Association of serum vitamin D level with glycemic control in patients with type 2 diabetes mellitus

Dler Anwer Kakil[1]*   Mohammed Qader Meena[2]

Abstract

Background and objective: Vitamin D deficiency appears to be related to the development of diabetes mellitus type 2 and metabolic syndrome. This study aimed to assess the association between the level of 25-hydroxy vitamin D{25(OH)D$_3$ and the glycemic control in patients with type 2 diabetes.

Methods: This case-control study involved 240 participants divided into two groups, 119 patients with type 2 diabetic mellitus and 120 healthy individuals as a control group. The study was conducted in Layla Qassim Diabetic Center in Erbil from March 2018 to March 2019. The data were collected from all the cases, including history and physical examination, using a specially designed questionnaire. From all cases, blood was taken, and samples were sent to the laboratory for serum vitamin D3 level estimation.

Results: From the total of 240 participants, the mean age of cases was 54.04 ± 10.56 years and of controls was 53.12 ± 9.84 years. The mean serum vitamin D3 level of the cases was 9.21 ± 5.69ng/ml, and it was non-significantly (P = 0.3) higher than the control (8.61±4.57)ng/ml. Both groups were within the vitamin D deficient range. Vitamin D level was non-significantly deficient in 84 (70.6%) of diabetic patients compared to 89(73.6%) of control. There was a non-significant difference in vitamin D level in poorly controlled diabetic patients compared to well-controlled diabetic patients (P = 0.584).

Conclusion: No significant association was detected between vitamin D level and glycemic control.

Keywords: Type 2 diabetes mellitus; Vitamin D3 level; Glycemic control.

Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors.[1] The prevalence of type 2 DM is rising much more rapidly, presumably because of increasing obesity, reduced activity levels as countries become more industrialized, and the aging of the population.[2] Understanding the pathogenesis of type 2 diabetes is complicated by several factors, including various degrees of insulin resistance and relative insulin deficiency, and both likely contribute to type 2 diabetes. Furthermore, each clinical feature can arise through genetic or environmental influences, making it difficult to determine the exact cause in an individual patient.[3] Vitamin D is a fat-soluble vitamin. Very few foods naturally contain vitamin D (fatty fish livers are the exception). Dermal synthesis is the major natural source of the vitamin. Vitamin D from the diet or dermal synthesis is biologically inactive and requires enzymatic conversion to active metabolites. Vitamin D is converted enzymatically in the liver to 25-hydroxyvitamin D (25[OH]D), the major circulating form of vitamin D, and then in the kidney to 1,25-dihydroxy vitamin D, the active form of vitamin D.[4] Overt

[1] Erbil Directorate of Health, Erbil, Iraq.
[2] Department of Internal Medicine, College of Medicine, Hawler Medical University, Erbil, Iraq.
* Correspondence: dler.dr@yahoo.com

vitamin D deficiency, characterized by hypocalcemia and/or hypophosphatemia, rickets, osteomalacia in children, and osteomalacia in adults, is now uncommon in most developed countries. However, subclinical vitamin D deficiency occurs even in developed countries and is associated with osteoporosis, increased risk of falls, and possibly fractures. Vitamin D stores decline with age, especially in winter. In temperate areas, the cutaneous production of vitamin D virtually ceases in winter. Thus, identification and treatment of vitamin D deficiency are important for musculoskeletal health and possibly even extraskeletal health, including the immune and cardiovascular systems.[1] In addition to its role in calcium and bone homeostasis, vitamin D potentially regulates many other cellular functions. The vitamin D receptor (VDR) is nearly universally expressed in nucleated cells. Approximately 3 percent of the human/mouse genome is under the control of 1,25-dihydroxy vitamin D, the active form of vitamin D. Furthermore, at least ten tissues outside the kidney express 1-alpha-hydroxylase (*CYP27B1*), the active hormone can be generated in an auto- or paracrine way. Thus, the spectrum of activity of the vitamin D endocrine system is much broader than calcium/bone homeostasis. In this regard, the vitamin D-VDR system resembles that of other ligands of nuclear receptors, such as thyroid hormone.[5] Vitamin D status is lower in individuals with obesity and type 2 diabetes. However, the causality of this relationship is unknown. A large genetic study of more than 40,000 individuals showed that higher body mass index (BMI) (and the genes that predispose for obesity) decreases serum 25(OH)D levels. In contrast, lower 25(OH)D levels (or the genes that are associated with reduced serum concentration of 25[OH]D) have, at most, very small effects on obesity.[6] However, in a meta-analysis of 23 trials evaluating the effect of vitamin D supplementation on glycemia, there was no effect of supplementation on glycemia (19 trials) or measures of insulin resistance (12 trials).[7] Vitamin D sufficiency is estimated by measuring 25-hydroxyvitamin D (25[OH]D or calcidiol) concentrations. The range of common agreement of optimal of serum 24(OH) D is 30 to 40 ng/mL (75 to 100 nmol/L), and levels lower than 20 ng/mL are suboptimal for skeletal health. The optimal serum 25(OH)D concentrations for extraskeletal health have not been established.[8] This study aimed to estimate vitamin D status among patients with type 2 diabetes and determine the relationship between low 25(OH) D levels and the marker of glycaemic control, HbA1c in Erbil city.

Methods

This study is a case control study conducted in adults with type 2 diabetes mellitus (DM) attending Layla Qassim Diabetic center in Erbil from March 2018toMarch2019. The controls were collected in the same place from relatives or who accompanied the patients. Consecutive 119 patients with type-2 diabetes mellitus and comparable 121 healthy subjects with no diabetes mellitus were enrolled in this study. Exclusion criteria were those with acute complications, comorbidities affecting HbA1c and vitamin D level, and pregnant ladies. For diagnosis of DM, we depended on the American Diabetes Association (ADA) criteria that affirmed by EASD (European Association for the Study of Diabetes), and WHO, which include the following: {FPG at or above 126 mg/dL (7.0 mmol/L), A1C ≥6.5 percent (48 mmol/mol), a two-hour value in an OGTT at or above 200 mg/dL (11.1 mmol/L), or a random (or "casual") plasma glucose concentration ≥200 mg/dL (11.1 mmol/L) in the presence of symptoms}.[9] Data were collected by interviews with diabetic and non-diabetic persons about socio-demographic characteristics, such as age, sex, resident, and marital status. Closed end questions were asked about diabetes, including date

of diagnosis, family history, type of diabetes, comorbidities, and whether the cases were indoors or not. The serum HbA1c level was measured by using high-performance liquid chromatography. Diagnosis of vitamin D deficiency was made according to the American Geriatric Society [AGS]) which suggests that a minimum normal level of vitamin D is 30 ng/mL (75 nmol/L), mild to moderate deficiency 10-30 ng/ml and sufficient and severe deficiency <10 ng/ml.[10] Biochemical blood measurement (serum concentration of 25(OH) D) was measured by enzyme linked immunosorbent assay (ELISA) method.

Ethical considerations:
This study was approved by the research ethics committee of the College of Medicine, Hawler Medical University. Verbal consent was obtained from all patients and normal groups in this study after a careful explanation of the study

and the procedures. Data were kept confidential, and access was restricted only to the researchers of the study.

Data Analysis:
The data analysis was performed with the statistical package for the social sciences (version 19.0). Chi-square and independent t-test were used for comparison between groups and variables. A P value of <0.05 was considered statistically significant.

Results

A total of 240 persons were recruited for this study, including 119 patients with type 2 diabetic patients and 121 healthy individuals served as controls. The mean age of diabetics was 54.04 ± 10.56 years, and that of the control group was 53.12 ± 9.84 years, which did not differ significantly (P = 0.2). Both groups did not differ significantly regarding sex distribution, as shown in Table 1.

Table 1: Basic characteristics of patient and control.

Characteristics	Diabetes (n = 119) No. (%)	Control (n = 121) No. (%)	*P* value
Gender			
Male	49 (41.2)	50 (41.3)	0.300
Female	70 (58.8)	71 (58.6)	
Age			
< 40	12 (10.1)	13 (10.7)	0.100
40-65	(59.7)	73 (60.3)	
> 65	36 (30.3)	35 (28.9)	
Mean Age	54.04 ± 10.56	53.12 ± 9.84	0.200
BMI *			
Normal	13 (10.9)	27 (22.3)	0.038
Overweight	36 (30.3)	26 (21.5)	
Obesity	70 (58.8)	68 (56.2)	
Mean BMI	31.98 ± 6.46	30.07 ± 6.04	0.019
Occupation			
Indoor	106 (89.1)	113 (93.4)	0.237
Outdoor	13 (10.9)	8 (6.6)	
Mean FBS	194.29 ± 62.29	92.84 ± 7.44	<0.001
Mean HbA1c	9.32 ± 2.14	4.96 ± 0.33	<0.001
Vitamin D			
Sufficiency	4 (3.4)	4 (3.3)	0.869
Insufficiency	31 (26.1)	28 (23.1)	
Deficiency	84 (70.6)	89 (73.6)	
Mean vitamin D	9.21 ± 5.69	8.61 ± 4.57	0.365

Although statistically not significant, the majority of both diabetic patients and control were obese (70% vs. 68%, respectively). Of the diabetic patients, 89% had an indoor lifestyle compared to 93% of the control group (*P* = 0.237). The mean vitamin D level was 9.2 ng/ml in the diabetic group compared to 8.6 ng/ml in the control group with no significant differences. The prevalence of vitamin D insufficiency and deficiency was equal in both cases and controls. No statistically significant differences were found in vitamin D level for age and sex, as shown in Table 2. The serum vitamin D level was not statistically significantly different for patients with poor glycemic control compared to that of fair and good glycemic control. Also, a non-significant difference in vitamin D levels was noticed (*P* = 0.051) in obese patients (65%) compared to normal BMI (25%).

Discussion

Our study did not find significant differences in vitamin D level neither between diabetics and control groups nor with glycemic controlled diabetic patients, and those were not controlled or poorly controlled patients. The prevalence of low vitamin D levels may be increasing globally.[11] In a systemic review of vitamin D status in different regions of the world, vitamin D levels <20ng/ml were prevalent in the majority of the regions studied.[12] Data from National Health and Nutrition Examination Survey (NHANES) in the United States showed a decrease in mean 25(OH)D concentrations from 30 to 24 ng/ml between surveys in 1988 and 2004 and from 24 to 19.9 ng/ml between 2004 and 2006. Factors such as changes in milk intake, use of sun protection, and body mass index (BMI) also contributed to the decline in vitamin D level.[13] In this study,

Table 2: Serum vitamin D level in diabetic patients.

Variable		Vitamin D ng/ml			*P* value
		Sufficient	**Insufficient**	**Deficient**	
HbA1c	<7	0 (0)	8 (32)	17 (68)	0.584
	7-9	3 (5.8)	14 (26.9)	35 (67.3)	
	≥10	1 (2.4)	9 (21.4)	32 (76.2)	
Age group	<40 y	0 (0)	1 (8.3)	11 (91.6)	0.256
	40-65 y	2 (2.81)	23 (32.39)	46 (64.78)	
	>65 y	2 (5.5)	7 (16.6)	27 (75)	
Gender	Male	2 (4.08)	15 (30.6)	32 (65.3)	0.570
	Female	2 (2.85)	16 (22.85)	52 (74.28)	
Occupation	Indoor	4 (4.1)	29 (30.2)	73 (76.04)	0.464
	Outdoor	0 (0)	2 (15.38)	11 (84.61)	
BMI*	<25	1 (7.69)	3 (23.07)	9 (69.23)	0.051
	25-29	2 (5.55)	15 (41.66)	19 (52.77)	
	≥30	1 (1.42)	13 (18.57)	56 (80)	

*Body Mass Index

we found that the majority (>90%) of the patients and control had low vitamin D status 24(OH) D concentration <25 ng/dl. Such a high prevalence of low vitamin D status is worth mentioning. It is favorably comparable to the studies done showing that low vitamin D level was progressively increasing in recent years as compared to previous years.[13] In addition, both patients and control groups had relatively similar and non-significant differences regarding the low level of vitamin D. Two important risk factors for low vitamin D status that present in both patients and control groups are poor sun exposure and overweight with obesity. The majority of cases and control groups were indoors and had high BMI. Kift et al. found that sun exposure prevents winter vitamin D deficiency in 95% of healthy white adult and 83% of adoescents.[14] Some studies have shown a strong and inverse relationship between sun exposure and vitamin D level.[15,16] As overweight and obesity share between patients and control, Reis assessing the USA population found that low 25(OH)D levels were strongly associated with overweight status and abdominal obesity (*P* for trend <0.001 for both).[13] Also, the evaluation of blood vitamin D concentration 24 hours after whole-body irradiation showed that the incremental increase in vitamin D was 57% lower in obese than in non-obese subjects.[18] The remarkable observations from this study were that, although there are differences in the low level of vitamin D results among normal and high BMI, the differences were statistically non-significant. This means that low vitamin D level raised non-significantly in normal weight people, whether diabetics or not. The same observation was true regarding differences of low vitamin D level among age difference in diabetic and control groups. These observations were explained and supported by NHANES data that vitamin D deficiency progressively increased due to lack of sun exposure, decrease intake, and obesity.[14] This was supported by a study done in Duhok for 337 diabetic patients showing that among the different age groups, gender, and different BMI groups, the prevalence of low vitamin D levels was not significant compared to those of sufficient levels.[16] In this study, if we take notice of the level of vitamin D in diabetic patients in comparing controlled and non-controlled blood sugar by estimating HbA1c, there is a non-significant difference in the level of vitamin D in controlled blood sugar and uncontrolled blood sugar even severe high blood sugar elevation (i.e., HbA1c >10) in spite of differences. This result does not correspond with other few studies that there is an inverse relationship between vitamin D level and severe hyperglycemia that patients with poor glycemic control had a higher prevalence of low vitamin D status.[16-18] However, some studies did not find a relation between type 2 diabetes and vitamin D deficiency. For example, Wang et al. conducted a survey in east China from 2014 to 2016 on 10,338 and 10,655 participants having diabetes and vitamin D-related genotyping information. The survey concluded no causal association between vitamin D and type 2 diabetes and pre-diabetes using a bidirectional MR approach in the Chinese population.[19] Pittas et al. also failed to prevent type 2 diabetes by giving vitamin D supplement to 2423 prediabetes participants, and after a median follow up of 2.5 years, the primary outcome of diabetes occurred in 293 participants in the vitamin D group and 323 in the placebo group (9.39 and 10.66 events per 100 person-years, respectively).[20] In a meta-analysis of 23 trials evaluating the effect of vitamin D supplementation on glycemia, there was no effect of supplementation on glycemia (19 trials) or measures of insulin resistance (12 trials).[21] Numerous epidemiological studies and meta-analyses have indicated a link between vitamin D insufficiency/ deficiency and type 2 diabetes and metabolic syndrome. However, raising the prevalence of low vitamin D levels

in normal people and vitamin D supplementation did not demonstrate an improvement effect in obesity, glucose, and lipid metabolism in any of these illnesses.

Conclusion

There is no significant association between low vitamin D level and type -2- diabetes mellitus or its glycemic control.

Competing interests

The authors declare no competing interests.

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