*., 2000). Both types are related with vitamin D insufficiency. Many studies showed that children with serum levels 25(OH) D3 less than ng/ml were tend to have high blood glucose levels than those who having levels more than 26 ng/ml (Reis *et al*., 2009). Moreover, the VDR is presents in pancreatic β cells. Thus, 1.25 (OH)2 D3 may act an important function in the secretion of insulin and sensitivity of it in type 2 diabetes by either increase the level of intracellular calcium through non-selective voltage dependent channels of calcium in the β-cell to stimulate insulin secretion or by the increase of the transformation of pro-insulin to insulin (Seshadri *et al*., 2011). Because of the fact that vitamin D receptor is the way which vitamin D exerts its effects. The VDR gene has become an elect receptivity gene for type 1 diabetes (Li *et al*., 2009). *FokI* polymorphism is presented within the DNA binding domain, near the 5'end and the other SNPs which are located in the 3'-UTR area within the ligand binding domain. The *FokI* polymorphism make an alternative ATG initiation codon in exon2 leads to a 3 amino-acids longer VDR protein by immediately creating a start codon (Colin *et al*., 2000). In this study we investigated vitamin D status in patients with T1DM and T2DM investigated the frequency of VDR *FokI* gene polymorphisms, its susceptibility to T1DM, T2DM and its association with serum levels of 25(OH) D in Iraqi population. In order to further evaluate the consequence of the polymorphism for vitamin D metabolism.

MATERIALS AND METHODS

Five ml of venous blood was collected from each Participant; 2ml of which was kept in EDTA tube for HbA1c test and extraction DNA, and the other 3ml in gel tube. The latter was undergone centrifugation where the serum was obtained in Eppendorf tube and Preserved at –20C until used for VD measurement using human VD3 ELISA Kit, cat. No. EQ_6411–9601 Euroimmun/ Germany. Blood glucose was measured by used Biolabo kit / France. Glycated Hemoglobin (HbA1c) test was measured for patients and controls by used Human/ Germany kit. DNA was extracted from blood Samples using ready Kit Genomic DNA (extraction Kit/ Promega/ USA).

The study includes 100 sample, 30 patient with T1DM (Males: 14, Females: 16), 45 patient with T2DM (Males: 31, Females: 14) and controls group 25 sample (males: 16, Females: 9. The mean±SD for TIDM compared with control group was (10.2±3.77) years while controls group was (29.1±14.1) years P – value ≤0.05. The main age of patient T2DM was (53.2±9.9) years while control group was (29.1 ± 14.1) value was ≤0.05. Informed consents From Patient's as well as control were taken which included age , previous and current occupation, Smoking, residence, Body mass Index (BMI). Ethical Permission was obtained from all volunteer to collect samples and conduct this study. The cases were selected through the help of Internal medicine and endocrinologists inside these hospitals. "The cases were collected from AL-Yarmouk teaching hospital for T2DM and control and from Pediatric Central Teaching Hospital for TIDM and control". Control was collected with notes that have normal glucose level and no first degree family history. The Study was conducted in Al-Nahrian University– Biotechnology research center. Extracted DNA from blood samples was used in PCR for amplification of (*VDR* gene) (*FokI* SNP). A pair of primers specific for (*VDR* gene) (*FokI* SNP) were used (F: 5 G A T G C C A G C TGGCCCTGGCACTG3,R:5ATGGAAA-CACCTTGCTTCTTCTCCCTC3, fragment: 273bp). PCR–protocol was [Initial denaturation: 95 °C for 5 min, (Denaturation: 94 °C for 30 sec, Annealing: 60 °C for 30sec, Elongation 72 °C for 30 sec) 40 cycles, final elongation 72 °C for 5 min]. The PCR product was digested by

the restriction enzyme *FokI* restriction endonuclease (New England Biolabs). The digestion reaction was carried out in a 0.5 mL sterile eppendrof tube, where 2 µL of PCR product were mixed with 0.5 unit of enzyme, with 1 µL buffer and completed to a final reaction volume of 10 µL with nuclease free water. The mixture was incubated at 37 °C for 1 hour. The digestion products electrophoretically separated on a 3% agarose gel stained with Red Safe stain. The PCR product was sent to Macrogen Company in Koria for sequencing, to confirm investigate the variation of SNP C/T of diabetic patients by RFLP-PCR. The sequencing result analyzed by BLAST website on NCBI (Nouri *et al*., 2015; Al-Qaisi *et al*., 2018; Al-Tekreeti *et al*., 2018).

Statistical analysis

All the statistical analyses were performed by IBM SPSS version 24. Genotype frequencies were tested for Hardy-Weinberg equilibrium equation. Odds ratio (OR) at 95% confidence interval (Cl) was determined by fisher test to describe the strength of association by logistic regression analysis. Mean ± SD was given for quantitative variables (Age, BMI, FBG, HbA1c, serum Vitamin D level). P value less than 0.05 was considered significant.

RESULTS AND DISCUSSIONS

The result of fasting blood glucose level shows significant between T1DM and T2DM Patient's P value ≤ 0.05 (282±76) (268±74), respectively. This result is for patients in comparison with controls (89±11) (Table 1). The increasing of FBS level's in agreement with many research result like (Hussein *et al*., 2012; Al-Shamma *et al*., 2013). Elevated FBS is due to Insulin hypo secretion in DM patients. It decreases the convert of extracellular glucose to intercellular storage in the form of macromolecular (Cryer *et al*., 1985). The level of glycated Hemoglobin (HbA1c %) in both Diabetes patient Type1 (8.49±2.22) Type 2 (8.88±1.85) was increased highly significantly (P≤ 0.05) in comparison with control group (4.33±1.27) (Table 1). This result was agreement with Previous studies which proved that concentration of (HbA1c) was higher (Mishra and Singh, 2013; Snell-Bergeon *et al*., 2010). The higher level of (HbA1c %) was associated with increasing of (FBS) level in two type of (DM). The testing of (HbA1c %) is used to know chronic glycaemia in diabetic patients, and it has been used as objective sign of average glycemic control in the oversight Patients which has diabetes (d'Emden, 2014). The result of vitamin D level has shown high significant differences between TIDM and T2DM compared with control group *P*≤ 0.05 (Table 1). A high Prevalence of vitamin D deficiency (VDD) among both types of diabetics was seen in this study.

This study agrees with (Lee *et al*., 2012) who found that (89%) of their study individuals suffered from a deficiency of this vitamin and only out of (300) persons had sufficient VD concentration (Lee *et al*., 2012).

The rate of the incidence VDD in TIDM is Saudi Arabian Population was found to be equal (84 %) (Bin-Abbas, 2011). The different incidence rates of VDD in T1DM Patients can be due to many reasons, the altered dietary custom or inadequate expose to the sunshine, moreover, VDD may be related to the occurrence of malabsorption state among the patients with type 1 Diabetes. It is clearly described that VD can prevent the death of islet cells (Riachy *et al*., 2006; Raeef *et al*., 2023). Consequently, there is a direct concept of dysfunctioning of beta cells, VDD, and resistance towards insulin. It has been mentioned that VD is effective for making positive improvements in the production of insulin (Chiu *et al*., 2004). In T2DM patients had reduced levels of VD than normal individuals. The insulin resistance is more in VDD.

Therefore, VD plays an important role in preserving norm glycemic condition by influencing insulin secretion. In vitamin D deficiency state, there is decreased insulin sensitivity and increase IR chronic VDD may be a suitable reason for T2DM (Mangukiya and Neha, 2014). The study of (Zeitz *et al*., 2003) concluded that administration of a single dose of 1, 25(OH) 2D3 (calcitriol) of VD to deficient rat increased insulin secretion and decreased blood glucose levels (Zeitz *et al*., 2003). The beneficial effects of calcium and VD on glucose homeostasis have been demonstrated in a series of investigational studies.

Table 1: Biochemical and clinical characteristics of the study subject.

P value (T1DM/T2DM)	Control	T2DM	T1DM	Parameter
NA	(16 / 9)	(31 / 14)	(14 / 16)	n (Male/Female)
0.0001 / 0.0001	29.1 ±14.1	53.2 ±9.93***	10.2 ±3.77***	Age (year)
0.0089 / 0.001	23.91±6.25	29.37±6.84***	21.73±8.15**	BMI (kg/m^2)
0.308 / 0.088	12	20 NS	0 NS	Smokers (%)
0.0001 / 0.0001	89.3±11.9	268.3±74.0***	282.7±76.8***	Fasting glucose (mg/dl)
0.0001 / 0.0001	4.335±1.27	8.885±1.85***	8.492±2.22***	HbA1c (%)
0.0001 / 0.0001	48.29±19.76	24.64±11.57***	21.86±7.97***	Vitamin D3 level (ng/ml)

T1DM , Type 1 Diabetes mellitus , T2DM , Type 2 Diabetes mellitus P * ≤0.05 , **≤0.01 , ***≤0.001 compared to controls, NS: Non Significant , NA: Non applicable.

Table 2: Allele frequency and genotypes of FOK1 Polymorphism between Patients and controls group.

P value T1DM/T2DM	ODDS Ratio(95% Cl) T1DM/T2DM	Controls n (%)	T2DM n (%)	T1DM n (%)	FOK1 polymorphism
0.425 / 0.394	1.36(0.42-4.43) / 1.59(0.39-6.45)	3(12.00%)	8(17.78%)	9(30.00%)	Genotype TT
0.138 / 0.171	0.46(0.16-1.38) / 0.54(0.20-1.45)	12(48.00%)	15(33.33%)	9(30.00%)	Genotype CT
0.608 / 0.322	1.36(0.42-4.43) / 1.00(0.35-2.90)	10(40.00%)	22(48.89%)	12(40.00%)	Genotype CC
0.224 / 0.498	1.45 (0.68-3.12) / 0.93(0.46-1.91)	18 (36%)	31(34.44%)	27(45%)	Frequency of T allele
0.259 / 0.455	0.69 (0.32-1.47) / 1.07(0.52-2.19)	32 (64%)	59(65.56%)	33 (55%)	Frequency of C allele

O.R > 1.0 (Etiological factor),O.R < 1.0 (Preventive factor).

The fact that pancreatic β-cells express vitamin D receptor (VDR), 1α-hydroxylase enzyme and calcium binding protein is consistent with an ability of this cell type to respond to the active form of the VD [1,25(OH)2D3] and increased insulin secretion *in vitro* (Bland *et al*., 2004).

Allele frequency

The allele C represented 55% in patients with T1DM and 65% in patients with T2DM in comparison with T allele, which represented 45% in T1DM and 34.4% in T2DM. While C allele in control samples ratio was 64% in comparison with T allele which showed 36% (Table 2). The Table 2 also shows that frequency distribution doesn't significant differences between patients and control samples (*P* value > 0.05), and results show that C allele showed significant frequency in patients with T1DM with ratio less than control samples. As for the samples with T2DM, C allele exhibited significant frequency in patients with ratio higher than control samples, these results were obtained by using Fisher's test, where was OR= (0.69) to allele (C) in T1DM with (95% CI= 0.32- 1.47), this ratio represents the allele as a preventive allele (preventive factor PF, OR < 1.0), but was OR= (1.07) for T2DM with (95% CI= 0.52- 2.19) with ratio represent as etiological allele (OR > 1.0).

The results of the study are consistent with what got by (Shen and Qiu, 2004; Vedralová *et al*., 2013) in terms of obtaining results consistent with the results of the current study, which shows that percentage of C allele in T1DM was higher in the control samples compared with patients, while T was significantly higher in patients compared to the control samples. The value of OR >1.0 and high allele frequency (T) significantly in patients, shows the extent of the role played by this allele with the risk of T1MD, while reduction of C allele frequency in patients and its height in the control samples and also the OR<1.0 shows how it is important as a preventive factor from diabetes. These finding were confirmed by several studies showing that the T allele in T1MD may be an important indicator of the risk of the disease progression and beta cell destruction, and suggest that the polymorphism of C allele may not be important in the development of T1MD but be a preventive factor of the risk of the disease (Hamed *et al*., 2013).

Another study concerned with the extent which the genetic polymorphism of the (VDR gene rs2228570 C/T) was associated with T1MD, showing that the (T) allele behaves as a preventive factor against risk of diabetes mellitus and this is contrary to the results of the study (Nasreen *et al*., 2016). The results of the study obtained are not consistent with the study carried out by (Ban *et al*., 2001) who found that the C allele frequency in patients with T1DM was higher than the control samples, and T allele frequency less than control samples, when the results showed that the allele T behaves as preventive factor reverse that C allele which acts as a risk factor for T1DM (Ban *et al*., 2001). Utilizing Fisher's test, T allele showed significant frequency in patients with T1DM was higher than controls, while the opposite in T2DM where showed significant frequency in controls higher than patients, where was OR= (1.45) to T allele in T1DM, with 95%CI= (0.68-3.12) which represents etiological allele. OR to T allele in T2DM was (0.93) with (95%CI= (0.46- 1.91) acts as PF (Table 2). The results of our study agree with Vedralová et al. (2013)which showed the significant frequency of C allele was higher in patients than the control samples in T2DM, where was behave as a risk factor for the diabetes mellitus disease, while proving that T allele ratio was lower in patients in comparison with control samples where it proved the T allele acts as preventive factor from disease. Another study showed significant frequency similar to our study for T and C alleles in T2DM, (Mahjoubi *et al*., 2016). The study conducted by Al-Daghri et al. (2012) was the opposite of the results obtained in our study, where they proved that the C allele acts as a preventive factor, while T allele acts as risk factor for T2DM.

Genotype

Genotyping analyzing results to *VDR* gene by using RFLP-PCR technique and Hardy Weinberg equilibrium offers three genotyping patterns in patients with T1DM, T2DM and control samples: CC= FF (wild type) when only one band appear as homozygous, TT= ff (mutant type) when two bands appear as homozygous, CT=Ff heterozygous variant while three bands appear (Figure 1). Results elucidated variation in genotyping frequency between patients with DM and healthy control, where CC genotype showed ratio similar to control samples in

comparison with T1DM with ratio 40%, and OR= (1.00) with CI= (0.35-2.90), also where CC pattern appears as genotype-related with risk of T1DM develop. While ratio of CT genotype in healthy control was higher than patients with T1DM (48, 30) % respectively, no significant difference was observed between controls and patients sample, where was OR= (0.46) with 95%CI= (0.16-1.38), which represents the pattern as preventive factor from T1DM. TT genotype ratio in patients with T1DM was higher than healthy control (30, 24) % respectively, non-significant differences were observed between patients and control (P > 0.05), OR= (1.36) with (95% CI= 0.42- 4.43), which represents genotype pattern increases diabetes mellitus risk factor (Table 2). The above results show that the (CC Homozygous) and (TT mutant) genotype are associated with risk and development of T1DM in patient sample. However, the correlation between (TT) genotype and the risk of diabetes was higher than that of (CC) genotype, so it was found that the (TT) genotype can be used as an indicator with the risk of T1DM.

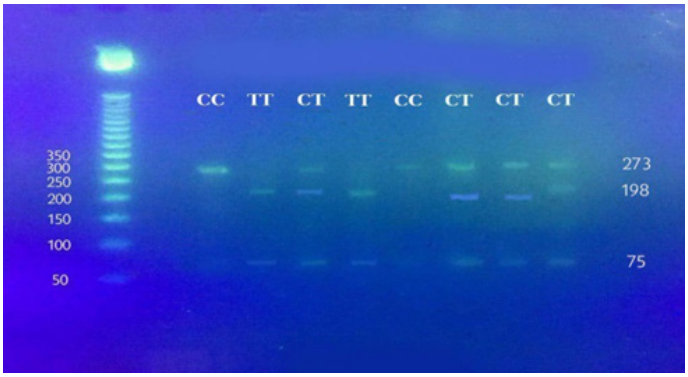

Figure 1: Photograph of the PCR products of the VDR gene after FOK1 enzyme digestion and on a 3% agarose gel, lane: (1-5) homozygous wild (CC-273pb), lane (2-4) homozygous mutant (TT-198,75bp) and lane (3, 6, 7, 8) heterozygous (CT – 273,198,75 bp).

The results also showed that heterozygous CT is important as a preventive genotype of diabetic. These results confirmed by many studies and agreed with them, as they agreed with the results of (Israni *et al.*, 2009). In terms of their high rates of genotype (TT and CC) in patients compared to control samples and that (TT genotype) frequency is the most dangerous. The studies by Bonakdaran *et al.* (2012). Which showed a relative consistency with our study showing the genotype (CC) work as a risk factor for diabetes, also showed the genotype (CT) was as a preventive factor, and this was consistent with the results of the study, while (TT) genotype showed as a preventive factor, this contrasted with our study that prove (TT) genotype was considered as the most dangerous factor for exposure to a T1DM in Iraqi patients. The results of this study agree with.

Genotype variation in T2DM were different from type 1, where CC genotype showed higher ratio than patients in comparison with control where ratio was (48.89-40) % respectively, non-significant difference was observed by using (Fishers test) between patients and controls, OR= (1.43) with 95% CI= (0.54 - 3.80). So, CC genotype act as a risk factor for diabetes type 2. While CT genotype ratio in control was higher than T2DM (48-33.33) % respectively, with OR= (0.54) where CT acts as preventive factor from risk of T2DM, no significant difference were observed in ($P \leq 0.05$).

TT genotype ratio in patients was higher than control (17.78, 12) % respectively, and by using (Fisher test), no significant difference was observed between patients and controls (P> 0.05), OR= (1.95) with 95% CI= (0.59- 6.45), where TT acts as a risk factor to diabetes (Table 2). The results of the genetic analysis of T2DM showed that the two kind of genotype (CC) and (TT) as the most dangerous factor for T2DM, while that CT genotype appears as a preventive factor from disease, The ration of genotype TT was higher in patients than control samples, where it is considered as the most dangerous indicator of the disease. While the result of the study proved that the genotype CT acts as preventive factor from diabetes. Saudi population confirmed our study in considering the genotype TT the most dangerous factor of T2DM, also in considering genotype CT as a preventive factor, while the results of this study differed with what was stated in our study that the genotype CC is a risk factor, while this study result showed that CC is a preventive factor. Tunisian population showed that CC, TT appears a risk factor of type2 diabetes and this consistent with our study. While study result differed with showing the genotype CT as a risk factor, and this contrary to our study that genotype appears as protective factor from T2DM.

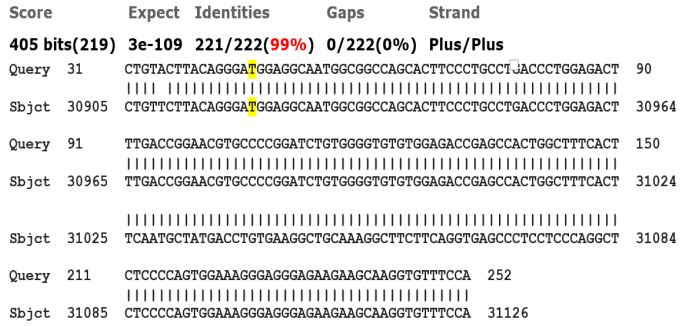

Figure 2: The alignment of sequencing, query represents a sequence of the sample; Sbjct represents VDR gene (complete gene) obtained from the database of National Center Biotechnology Information (NCBI).

Sequencing

The results of samples sequencing were confirmed with the results of RFLP-PCR. The samples of patients have sequencing ID LC342080.1 and LC342081.1, and 99% identities, score 219 with reference at NCBI (Figure 2).

CONCLUSION

The study showed relation between Vitamin D deficiency and high level of glucose with DM patient. There was no association between (*FokI*) polymorphism and diabetes mellitus, but this study showed which allele distribution and genotype were as preventive factor and which was as etiological factor in both types. The samples of patients have sequencing ID LC342080.1 and LC342081.1, and 99% identities, score 219 with reference at NCBI.

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NOVELTY STATEMENT

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AUTHOR'S CONTRIBUTION

AAR: Writing the manuscript. HHA: Analysis and interpretation of results. MMFA-H: Manuscript and reference review. AFH: Submitting the manuscript to the journal and correspondence.

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Generative AI and AI-assisted technology statement

The authors declare that no generative AI and AI assisted technology was used in the creation of this manuscript.

Conflict of interest

The authors have declared no conflict of interest.

REFERENCES

Al-Daghri NM, Al-Attas O, Alokail MS, Alkharfy KM, Draz HM, Agliardi C, Clerici M (2012). Vitamin D receptor gene polymorphisms and HLA DRB1* 04 cosegregation in Saudi type 2 diabetes patients. J. Immunol., 188(3): 1325-1332. https://doi.org/10.4049/jimmunol.1101954

Al-Qaisi RM, Al-Ani L, Al-Halbosiy MM (2018). Genetic polymorphism of ITGA2 gene and the risk of heart attack and stroke in Al-Anbar population/Iraq. J. Pharma. Sci. Res., 10(9): 2305-2308.

Al-Shamma ZA, Farid YY, Hashim HM (2013). Gonadal dysfunction with postprandial hypertriglyceridemia is risk predictors of cardiovascular disease in men with Type 2 diabetes mellitus. Iraqi J. Med. Sci., 11(2).

Al-Tekreeti AR, Al-Halbosiy MM, Dheeb BI, Hashim AJ, Al-Zuhairi AFH, Mohammad FI (2018). Molecular identification of clinical Candida isolates by simple and randomly amplified polymorphic DNA-PCR. Arab. J. Sci. Eng., 43(1): 163-170. https://doi.org/10.1007/s13369-017-2762-1

Aranaz P, Navarro-Herrera D, Zabala M, Miguéliz I, Romo-Hualde A, López-Yoldi M (2023). American Diabetes Association 2010. Diagnosis and classification of diabetes mellitus. Diabetes Care, 33(1): S62-69. https://doi.org/10.2337/dc10-S062

Ban Y, Taniyama M, Yanagawa T, Yamada S, Maruyama T, Kasuga A, Ban Y (2001). Vitamin D receptor initiation codon polymorphism influences genetic susceptibility to type 1 diabetes mellitus in the Japanese population. BMC Med. Genet., 2(1): 7. https://doi.org/10.1186/1471-2350-2-7

Benedict C, Hallschmid M, Hatke A, Schultes B, Fehm HL, Born J, Kern W (2004). Intranasal insulin improves memory in humans. Psychoneuroendocrinology, 29(10): 1326-1334. https://doi.org/10.1016/j.psyneuen.2004.04.003

Bin-Abbas B (2011). Vitamin D levels in Saudi children with type 1 diabetes Reply. Saudi Med. J., 32(11): 1211-1211.

Bland R, Markovic D, Hills CE, Hughes SV, Chan SL, Squires PE, Hewison M (2004). Expression of 25-hydroxyvitamin D3-1α-hydroxylase in pancreatic islets. J. Steroid Biochem. Mol. Biol., 89: 121-125. https://doi.org/10.1016/j.jsbmb.2004.03.115

Bonakdaran S, Abbaszadegan MR, Dadkhah E, Khajeh-Dalouie M (2012). Vitamin D receptor gene polymorphisms in type 1 diabetes mellitus: a new pattern from Khorasan province, Islamic Republic of Iran. Eastern Mediterran. Health J., 18(6). https://doi.org/10.26719/2012.18.6.614

Chagas CEA, Borges MC, Martini LA, Rogero MM (2012). Focus on vitamin D, inflammation and type 2 diabetes. Nutrients, 4(1): 52-67. https://doi.org/10.3390/nu4010052

Chiu KC, Chu A, Go VLW, Saad MF (2004). Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. Am. J. Clin. Nutr., 79(5): 820-825. https://doi.org/10.1093/ajcn/79.5.820

Colin EM, Weel AE, Uitterlinden AG, Buurman CJ, Birkenhäger JC, Pols HA, Van Leeuwen JP (2000). Consequences of vitamin D receptor gene polymorphisms for growth inhibition of cultured human peripheral blood mononuclear cells by 1, 25- dihydroxyvitamin D3. Clin. Endocrinol., 52(2): 211-216. https://doi.org/10.1046/j.1365-2265.2000.00909.x

Cryer PE, Gerich JE (1985). Glucose counterregulation, hypoglycemia, and intensive insulin therapy in diabetes mellitus. New Eng. J. Med., 313(4): 232-241. https://doi.org/10.1056/NEJM198507253130405

d'Emden M (2014). Glycated haemoglobin for the diagnosis of diabetes. Australian Prescriber, 37(3). https://doi.org/10.18773/austprescr.2014.037

Evans JL, Goldfine ID, Maddux BA, Grodsky GM (2002). Oxidative stress and stress-activated signaling pathways: A unifying hypothesis of type 2 diabetes. Endocr. Rev., 23(5):

599-622. https://doi.org/10.1210/er.2001-0039
Holick FM (2011). Vitamin D: Evolutionary, physiological and health perspectives. Curr. Drug Targets, 12(1): 4-18. https://doi.org/10.2174/138945011793591635
Gogas-Yavuz D, Keskin L, Kıyıcı S, Sert M, Yazıcı D, Şahin İ, Akalın S (2011). Vitamin D receptor gene BsmI, FokI, ApaI, TaqI polymorphisms and bone mineral density in a group of Turkish type 1 diabetic patients. Acta Diabetol., 48(4): 329-336. https://doi.org/10.1007/s00592-011-0284-y
Hamed EO, Abdel-Aal AM, Din AK, Atia MM (2013). Vitamin D level and Fok-I vitamin D receptor gene polymorphism in Egyptian patients with type-1 diabetes. Egypt J. Immunol., 20(2): 1-10.
Holick MF (2004). Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am. J. Clin. Nutr., 80(6): 1678S-1688S. https://doi.org/10.1093/ajcn/80.6.1678S
Hussein Z, Al-Qaisi J (2012). Effect of diabetes mellitus type 2 on pituitary gland hormones (FSH, LH) in men and women in Iraq. Al-Nahrain J. Sci., 15(3): 75-79. https://doi.org/10.22401/JNUS.15.3.11
Israni N, Goswami R, Kumar A, Rani R (2009). Interaction of vitamin D receptor with HLA DRB1* 0301 in type 1 diabetes patients from North India. PLoS One, 4(12): e8023. https://doi.org/10.1371/journal.pone.0008023
Karuna SP, Haritha YK, Venta RY (2013). Pharmacogenomics in diabetes mellitus: Pathway to personalized medicine.
Lee J., Oh-SuJin OS, WonChul HW, HyukSang KH, TaeSeo ST, HyunShik SH, BongYun CB (2012). Serum 25-hydroxyvitamin D concentration and arterial stiffness among type 2 diabetes. https://doi.org/10.1016/j.diabres.2011.09.006
Li C, Li Y, Gao LB, Wang YY, Zhou B, Lv ML, Zhang L (2009). Vitamin D receptor gene polymorphisms and the risk of colorectal cancer in a Chinese population. Diges. Dis. Sci., 54(3): 634-639. https://doi.org/10.1007/s10620-008-0375-y
Mahjoubi I, Kallel A, Sbaï MH, Ftouhi B, ben Halima M, Jemaa Z, Kaabachi N (2016). Lack of association between FokI polymorphism in vitamin D receptor gene (VDR) and type 2 diabetes mellitus in the Tunisian population. Indian J. Med. Res., 144(1): 46-51. https://doi.org/10.4103/0971-5916.193282
Mangukiya K, Neha S (2014). Clinical correlation between diabetes mellitus type 2 and Vitamin D3 (25 OH-cholecalciferol) level. Int. J. Sci. Nat., 5(3): 440-442.
Mishra N, Singh N (2013). Blood viscosity, lipid profile, and lipid peroxidation in type-1 diabetic patients with good and poor glycemic control. N. Am. J. Med. Sci., 5(9): 562. https://doi.org/10.4103/1947-2714.118925
Nasreen M, Lone KP, Khaliq S, Khaliq S (2016). Serum vitamin D levels and gene polymorphisms (Fok1 and Apa1) in children with type I diabetes and healthy controls. J. Pakistan Med. Assoc., 66(1215).
Nouri MA, Al-Halbosiy MM, Dheeb BI, Hashim AJ (2015). Cytotoxicity and genotoxicity of gliotoxin on human lymphocytes *in vitro*. J. King Saud Univ. Sci., 27(3): 193-197. https://doi.org/10.1016/j.jksus.2014.12.005
Pittas AG, Sun Q, Manson JE, Dawson-Hughes B, Hu FB (2010). Plasma 25-hydroxyvitamin D concentration and risk of incident type 2 diabetes in women. Diabetes Care, 33(9): 2021-2023. https://doi.org/10.2337/dc10-0790
Raeef AA, Al-Shaabani MJ, Al-Ani SK (2023). The relation between vitamin D insufficiency and thyroid hormones in Iraqi women living in Al-Khalidiya, Anbar Province. J. Biotechnol. Res. Center, 17(1): 45-54. https://doi.org/10.24126/jobrc.2023.17.1.700
Reis JP (2009). Vitamin D status and cardiometabolic risk factors in the United States adolescent population. Pediatrics, 124.3: e371-e379. https://doi.org/10.1542/peds.2009-0213
Riachy R, Vandewalle B, Moerman E, Belaich S, Lukowiak B, Gmyr V, Pattou F (2006). 1, 25-Dihydroxyvitamin D3 protects human pancreatic islets against cytokine-induced apoptosis via down-regulation of the Fas receptor. Apoptosis, 11(2): 151-159. https://doi.org/10.1007/s10495-006-3558-z
Seshadri KG, Tamilselvan B, Rajendran A (2011). Role of vitamin D in diabetes. J. Endocrinol. Metab., 1(2): 47-56. https://doi.org/10.4021/jem23w
Shen BS, Qiu MC (2004). The association of vitamin D receptor gene polymorphism with diabetes mellitus in the Han nationality of Tianjin area. Master's thesis of Tianjin Medical University, 01-49.
Snell-Bergeon JK, West NA, Mayer-Davis EJ, Liese AD, Marcovina SM, D'Agostino Jr RB, Dabelea D (2010). Inflammatory markers are increased in youth with type 1 diabetes: the SEARCH Case-Control study. J. Clin. Endocrinol. Metab., 95(6): 2868-2876. https://doi.org/10.1210/jc.2009-1993
Vedralová M, Kotrbova-Kozak A, Železníková V, Zoubková H, Rychlík I, Černá M (2013). Polymorphisms in the vitamin D receptor gene and parathyroid hormone gene in the development and progression of diabetes mellitus and its chronic complications, diabetic nephropathy and non-diabetic renal disease. Kidney Blood Pressure Res., 36(1): 1-9. https://doi.org/10.1159/000339021
Vieth R (1999). Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am. J. Clin. Nutr., 69(5): 842-856. https://doi.org/10.1093/ajcn/69.5.842
Zeitz U, Weber K, Soegiarto DW, Wolf E, Balling R, Erben RG (2003). Impaired insulin secretory capacity in mice lacking a functional vitamin D receptor. FASEB J., 17(3): 1-14. https://doi.org/10.1096/fj.02-0424fje
Zmuda JM, Cauley JA, Ferrell RE (2000). Molecular epidemiology of vitamin D receptor gene variants. Epidemiol. Rev., 22(2): 203-217. https://doi.org/10.1093/oxfordjournals.epirev.a018033