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RESEARCH ARTICLE

ASSESSMENT OF VITAMIN D IN EGYPTIAN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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Abstract

Objective: To study vitamin D status in patients with type 1 diabetes mellitus (T1DM) and to investigate any factors associated with vitamin D deficiency in these patients.

Patients and Methods: This study included 130 patients with T1DM diagnosed according to American Diabetes Association (ADA) criteria, and 40 healthy non-diabetic. Age and sex matched subjects served as a control group. All participants were subjected to full history taking, thorough clinical examination and laboratory investigations including fasting and 2-hour postprandial plasma glucose, HbA1c, serum calcium, inorganic phosphorus, magnesium, total alkaline phosphatase, liver and kidney function tests, and urinary albumin to creatinine excretion ratio. Serum parathormone (PTH) and 25-hydoxyvitamin D levels were also measured.

Results: Serum level of 25(OH) vit D (25-hydroxyvitamin D) was significantly lower in T1DM patients than controls **(**23.8 ± 13.4 vs 32.9 ± 15.7 ng/mL). Also, diabetics had significantly higher serum PTH than controls **(**54.7 ± 26.5 vs 41-9 ± 24.5 pg/mL**)**. The association between vitamin D status and HbA1c was significant (P <0.05) with HbA1c levels of 7.9 ±2.2, 9.3±2.3, and 10.7±2.8 for categories of vitamin D sufficiency, insufficiency, and deficiency respectively. There were more cases with vitamin D deficiency and insufficiency amongst patients with diabetes-related complications, but the association was not significant (P >0.05).

Conclusion: Vitamin D deficiency and insufficiency are common in T1DM and are associated with worse glycemic control. Therefore, assessment of vitamin D status in all patients with T1DM is recommended.

INTRODUCTION

Rates of type 1 diabetes mellitus (T1DM) are increasing all over the world. In Europe, the Middle East, and Australia, rates of T1DM are increasing by 2-5% per year. Scandinavia has the highest prevalence rates for T1DM (approximately 20% of the total number of people with DM), while China and Japan have the lowest prevalence rates, with less than 1% of all people with diabetes. The incidence of childhood T1DM varies based upon geography, age, gender, and family history[1].

In Egypt, T1DM incidence and prevalence are increasing. It was found that, in Egypt, T1DM is higher in females and more cases are found to originate from rural areas[2].

Type 1 diabetes mellitus (T1DM) results from autoimmune destruction of the insulin-producing beta cells in the islets of Langerhans[3]. This process occurs in genetically susceptible subjects, is probably triggered by one or more

environmental agents, and usually progresses over many months or years during which the subject is asymptomatic and euglycemic[4].

Many studies have linked several environmental factors to an increased risk of type 1 diabetes. They include: viral infections, immunizations, diet, especially exposure to cow's milk at an early age, vitamin D deficiency and perinatal factors[5].

The well-recognized role of vitamin D on skeletal homeostasis is mediated by the binding of vitamin D to its receptor (VDR), a member of the nuclear receptor superfamily. VDR has a wide distribution, essentially in all tissues and cells in the body, extended the potential role of vitamin D on a variety of non-skeletal functions. These include modulation of the immune response, regulation of cellular proliferation and differentiation, as well as regulation of insulin secretion and action. Vitamin D deficiency is now being recognized as one of the most common medical conditions worldwide. Vitamin D has been reported to have a variety of non-skeletal actions. Evidence suggests a role for vitamin D in the pathogenesis and prevention of diabetes mellitus[6]. Multiple components in the metabolic pathway of vitamin D may be altered in T1DM and, collectively, have the potential to influence disease pathogenesis[7].

The present study was carried out to investigate vitamin D status in patients with T1DM and to examine any factors associated with vitamin D deficiency in these patients.

PATIENTS AND METHODS

The present study included 130 T1DM diagnosed according to American Diabetes Association (ADA) criteria[8]. Patients were collected from those attending the Outpatient clinic of Endocrinology, Zagazig University Hospitals in the period from March 2014 to January 2015. It also included 40 healthy non-diabetic age and sex matched subjects served as a control group.

Exclusion criteria:

- Therapy with corticosteroids, vitamin D or calcium during the previous 6 months.
- Current smoking.
- History of bone fractures during the previous year.

Written consents were obtained from all patients and controls and the study was approved by the local ethics committee.

All participants were subjected to complete history taking, thorough clinical examination. Patients' blood sugar and HbA1c profiles, and evidence of ischemic heart disease (history, ECG, documented cardiac investigations) were reviewed. During Clinical examination, special emphasis was put on signs of diabetic neuropathy, nephropathy, retinopathy, and cardiac diseases. Dilated fundus examination by an ophthalmologist was done. Patients with complications were defined according to ADA criteria.

Laboratory investigations:

Routine investigations were performed using autoanalyzer methods (Hitachi 736-15, Tokyo, Japan) to measure serum calcium, inorganic phosphorus, magnesium, total alkaline phosphatase, liver and kidney functions tests. Morning urine samples were used for determination of urinary albumin to creatinine excretion ratio.

Serum PTH concentration was estimated using immunoenzymetric assay (ELISA) developed by Diagnostic Products Corporation, 5700 West 96th Street, Los Angeles, CA. HbA1c level was measured with high-performance liquid chromatography standardized to the DCCT using assay developed by Stanbio Laboratory, 1261 North Main Street, Boerne, TX

Serum 25-hydoxyvitamin D level was determined using 25-OH Vitamin D EIA Kit, an assay developed by **Immundiagnostik, Bensheim and Biomedica, Wien**, is a competitive protein binding assay for the measurement of 25-OH Vitamin D (e.mail: Info@immundiagnostik.com,www.Immundiagnostik.com). The criteria used to define vitamin D sufficiency, insufficiency, and deficiency were 25OHD levels ≥30 ng/mL, from 10 to<30ng/mL, and <10 ng/mL, respectively.[9]

Statistical Analysis:

All the data were managed using SPSS-version version 20.0 (released August 16, 2011 by IBM Corporation; Website: http://www01.ibm.com/software/analytics/spss). A two-sided P value of less than 0.05 was considered to indicate statistical significance.

The association between categorical data was tested by chi-square and fisher exact tests. The Pearson Chi-square was used as a test for significance of the relationship between categorical variables (e.g. deficiency, insufficiency,

and sufficiency of 25(OH) vit D in cases and controls). Fisher's exact test is a statistical significance test that was used in the analysis of contingency tables where sample sizes were small.

The t-test was used to assess whether the means of two groups were statistically different from each other (compare cases and controls regarding biochemical variables).To compare between more than two groups, ANOVA was used.

Continuous data were categorized according to their normal levels. Pearson correlation (r) was done between continuous variables (age, duration of DM, BMI, HbA1c,). The Pearson correlation coefficient was used as a measure of the correlation (linear dependence) between two variables, giving a value between +1 and −1 inclusive.

RESULTS

Table (1): Demographic data of the studied groups

There are non-significant differences between the two groups regarding age, sex and BMI (P >0.05).

Table (2): Laboratory findings of the studied groups

There are non-significant differences between diabetic patients and controls regarding biochemical variables except for 25(OH) vit D, PTH, plasma glucose, and HbA1c**.**

Table (3): Comparison between the studied groups according to vitamin D status

Vitamin D deficiency and insufficiency are significantly higher in diabetic patients than in controls (P <0.05).

Table (4): Correlation between the level of 25(OH) vit D and age, duration of DM, BMI and HbA1c in T1DM patients

There are negative correlations between vitamin D status and age, duration of DM BMI, and HbA1c but the correlation is statistically significant only in the case of HbA1c .

Table (5): Relation between vitamin D status and laboratory findings in T1DM patients

The association between vitamin D status and biochemical characteristics is significant in relation to HbA1c and PTH (P value <0.05) but non-significant in relation to other biochemical findings (P value>0.05).

Table (6): Relation between vitamin D status and diabetes - related complications in T1DM patients

There is an association between vitamin D status and the presence of individual diabetes - related complications. There are more cases with vitamin D deficiency and insufficiency amongst patients with complications, but the association is non-significant (P >0.05).

Table (1): Demographic data of the studied groups

Variable		**Patients No (130)**	**Controls No (40)**	**t-test**	**P value**
Age (years): (Mean ± SD)		23.2±7.6	22.8 ± 7.2	0.34	>0.05
Sex	**Male** **Female**	62 68	19 21	———	———
Duration of DM (years) (Mean ± SD)		11.7 ± 9.3	———	———	———
BMI kg/m^2 (Mean ± SD)		20.8 ± 5.9	21.2 + 5.8	0.28	>0.05

Table (2): Laboratory findings of the studied groups

Variable	Patients No (130) mean ± SD	Controls No (40) mean ± SD	t-test	P value
Calcium(mg/dL)	8.8 ± 0.97	9.2±0.84	1.02	>0.05
Phosphorus(mg/dL)	3.8 ± 1.14	4.1±0.93	0.79	>0.05
Total Alkaline phosphatase (IU/L)	138.7 ± 85.7	131.5± 89.8	0.46	>0.05
Magnesium (mg/dL)	1.94 ± 0.56	1.87 ± 0.49	1.36	>0.05
Parathormone (pg/mL)	54.7 ± 26.5	41-9 ± 24.5	2.32	<0.05
25(OH)vitamin D(ng/mL)	23.8 ± 13.4	32.9 ± 15.7	2.76	<0.05
Total cholesterol (mg/dL)	192.1 ± 19.7	187.6 ± 28.3	1.06	>0.05
LDL- cholesterol (mg/dL	112.8 ± 25.8	109.6 ± 24.9	0.22	>0.05
HDL- cholesterol (mg/dL)	49.2 ± 9.4	51.3 ± 11.9	0.73	>0.05
Triglycerides (mg/dL)	151.1 ± 21.1	149.2 ± 17.1	0.55	>0.05
Urinary albumin to creatinine ratio	21.9 ± 15.3	18.2±12.7	1.33	>0.05
Fasting plasma glucose (mg/dl)	183.7 ± 61.6	87.6± 12.9	7.75	<0.05
2-hour postprandial plasma glucose (mg/dl)	245.9 ± 60.6	153.1± 28.4	8.09	<0.05
HbA1c	9.7 ± 2.9	5.6 ± 1.3	8.74	<0.05

Table (3): Comparison between the studied groups according to vitamin D status

25(OH) vitamin D	Patients No (130)	Controls No (40)	Test of significance & P value
• **Deficiency**	**27**	**3**	$X^{2=}12.105$ **(P < 0.05)**
• **Insufficiency**	**71**	**13**	
• **Sufficiency**	**32**	**24**	
Total	**130**	**40**	

Table (4): Correlation between serum level of 25 (OH) vitamin D and age, duration of DM, BMI and **HbA1c in T1DM patients (no=130)**

Variable	25 (OH) vitamin D	
	r	P value
Age	-0.067	>0.05
Duration of DM	-0.045	>0.05
BMI	-0.031	>0.05
HbA1c	-0.402	<0.05

Table (5): Relation between vitamin D status and laboratory findings in T1DM patients (no=130)

Laboratory findings	Vitamin D sufficient (no=32)	Vitamin D insufficient (No=71)	Vitamin D deficient (No=27)	ANOVA test	p value
Calcium (mg/dL)	8.9± 0.91	8.7 ±1.09	8.4±1.03	1.07	>0.05
Phosphorus (mg/dL)	4.1±1.11	3.9±1.13	3.8±1.04	0.86	>0.05
Total Alkaline phosphatase (IU/L)	132.3±86.3	135.5±87.6	141.5±91.2	0.22	>0.05
Magnesium (mg/dL)	2.03±0.42	1.95±0.53	1.90±0.67	0.12	>0.05
Parathormone (pg/mL)	43.2±11.3	52.9±14.5	59.3±15.3	5.64	<0.05
Total cholesterol (mg/dL)	196±20.3	197±19.8	201±20.5	0.78	>0.05
LDL- cholesterol (mg/dL	115.6±25.1	118.7±26.3	121.5±27.3	0.52	>0.05
HDL- cholesterol (mg/dL)	52.7±10.5	49.8±10.2	47.8±9.7	0.19	>0.05
Triglycerides (mg/dL)	134.8±19.6	140.1±18.8	145.7±28.1	0.75	>0.05
Urinary albumin to creatinine ratio	21±18.2	28±21.7	36±25.5	2.86	>0.05
HbA1c	7.2 ±2.6	9.6±3.1	10.9±3.3	5.03	<0.05
Fasting plasma glucose (mg/dl)	170.6± 51	178.4± 48	181.1± 52	0.24	>0.05
2-hour postprandial plasma glucose(mg/dl)	239.5± 55	248.3± 61	259.2±71	0.63	>0.05

Table (6): Relation between vitamin D status and diabetes - related complications in T1DM patients (no=130)

Complications		Deficient & Insufficient No (98)		Sufficient No (32)		P value
		No	**%**	**No**	**%**	
Peripheral Neuropathy	**Present**	16	16.3%	4	12.5%	>0.05
	Absent	82	83.7%	28	87.5%	
Nephropathy	**Present**	21	21.4%	6	18.8%	>0.05
	Absent	77	78.6%	26	81.2%	
Retinopathy	**Present**	13	13.3%	3	9.4%	>0.05
	Absent	85	86.7%	29	90.6%	
Ischemic Heart Disease	**Present**	11	11.2%	2	6.3%	>0.05
	Absent	87	88.8%	30	93.7%	

DISCUSSION

The present work aimed to assess vitamin D status in patients with T1DM and to examine any factors associated with vitamin D deficiency in these patients.

In the present study, it was found that vitamin D deficiency and insufficiency were significantly higher in diabetic patients than in controls. There were significant differences between diabetic patients and controls regarding serum 25(OH) vit D and PTH levels (P value <0.05). 25(OH) vitamin D levels were lower and PTH levels higher in T1DM patients than in controls.

The lower levels of vitamin D in T1DM patients may be explained by the presence of a pre-existing vitamin D insufficiency state preceding the development of T1DM,considering the possible etiologic relationships between the two conditions. Other explanations may include altered dietary habits, or less exposure to sunlight in T1DM patients. Another less likely explanation may be the presence of malabsorptive state in T1DM leading to vitamin D deficiency. The rise in PTH levels is probably a secondary response to decreased vitamin D levels leading to lower calcium levels, which stimulate PTH release by the parathyroids[10].

The results of the present study showed that there were negative correlations between vitamin D status and age, duration of DM, BMI, and HbA1c but significant only in the case of HbA1c (P value <0.05).

The above mentioned findings coincide with a number of studies. A similar study aimed to assess bone status by measurement of PTH and 25(OH) vit D serum levels in children and adolescents with T1DM and its relation to disease duration, puberty stage, and metabolic control was performed. Diabetic patients showed significant increase in PTH levels, while significant decrease in Calcium, and serum 25(OH) vit D levels. As much as 52.8% of patients showed reduced 25(OH)vit D, and 30.65% showed elevated PTH serum levels[11]**.** However, in another study, in adolescents with T1DM, the relationships between metabolic control, bone mineral density (BMD), and bone anabolic and turnover markers were evaluated. There were no differences between HbA1c groups in BMD, or 25(OH) vit D status [12]**.**

The relation between vitamin D status and HbA1c may be explained by the effects of vitamin D on beta cell secretory function, on insulin action, and on systemic inflammation. A less likely explanation is the presence of altered dietary habits, or nutritional status in patients with worse glycemic control. Giving the inconclusive results of the above-mentioned studies on the relation between vitamin D status and HbA1c, it may be concluded that relationship between vitamin D and T1DM may differ in various populations and that the etiopathologic relations may differ in different subsets of T1DM patients[13]**.**

The relationship between vitamin D and T1DM may extend beyond glycemic control, and may involve effects on the development of diabetic complications. In our study, there were more patients with vitamin D deficiency and insufficiency among diabetic patients had complications (16.3% had peripheral neuropathy, 21.4% had nephropathy, 13.3% had retinopathy and 11.2% had ischemic heart disease), but the association between vitamin D status and the presence of individual diabetic complications was found to be insignificant (P value>0.05).

These findings are in agreement with a number of studies that mentioned that T1DM exhibits increased inflammation, which is pronounced with microvascular complications. Patients with T1DM and T1DM-microvascular complications were significantly vitamin D deficient compared with control subjects. There was a significant negative correlation between vitamin D levels and high-sensitivity C-reactive protein i.e. low vitamin D levels may contribute to increased inflammation in T1DM [14,15,16]**.**

A possible explanation of these inconclusive results regarding the relationship between vitamin D status and diabetic complications may be the heterogeneity of our subjects regarding the duration of DM, and the small number of patients with complications. Another explanation may be the initial selection of patients, as subjects taking medications affecting calcium and vitamin D metabolism were excluded.

Early detection and effective treatment of inadequate vitamin D concentrations in persons with diabetes or those at risk for diabetes may be an easy and cost-effective therapy which could improve their long-term health outcomes as well as their quality of life. **Yeshayahu and colleagues**[17] stated that type 1 DM is an independent risk factor for vitamin D deficiency beyond initial diagnosis. They also stated that because adolescence is a critical period of bone loss and progression of diabetic complications, consideration should be given for promotion of a vitamin D fortified diet for patients with type 1 DM.

From the present study, it can be recommended that measurement of vitamin D status should be a part of the routine assessment of TIDM to optimize vitamin D levels in patients with vitamin D deficiency and insufficiency. Vitamin D analogues may have a role to play in the pharmacologic management of DM, or as a preventive therapy in T1DM patients. Large scale prospective studies are needed to determine this role.

REFERENCES

1. **Patterson CC, Dahlquist GG, Gyürüs E, et al:** Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study**.** Lancet **2009**; 373:2027.
2. **El Ziny MA, Salem NA, El Hawary AK, et al:** Epidemiology of childhood type 1 diabetes mellitus in Nile delta and Northern Egypt – A retrospective study. J Clin Res Pediatr Endocrinol 2014, 6 (1):9.
3. **Atkinson MA and Maclaren NK:** The pathogenesis of insulin-dependent diabetes mellitus. N Engl J Med **1994**; 331:1428.
4. **McCulloch DK and Palmer JP:** The appropriate use of B-cell function testing in the preclinical period of type 1 diabetes. Diabet Med **1991**; 8:800.
5. **Hyppönen E, Läärä E, Reunanen A, et al :** Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet **2001**; 358 (9292):1500.
6. **Holick MF:** Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Robert H. Herman Memorial Award in Clinical Nutrition Lecture, 2003. Am J Clin Nutr **2004**; 79:362.
7. **Blanton D,Han Z, Bierschenk L, et al.:** Reduced serum vitamin D-binding protein levels are associated with type 1 diabetes. Diabetes **2011** ; 60 (10): 2566.
8. **American Diabetes Association:** Diagnosis and classification of diabetes mellitus. Diabetes Carevol. **2011**; 34 Supplement 1, S62**.**
9. **Rosen CJ:** Vitamin D Insufficiency. N Engl J Med 2011; 11; 364:248.
10. **Mutu A, Mutu GY,Ozsu E, et al:** Vitamin D deficiency in children and adolescents with type 1 diabetes. J Clin Res Pediatr Endocrinol **2011**;3(4):179 .
11. **Hamed EA, Abu Faddan NH, AbdElhafeez HA, et al:** Parathormone -25(OH)vit D axis and bone status in children and adolescents with type 1 diabetes. Pediatric Diabetes **2011**; 12 (6): 536.
12. **Simmons JH, Raines M, Ness KD, et al:** Metabolic control and bone health in adolescents with type 1 diabetes. Int J Pediatr Endocrinol; **2011** (1):13.
13. **Devaraj S, Yun JM, Duncan-Staley CR, et al:** Low vitamin D levels correlate with the proinflammatory state in type 1 diabetic subjects with and without microvascular complications. Am J Clin Pathol **2011**; 135 (3):429.
14. **Diaz VA, Mainous AG 3rd, Carek PJ, et al:** The Association of Vitamin D Deficiency and Insufficiency with Diabetic Nephropathy:Implications for Health Disparities. J Am Board Fam Med **2009**; 22: 521.
15. **Payne JF, Ray R, Watson DG, et al:** Vitamin D Insufficiency in Diabetic Retinopathy. Endocr Pract. **2011**; 1; 18 (2):185.
16. **Wang TJ, Pencia MJ, Booth SL, et al:** Vitamin D deficiency and risk of cardiovascular disease. Circulation **2008**; 117:503.
17. **Yeshayahu Y, Sochett EB, Deda L, et al:** Type 1 diabetes as a risk factor for impaired vitamin D status in a multi – ethnic cohort of Canadian adolescents. Canadian Journal of Diabetes 2012, 36(6):314.