Impact of Vitamin D Elements in Insulin Sensitivity in Type 2 Diabetes Mellitus (DM2)

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Abstract

Numerous non-skeletal diseases have been reported to be associated with vitamin D status including type2 diabetes mellitus (T2DM). Different studies provide evidence that vitamin D status as well as other elements such as vitamin D binding protein (DBP) and vitamin D receptor (VDR) may play substantial role in glucose tolerance. Present study was designed to investigate the role of vitamin D status and their elements in insulin resistance or sensitivity in T2DM patients Current study includes 84 participants of both gender (56 patients and 28 as control). Clinical samples were collected from clinically proved DM2 patients. Serum levels of insulin, FBS, VD, VDR, and DBP were measured of each subjects. Using of Homeostasis Model Assessment Insulin resistance (HOMA-IR), T2DM patients were sub grouped to insulin resistance (IR) and insulin sensitivity (IS) groups. Relations among studied factors, FBS showed significant positive and negative relation with HOMA-IR and VD3 respectively, furthermore HOMA-IR revealed significant positive relation with DBP and VDR. Also, DBP revealed significant positive relation with each of VDR and HOMA-IR. On the other hand, VD3 levels showed significant and non-significant elevation in IS group compared to C and IR group respectively, while DBP revealed significant and non-significant dropping in IS group compared to C and IR groups respectively. Levels of VDR in IS group showed significant dropping compared to C and IR groups respectively. Our study concludes that VD3 alone or with its elements play substantial role in regulation of blood sugar levels particularly related to insulin sensitivity.

Keywords: *T2DM, Vitamin D elements, HOMA-IR.*

Introduction

Diabetes mellitus is a chronic disorder that affects several populations among the whole world and it is regarded as a widespread health problem[1]. Diabetes also affects individuals of different ages and health status, as it affects the rich and poor, men and women, as well as adults and children, and it is a disease that has sufficient capacity to destroy the body[2]. Also, diabetes is caused by an imbalance of hormones such as insulin and glucagon, which are the hormones responsible for regulating the level of glucose in the blood in order to stabilize the level of glucose[3].

Since there is scientific evidence on the relationship between the deficiency of VD3 levels and diabetes, people at risk of diabetes should be examined for low VD3 levels to improve their health in the long run, as vitamin D deficiency is linked to high blood glucose, insulin resistance, high blood pressure, and heart disease[4].

Deficiency of vitamin D was found to have the principal role among insulin resistance. Hence, there may be a risk of developing diabetes. Many studies have explained that vitamin D deficiency plays a role in insulin deficiency, and it is closely linked to an inherited polymorphism, including the protein associated with vitamin D (vitamin D binding protein (VDBP), the vitamin D receptor (VDR), and the alpha-hydroxylase gene vitamin D1. All of these measures work to balance glucose in addition to mediating insulin sensitivity. There is an evidence explores the relation between VD3 case and insulin resistance, but further discoveries are required. From those evidences, it is clear that VD3 plays an important role in the molecular processes of

synthesis, secretion as well as the peripheral sensitivity of insulin [5].

The pathophysiology of T2DM development, which plays the role of insulin resistance in muscle and liver cells, can be mentioned here, which means weak insulin signal given to cells, resulting in decrease in the glucose uptake and increase in the output of hepatic glucose, accompanied by failure of beta cells in the pancreas for producing enough insulin in order to maintain normal levels of glucose in blood and to prevent releasing of adipose fatty acids [6].

VDR are expressed by the pancreatic cells, human skeletal muscle as well as adipose tissue that are the main elements of peripheral insulin sensitivity[7].

The present study was designed for investigating the effects of vitamin D elements as VDR andV BDP in insulin sensitivity in development of type 2 diabetic patients.

Materials and Method

In this study, 84 participants of both gender (56 patients and 28 as control). Clinical samples were collected from patients who were clinically proved with T2DM. From patients and control subjects, in fasting state by venipuncture, using a 5ml syringe between 8 to 9 A.M, 3 ml of blood were obtained and dispensed in a plain tubes and left for hour to clot at room temperature (22ºC). Then, it was centrifuged at 3000 rpm for 10 minutes to collect serum . The serum was divided in to aliquots in eppendorff tube for measuring the (VD3, VDR, VDBP, FBS, and Insulin). Estimation of serum levels of vitamin D3, VDR, DBP, and insulin was done using the commercial ELISA kit of Sun long/China, in addition to measuring of serum levels of fasting blood sugar (FBS) using Biolab Glucose kit.

Statistical analysis was done using SPSS (Statistical Packages for Social Sciences- version16).

Table (1) Patients and control classified according to HOMA model

Factor	C M±SD	IS M±SD	IR M±SD		P-value	
HOMA-IR	1.231±0.409	2.058±0.527	3.65±1.229	C:IS	C:IR	IS:IR
				0.000	0.000	0.000
Insulin (mU/L)	5.576±1.849	4.594±0.936	6.391±2.046	0.020	0.072	0.000
FBS (mg/dl)	89.308±8.957	184.72±42.415	234.076±54.922	0.000	0.000	0.000

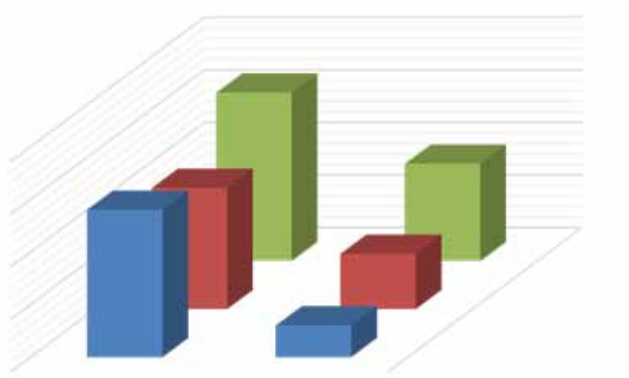

Figure (1) Patients and control classified according to HOMA-IR model.

Results and Discussion

Table (2) and Fig (2) show the mean of VD3 in studied group. There was highly significant difference between C and IS patient group (20.118±9.371), (28.481±7.909), p-value (0.004) respectively . While there was non significant difference between C and IR patient group (20.118±9.371), (25.666±10.416), p-value (0.07), also there was non significant difference between IS and IR patient group (28.481±7.909), (25.666±10.416), p-value (0.361) respectively.

Table (2) show the mean VD3 in studies group:

Factor	C M±SD	IS M±SD	IR M±SD	P value		
				C: IS	C: IR	IS: IR
VD3	20.118±9.371	28.481±7.909	25.666±10.416	0.004	0.075	0.361
DBP	0.47±0.255	0.394±0.14	0.582±0.226	0.152	0.050	0.001
VDR	2.082±0.975	1.644±0.394	1.905±0.772	0.026	0.979	0.024
FBS	89.308±8.957	184.72±42.415	234.076±54.922	0.000	0.000	0.000
HOMA-IR	1.231±0.409	2.058±0.527	3.65±1.229	0.000	0.000	0.000
INSULIN	5.576±1.849	4.594±0.936	6.391±2.046	0.020	0.072	0.000

Insulin sensitivity and insulin resistance are two aspects of the same coin, meaning that decrease the body sensitivity to insulin means presence of insulin resistance. Whereas insulin resistance is harmful to the body health, insulin sensitivity is advantageous[5]. Vitamin D deficiency can be the reason for imbalance of glucose and also can play a role in insulin resistance as well as the.

T2DM pathogenesis, via its impacts on both β-cell function and insulin sensitivity. It was found that vitamin D deficiency could affect insulin resistance throughout different mechanisms involving the increase in related pro-inflammatory cytokines as well as acute phase reactants. So, correction of VD3 levels help in regulation of insulin secretion from the pancreatic beta cells[8]. This results disagree with the results of Tee garden & Donkin[9] who found that serum concentration of VD3 status, has been related with improved glucose homeostasis and increased insulin sensitivity. The supposed effect of VD3 on insulin sensitivity might be via increasing the muscle mass that could enhance the insulin sensitivity within whole body.

Nag pal et al.[10] has revealed that VD3 supplementation could possibly affect the peripheral insulin sensitivity.

Numerous studies have revealed the effect of VD3 supplementation on glucose homeostasis. It was revealed that insulin resistance appeared to be diminished in patients with T2DM who had received VD3. Gagnon et al.[11] showed an improvement in insulin sensitivity by increasing the concentration of 25 (OH)D in serum.

In the present study, a significant negative correlation was found between VD3 and fasting blood sugar (FBS) as (p-value = 0.041) indicating that VD3 deficiency is significantly correlated to increasing the fasting blood glucose levels which helps in predicting T2DM. The findings of this study agree with the findings by Mackawy & Badawi, have detected a significant negative correlation between vitamin D levels and FPG (p-value=0.036), insulin levels and HOMA-IR (pvalue=0.563)[12].

Table (2) and Fig (2) show the mean of VDBP in studied group . There was non significant difference between C and IS patient group (0.47±0.255), (0.394±0.14),p-value (0.152) respectively . AS well as there was significant difference between C and IR patient group (0.47±0.255), (0.582±0.226),p-value (0.050), also there was highly significant difference between IS and IR patient group (0.394±0.14), (0.582±0.226), p-value (0.001).

Identification of VDBP levels in serum is valuable in understanding the diabetic state[13]. Fawzy & Beladi[14] have studied the correlation between circulating VD3, DBP, and VDR expression and the diabetic nephropathy severity in a group of Saudi population with T2DM. It was found that serum levels of VDBP were significantly increased in the whole patient groups.

Ashraf et al.[15] have conducted a study to investigate relations between the total, free, as well as the bioavailable 25(OH) D and vitamin DBP in addition to evaluating the correlations of vitamin VDBP with insulin resistance indicators. From that study, it was suggested that concentrations of VDBP were controlled by total 25(OH)D levels for maintaining suitable concentrations of bioavailable 25(OH)D. Also, there was an inverse correlation between VDBP concentrations and insulin resistance.

Table (2) and Fig (2) show the mean of VDR in

studied group . There was significant difference between C and IS patient group (2.082±0.975), (1.644±0.394), p-value (0.026) respectively . On the other hand there was non significant difference between C and IR patient group (2.082±0.975), (1.905±0.772), p-value (0.979), While there was significant difference between IS and IRpatient group (1.644±0.394), (1.905±0.772), p-value (0.024) respectively.

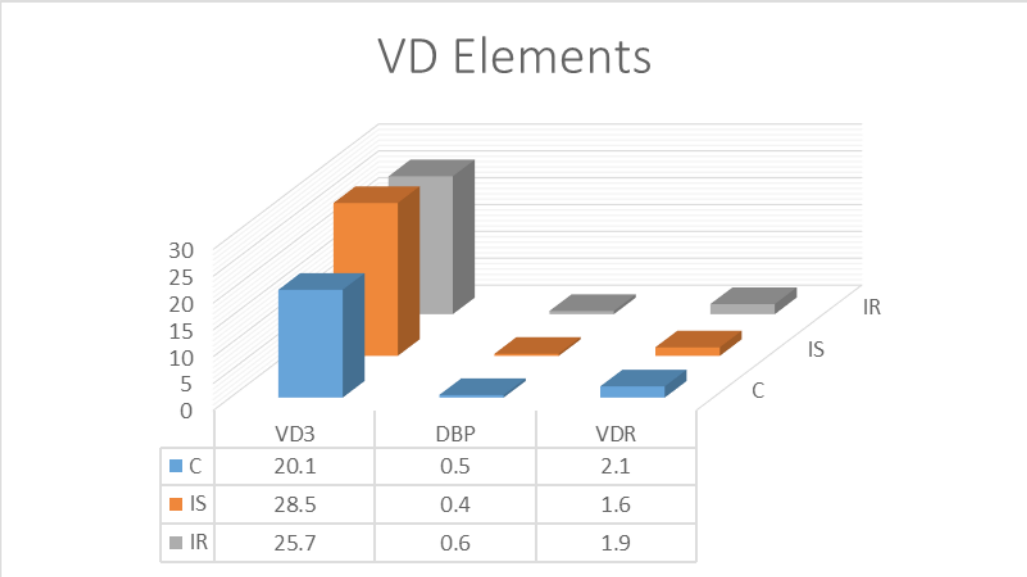

Figure (2) VD3 in studies group

Similarly, there was statistically significant differences between the means of HOMA-IR according to C group, IS group, and IR group = (1.231±0.409, 2.058±0.527, and 3.65±1.229, respectively) and p-value for all = (0.000).

The assesses of HOMA-IR as well as fasting insulin were found to be reduced with high levels of 25(OH) D[16]. The findings of this study have revealed a negative correlation between HOMA-IR and VD 3, although it was non-significant (p-value= 0.563). The findings of the current study agree with chun et al [17] who has conducted a study on Chinese people with T2DM, and he found a negative correlation of IR and the related biomarkers with 25(OH)D status. Similarly, an inverse correlation of IR with 25(OH)D concentration has been detected for values of 25(OH)D between (16-36) ng/ mL[17].

Correlation between parameters: There was positive non significant correlation between VD3 with VDBP (p-value=0.318),also there was positive non significant correlation between VD3 with VDR (p-value=0.432),Also there was negative significant correlation between VD3 with FBS (p-value=0.036), Aswell as negative non significant correlation between VD3 with HOMA-IR(p-value=0.563), On the other hand there was positive non significant correlation between VD3 with insulin (p-value=0.276).

Table (3) Correlation between vitamin D3 and different parameters:

Item		VD3	DBP	VDR	FBS	HOMA-IR	Insulin
VD3	Pearson Correlation	1	.108	.085	-.223*	-.062-	.117
	Sig. (2-tailed)		.318	.432	.036	.563	.276
	N	88	88	88	88	88	88
DBP	Pearson Correlation	.108	1	.771**	-.027-	.424**	.743**
	Sig. (2-tailed)	.318		.000	.801	.000	.000
	N	88	88	88	88	88	88

Item		VD3	DBP	VDR	FBS	HOMA-IR	Insulin
VDR	Pearson Correlation	.085	.771**	1	-.088-	.368**	.737**
	Sig. (2-tailed)	.432	.000		.415	.000	.000
	N	88	88	88	88	88	88
FBS	Pearson Correlation	-.223*	-.027-	-.088-	1	.722**	-.049-
	Sig. (2-tailed)	.036	.801	.415		.000	.648
	N	88	88	88	88	88	88
HOMA-IR	Pearson Correlation	-.062-	.424**	.368**	.722**	1	.598**
	Sig. (2-tailed)	.563	.000	.000	.000		.000
	N	88	88	88	88	88	88
Insulin	Pearson Correlation	.117	.743**	.737**	-.049	.598**	1
	Sig. (2-tailed)	.276	.000	.000	.648	.000	
	N	88	88	88	88	88	88

Conclusion

From this study, it is concluded that, there is a relation between VD3 either alone or with its elements as VDBP and VDR, play a significant role in regulation of blood sugar levels particularly related to insulin sensitivity.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

Conflict of Interest: The authors declare that they have no conflict of interest.

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Reference

1. Dilaveris P, Antoniou CK, Manolakou P, Tsiamis E, Gatzoulis K, Tousoulis D. Biomarkers associated with atrial fibrosis and remodeling. Current Medicinal Chemistry. 2019 Feb 1;26(5):780-802.
2. Bastaki A. Diabetes mellitus and its treatment. International journal of Diabetes and Metabolism. 2005 Jan 1;13(3):111.
3. Lotfy M, Adeghate J, Kalasz H, Singh J, Adeghate E. Chronic complications of diabetes mellitus: a mini review. Current diabetes reviews. 2017 Feb 1;13(1):3-10.
4. Asif M. The prevention and control the type-2 diabetes by changing lifestyle and dietary pattern. Journal of education and health promotion. 2014;3.
5. Nakashima A, Yokoyama K, Yokoo T, Urashima M. Role of vitamin D in diabetes mellitus and chronic kidney disease. World journal of diabetes. 2016 Mar 10;7(5):89.
6. Espes D, Martinell M, Carlsson PO. Increased circulating betatrophin concentrations in patients with type 2 diabetes. International journal of endocrinology. 2014 Oct;2014.
7. Szymczak-Pajor I, Śliwińska A. Analysis of association between vitamin D deficiency and insulin resistance. Nutrients. 2019 Apr;11(4):794.
8. Gorska-Ciebiada M, Ciebiada M. Association of hsCRP and vitamin D levels with mild cognitive impairment in elderly type 2 diabetic patients. Experimental Gerontology. 2020 Mar 17:110926.
9. Teegarden D, Donkin SS. Vitamin D: emerging new roles in insulin sensitivity. Nutrition research reviews. 2009 Jun;22(1):82-92.
10. Nagpal J, Pande JN, Bhartia A. A double-blind, randomized, placebo-controlled trial of the short-term effect of vitamin D3 supplementation on insulin sensitivity in apparently healthy, middle-aged, centrally obese men. Diabetic Medicine. 2009 Jan;26(1):19-27.
11. Gagnon C, Daly RM, Carpentier A, Lu ZX, Shore-Lorenti C, Sikaris K, Jean S, Ebeling PR. Effects of combined calcium and vitamin D supplementation on insulin secretion, insulin sensitivity and β-cell function in multi-ethnic vitamin D-deficient adults at risk for type 2 diabetes: a pilot randomized, placebo-controlled trial. PloS one. 2014 Oct 9;9(10):e109607.

12. Mackawy AM, Badawi ME. 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 Dec 1;2:540-56.
13. Wang Y, Shi H, Jiang S, Zhao J. Changes in serum and urine vitamin D binding protein concentrations in type 2 diabetes. Chinese Journal of Endocrinology and Metabolism. 2015 Jan 1(7):592-5.
14. Fawzy MS, Beladi FI. Association of Circulating Vitamin D, VDBP, and Vitamin D Receptor Expression with Severity of Diabetic Nephropathy in a Group of Saudi Type 2 Diabetes Mellitus Patients. Clinical laboratory. 2018 Oct 1;64(10):1623.
15. Ashraf AP, Huisingh C, Alvarez JA, Wang X, Gower BA. Insulin resistance indices are inversely associated with vitamin D binding protein concentrations. The Journal of Clinical Endocrinology & Metabolism. 2014 Jan 1;99(1):178-83.
16. Fawzy MS, Abu AlSel BT. Assessment of vitamin D-binding protein and early prediction of nephropathy in type 2 saudi diabetic patients. Journal of diabetes research. 2018 Apr 3;2018.
17. Chun RF. New perspectives on the vitamin D binding protein. Cell biochemistry and function. 2012 Aug;30(6):445-56.