Open Journal of Endocrine and Metabolic Diseases, 2013, 3, 137-143
http://dx.doi.org/10.4236/ojemd.2013.32021 Published Online May 2013 (http://www.scirp.org/journal/ojemd)

Vitamin D Status in Saudi Patients with Type 1 Diabetes Mellitus

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Received January 7, 2013; revised February 6, 2013; accepted March 6, 2013

ABSTRACT

Aims/Introduction: There are studies in different countries regarding the prevalence of vitamin D deficiency in non diabetic population. Few studies were done in adults with type 1 diabetes mellitus. This study was conducted to determine Vitamin D Status among Saudi patients with type 1 diabetes and to correlate the associated environmental risk factors. **Materials and Methods:** A cross-sectional single centre study was conducted in 221 Saudi patients with type 1 diabetes mellitus. These patients were recruited through the Diabetes Centre at King Fahad Armed Forces Hospital between January 2008 and June 2009. 25-hydroxy-vitamin D, Parathyroid hormone, calcium, phosphate and alkaline phosphatase were measured. **Results:** There were 221 patients with type 1 diabetes mellitus, 92 males (42%) and 129 females (58%). The mean age was 21.3 ± 7.2 and the mean diabetes duration was 7.5 ± 5.7. The frequency of 25-hydroxyvitamin D < 50 nmol/l and <25 nmol/l were 97% and 60% respectively. The frequency of 25-hydroxyvitamin D < 25 nmol/l was significantly more frequent in female. 67% were either only exposed face or totally covered. Duration of sun exposure in 64% was less than 30 minutes per day. The area of skin exposed and duration of sunlight exposure associated significantly with Vitamin D levels ($p < 0.0001$ and $p < 0.0001$ respectively). Age was associated with more vitamin D < 25 nmol/l (the odds ratio (95% confidence interval); 4.8 (4.6,14.5), p = 0.005; 5.3 (1.8,15.5), p = 0.003; 3.9 (1.5,10.5), p = 0.007 for age groups 12 - 15, 16 - 19 and 20 - 24 years old consequently. Male gender and exposing face, arms and legs to sun were associated with vitamin D ≥ 25 nmol/l; the odds ratio (95% confidence interval); 0.27 (0.11,0.6), p = 0.001; 0.26 (0.09,0.75), p = 0.01 consequently. **Conclusions:** Prevalence of vitamin D deficiency in patients with type 1 diabetes mellitus is high. We recommend to create awareness to increase sunlight exposure and high intake of vitamin D rich food at mass level and starting of Vitamin D food fortification program at government level.

Keywords: Type 1 Diabetes Mellitus; Vitamin D Deficiency; Frequency

1. Introduction

Type 1 Diabetes mellitus is thought to be the consequence of an autoimmune destruction of the insulin producing beta cell as a result of interactions between different susceptibility genes and environmental exposure [1]. The increasing incidence of type 1 diabetes mellitus strongly suggests the importance of environmental factors; the major factors being pursued incude diet and viruses [2]. Serum 25-hydroxyvitamin D (25(OH)D) concentrations are largely determined by environmental factors, mainly through vitamin D intake and ultraviolet exposure. The sun is the primary source of vitamin D, which is synthesized endogenously in the skin to produce cholecalficerol (vitamin D3), although a small proportion (<20%) of vitamin D comes through diet from a limited range of foods (in the form of ergocalciferol [vitamin D2] and vitamin D3) [3]. The main marker of vitamin D status is the metabolite 25(OH)D, which is synthesized in the liver [3,4]. Deficiency of Vitamin D remains a major health problem in many parts of the world [3]. The relationship between type 1 diabetes mellitus and vitamin D deficiency has been reported to be 15% to 90.6% [4-11]. Studies from Saudi Arabia in a cohort of subjects without history of diabetes mellitus showed high prevalence of vitamin D deficiency ranging from 21.9% to 81% among children and adolescents school girls respectively [12,13]. We conducted a cross sectional study to define Vitamin D Status and the associated environmental risk factors in young patients with type 1 diabetes mellitus.

2. Materials and Methods

A cross-sectional single centre study was conducted in

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221 patients with type 1 diabetes mellitus. These patients were recruited randomly through the Diabetes Centre at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia between January 2008 and June 2009. Eligible patients were older than 12 years old, had type 1 diabetes mellitus [1]. Exclusion criteria were known hepatic or renal disease, metabolic bone disease, malabsorption, hypercortisolism, malignancy, immobility for more than one-week, pregnancy, lactation, and medications influencing bone metabolism. All the patients gave their or their guardian informed consent prior to their inclusion. The study was approved by the ethical board of King Fahad Armed Forces Hospital. The subjects were asked to complete a questionnaire at the time of inclusion. The questionnaire included details of duration of exposure to sun light in previous month (less than 30 minutes/more than 30 minutes/day), clothing (exposure of hand and face or more than). In order to quantify the level of vitamin D and calcium consumption in the previous month, a dietary products frequency was assessed through the intake of dietary products as daily, twice per week or none. Furthermore study subjects were not able to recall quantity of vitamin D containing foodstuff taken by them. Due to these limitations exact estimation of dietary intake of vitamin D was not possible. Any vitamin D or calcium formulation intake was recorded. Height and weight were measured at this stage. Body mass index (BMI) was calculated as weight (kilograms) divided by height squared (square meters). Their health status was assessed by medical conditions, family history, BMI, past or present clinical manifestations, 25(OH)D, Calcium, phosphorus, magnesium, alkaline phosphatase, glycosylated hemglobin, Parathyoid hormone, analysis. The serum level of 25(OH)D was measured by competitive protein binding assay using kits (Immunodiagnostic, Bensheim, Germany). Vitamin D deficiency was defined as serum 25-OHD levels <50 nmol/L while a level <25 nmol/L was defined as severe vitamin D deficiency [3]. Glycosylated hemglobin was measured using the high performance liquid chromatography. The serum levels of calcium, phosphate. Magnesium and alkaline phosphatase activity were measured using routine laboratory methods to get additional information about vitamin D status.

Statistical Analysis

Unpaired t-test was employed to compare single parameters between groups. Chi square (X^2) test were used for categorical data comparison. For the correlations between environmental factors and vitamin D deficiency, multivariate regression analyses was performed to adjust potential confounders. We fit regression model by specifying full models with potential effect modifiers and confounding variables (age, diabetes duration, BMI, HbA1c, body parts exposed to sun, duration of sun exposure, intake of diary products and vitamin D or calcium. All statistical analyses were performed using SPSS Version 17.0. All p values were based on two-sided tests. The difference between groups was considered significant when $p < 0.05$.

3. Results

There were 221 patients with type 1 diabetes mellitus, 92 male (42%) and 129 female (58%). The mean age was 21.3 ± 7.2 and the mean diabetes duration was 7.5 ± 5.7. 25-hydroxyvitamin D < 50 nmol/l and <25 nmol/l were found in 97% and 60% respectively, **Table 1**. **Figure 1** showed the frequencies of various levels of vitamin D. 25-hydroxyvitamin D < 25 nmol/l was significantly more frequent in female than male, 77% vs. 37%, $p < 0.0001$, **Table 2**. When outdoor most of them either only exposed face or totally covered (67%). Duration of sun exposure in majority was less than 30 minutes (64%). Regarding dietary habits most of the participants consumed food good in diary products (52%) whereas almost all of them are taken vitamins (97%), **Table 3**. Area of skin exposed and duration of sunlight exposure associated significantly with Vitamin D levels < 25 nmol/l ($p < 0.0001$ and $p < 0.0001$ respectively), **Figure 2**.

Multivariate regression analyses was performed to adjust potential confounders (age, diabetes duration, BMI, HbA1c, body parts exposed to sun, duration of sun exposure, intake of diary products and vitamin D or calcium),

Table 1. Patient characteristics.

Parameters		Values
Numbers		221
Male/female (n (%))		92 (42)/129 (58)
Age (years)		21.3 ± 7.2
Body mass index (Kg/m^2)		18.8 ± 4.6
Diabetes duration (years)		7.5 ± 5.7
Calcium (2.2 - 2.6 mmol/L)		2.3 ± 0.2
Phosphorus (0.8 to 1.4 mmol/l)		1.3 ± 0.3
Magnesium (0.69 - 0.94 mmol/l)		0.8 ± 0.1
Parathyroid hormone (1.3 - 7.6 pmol/l)		5.8 ± 5.1
Alkaline phosphatase (30 - 115 U/liter)		136.0 ± 96.2
Glycosylated hemoglobin		9.4 ± 2.3
25-hydroxyvitamin D level (n (%))	<25 (nmol/L)	133 (60)
	<50 (nmol/L)	214 (97)

Data are presented as mean ± standard deviation with normal laboratory values between brackets.

Table 2. Results between vitamin D level groups.

Parameters	25-hydroxyvitamin D levels (nmol/L)		p values
	<25	≥25	
Numbers (%)	133 (60)	88 (40)	
Male/female (%)	37/77	63/23	<0.0001
Age (years)	20.6 ± 6.4	22.3 ± 8.2	0.09
Body mass index (Kg/m^2)	18.9 ± 4.7	18.7 ± 4.5	0.8
Diabetes duration (years)	7.8 ± 5.9	7.2 ± 5.5	0.5
Calcium	2.3 ± 0.2	2.3 ± 0.1	0.9
Phosphorus	1.3 ± 0.3	1.3 ± 0.3	1.0
Magnesium	0.8 ± 0.1	0.8 ± 0.1	0.5
Parathyroid hormone	6.4 ± 5.5	6.1 ± 9.2	0.03
Alkaline phosphatase	138.2 ± 100.5	132.6 ± 89.4	0.7
Glycosylated hemoglobin	9.4 ± 2.2	9.5 ± 2.5	0.9

Data are presented as mean ± standard deviation.

Table 3. Relation of age, sun exposure and dietary habits to vitamin D level < 25 nmol/l in males and females Saudi patients with type 1 diabetes mellitus represented as percentage.

Parameters		Gender			p
		Total	Male	Female	
Age (years)	12 - 15	27	45	77	0.01
	16 - 19	22	44	77	0.03
	20 - 24	25	45	80	0.009
	>25	26	19	73	<0.0001
Body parts exposed to sun	Face, arms & legs	13	71	29	0.08
	Face & arms	20	35	65	0.02
	Face only or total coverage	67	14	86	0.002
Duration of sun exposure	>30 min/day	36	35	77	<0.0001
	<30 min/day	64	45	77	0.007
Diary products	Daily intake	52	33	70	<0.0001
	Twice per week	32	36	83	<0.0001
	None	16	50	89	0.04
Sea food	Daily	2	67	0	1.0
	Twice weekly	29	44	77	0.01
	None	69	31	77	<0.0001
Vitamins	Yes	98	36	77	<0.0001
	No	2	50	50	1.0
Drugs	Yes	98	36	77	<0.0001
	No	2	67	33	1.0

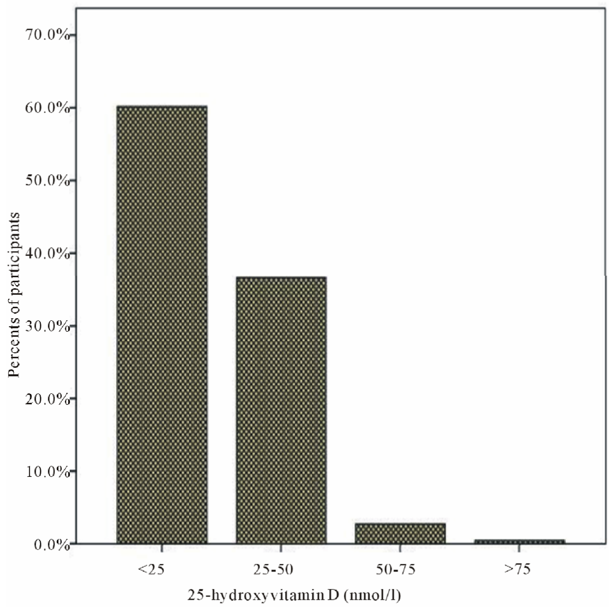

Figure 1. Frequency of variable Vitamin D levels (nmol/l).

age was associated with more vitamin D < 25 nmol/l (the odds ratio (95% confidence interval); 4.8 (4.6, 14.5), p = 0.005; 5.3 (1.8, 15.5), p = 0.003; 3.9 (1.5, 10.5), p = 0.007 for age groups 12 - 15, 16 - 19, and 20 - 24 years old consequently. Male gender and exposing face, arms and legs to sun were associated with vitamin D ≥ 25 nmol/l; (the odds ratio (95% confidence interval); 0.27 (0.11, 0.6), p = 0.001; 0.26 (0.09, 0.75), p = 0.01 consequently.

4. Discussion

Studies in non diabetic population have shown high prevalence of vitamin D deficiency ranging from 44% - 95% [14-23]. A most important finding is that the frequency of vitamin D deficiency was higher among type 1 diabetes mellitus subjects (97%) in Saudis residing in Jeddah despite abundant sunlight throughout the year. It is of importance to state that the sample size is representative for a number of subjects suffering from type 1 diabetes mellitus in the area and study population of one diabetic centre does not represent the entire city of Jeddah, in addition the study sample confined to patients with type 1 diabetes but without comparable groups. A number of studies from different regions of the world have highlighted the high prevalence of vitamin D deficiency in children with type 1 diabetes mellitus. Greer *et al.* in Australia, found a three-times higher risk of having levels below 20 ng/ml in adolescents with newly diagnosed diabetes than in the controls [7]. Another study from Italy examined 25(OH)D levels in 88 children newly diagnosed with type 1 diabetes mellitus and 57 healthy age- and sex-matched controls. Levels of both 25(OH)D were significantly lower in the diabetic adolescents [10]. A recent study from Boston measured 25(OH)D levels in 128 children with established and newly diagnosed type 1 diabetes mellitus. A total of 24% had levels above 75 nmol/L, but 61% had levels between 52 to 72 nmol per liter and 15% were deficient (<50 nmol/L) [24]. Bener *et al.* compared 25(OH)D levels in 170 age-, race- and sex-matched type 1 diabetes mellitus cases and healthy controls in Qatar, a region with ample sunshine all year round. There was a high prevalence of deficiency/insufficiency (<75 nmol/L) in both the groups (90.6 vs 85.3%), but it was significantly higher in the diabetic children [9]. Janner *et al.*, Of the 129 children and adolescents with type 1 diabetes mellitus, 78 (60.5%) were vitamin D deficient, defined as a 25-hydroxy-vitamin-D level below 50 nmol/L [25].

In contrast, 25D levels were usually above 50 nmol/L in young adults at diagnosis of type 1 diabetes mellitus in Sweden [11]. These overall differences might be explained by the variability of geographical environment, the age of the subjects, duration of diabetes, glycaemic control [24].

The effect of sunlight on Vitamin D status has been well documented and confirms the importance of sunlight exposure in the synthesis of vitamin D [26,27].

Sunlight exposure was the most important determinant of Vitamin D levels in the study population. The area of skin exposed and duration of sunlight exposure associated significantly with Vitamin D levels (p < 0.0001 and p < 0.0001 respectively) in this study as shown similarly by other studies [14,16,19,22,23,28]. As dark skin requires more sun exposure than less pigmented skin to produce similar amount of vitamin D [26], it is not surprising that hypovitaminosis D is so prevalent in this country. Avoidance of sun light due to fear of darkening of skin and covering of whole body religiously or the only exposing face and hands traditionally in female patients when going outdoor were the main attributing factors. Male patients may avoid sun exposure as misconception regarding harmful effects of sunlight and unawareness regarding the source of Vitamin D.

Dietary factor was another determinant of the study regarding high prevalence, the history of Vitamin D rich food and use of calcium and Vitamin D supplements among study subjects were not enough to minimize the high prevalence but some previous studies [14-20] showed no such association whereas other studies [22,23] showed significant correlation. In addition, the true estimation of vitamin D intake was not possible owing to unawareness regarding quantity of consuming diet by participants.

Recent studies have shown that body mass index and body fat content are inversely related to serum 25(OH)D levels and directly related to PTH levels [29-32], which

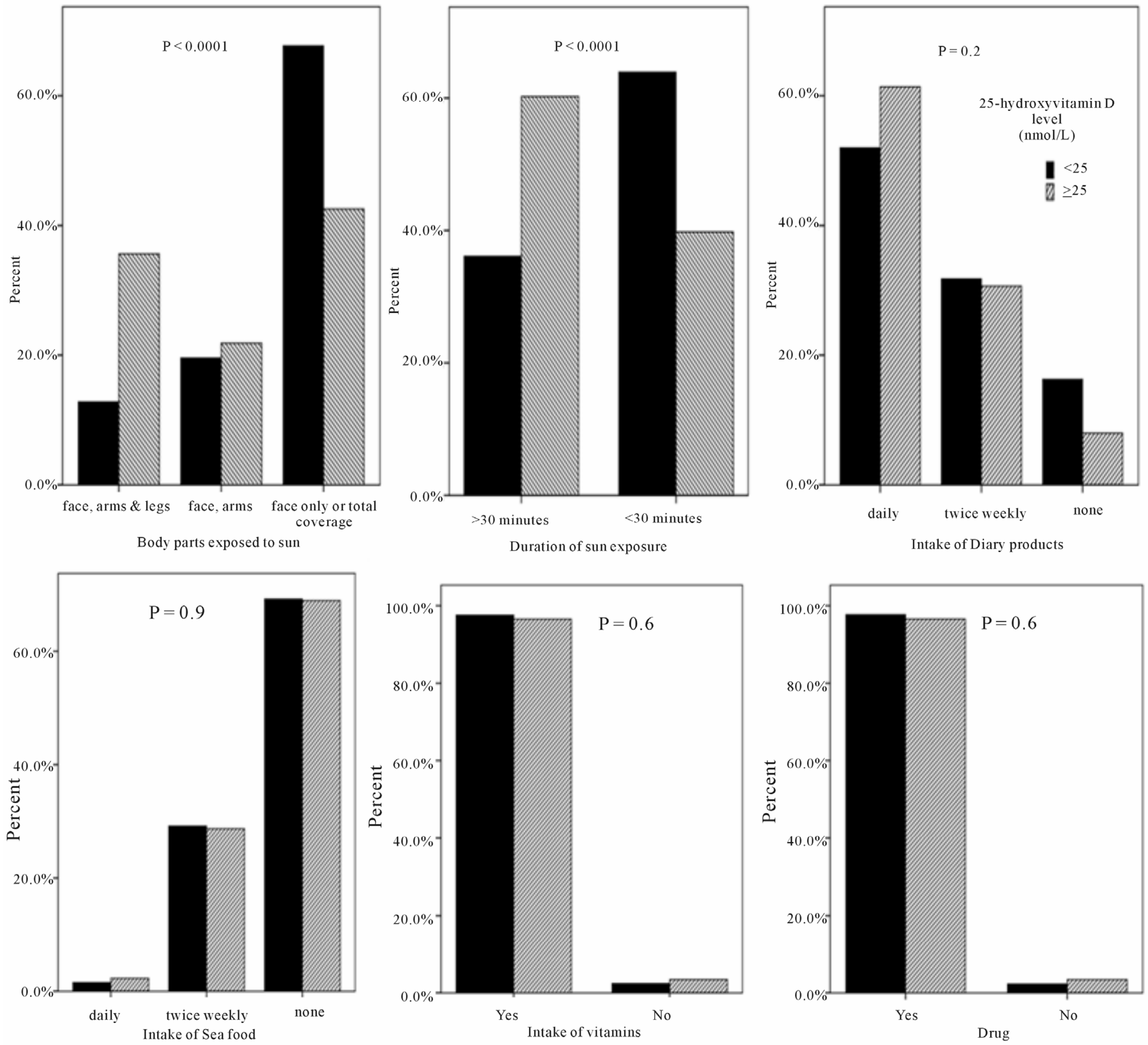

Figure 2. Relation of age, sun exposure and dietary habits to vitamin D level.

is likely due to vitamin D sequestration in body fat compartments. Even slight vitamin D deficiency results in secondary hyperparathyroidism and increased bone resorption [33,34]. In adults, PTH levels are expected to rise steeply above 40 pg/ml at 25 D levels below 50 nmol/L and above 50 pg/ml at 25 D levels below 25 nmol/L [35]. We have two possible explanations why PTH levels did not show the expected rise in diabetics. First, the PTH-vitamin D axis has a blunted response in diabetic patients, a finding supported by several studies [36,37]. In one study a blunted response of PTH was associated with low magnesium levels and corrected after magnesium repletion [38]. Our patients, however, did not show any magnesium depletion. A blunted response of PTH would result in inadequately normal PTH levels with low ionised calcium. However, we did not find differences in calcium levels between vitamin D deficient groups.

Limitation of the study: We had several limitations. The study was done at only one centre and was done at one point of time. The study sample confined to patients with type 1 diabetes but without comparable groups. Duration of sun exposure was based on recall rather than actual. We were not able to calculate the daily dietary intake of vitamin D due to several reasons.

In conclusion, Prevalence of vitamin D deficiency in patients with Type 1 diabetes is high. We recommend to create awareness to increase sunlight exposure and high intake of vitamin D rich food at mass level and starting of Vitamin D food fortification program at government level.

5. Acknowledgements

There is no any financial support or relationships that may pose conflict of interest.

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