International Journal of Chinese Medicine
2017; 1(3): 108-112
http://www.sciencepublishinggroup.com/j/ijcm
doi: 10.11648/j.ijcm.20170103.16

25-Hydroxyvitamin D_3 Deficiency and Dyslipidemia in Type 2 Diabetic Subjects

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To cite this article:

Azhar Memon, Muhammad Atif Ata, Shumaila Shaikh, Haji Khan Khoharo. 25-Hydroxyvitamin D_3 Deficiency and Dyslipidemia in Type 2 Diabetic Subjects. *International Journal of Chinese Medicine*. Vol. 1, No. 3, 2017, pp. 108-112. doi: 10.11648/j.ijcm.20170103.16

Received: February 12, 2017; **Accepted**: April 13, 2017; **Published**: July 11, 2017

Abstract: The present Observational study was conducted to estimate the 25-hydroxyvitamin D_3 deficiency and its association with dyslipidemia in type 2 Diabetes mellitus subjects at the Department of Medicine, Isra University Hospital and Consultant Clinics Hyderabad from January 2014 to July 2014. A sample of 310 diagnosed type 2 DM were selected through non-probability purposive sampling according to inclusion and exclusion criteria. Serum 25-OH-D_3 was estimated by ARCHITECT I 1000 system. Lipids sub fractions were analyzed according to standard methods. Data was analyzed on SPSS version 21.0. Data was analyzed on SPSS version 21.0. Continuous and categorical variables were analyzed by student's t test and chi square test respectively. The associations of various lipid fractions with vitamin D_3 were analyzed by Pearson's correlation. The significant p-value was taken at ≤ 0.05. Reduced 25-hydroxyvitamin D_3 levels were observed in 84.1% (n = 261). The 25-hydroxyvitamin D_3 levels as low as 6ng/dl was observed in present study. The lipid profile status of subjects with normal and reduced 25-hydroxyvitamin D_3 showed significant differences ($p = 0.001$). Triglycerides, LDLc, VLDLc, and Cholesterols exhibited an inverse correlation with 25 hydroxyvitamin D_3; however a positive correlation was noted for HDL cholesterol. In conclusion, the vitamin D_3 deficiency was observed in type 2 diabetic subject and showed independent association with dyslipidemia in type 2 diabetics.

Keywords: 25-Hydroxyvitamin D_3, Dyslipidemia, Diabetes Mellitus, Sindh

1. Introduction

The rising prevalence of vitamin D deficiency is estimated as 50% for the worldwide population and 2%–30% for the European adults [1]. The prevalence of 25-hydroxyvitamin D_3 deficiency is approximated to 30% to 50% in the general population [2]. 25-hydroxyvitamin D_3 is a sensitive indicator of total body vitamin D status of an individual as it accounts for most of the circulating vitamin D [3]. Approximately > 95% of circulating vitamin D exists as the 25-hydroxyvitamin D_3. The 25-hydroxyvitamin D_3 provides a good estimate of dietary and skin related vitamin D supply. Recently, the 25-hydroxyvitamin D_3 has taken much attention in the disease process. A previous study reported the 36% vitamin D_3 deficiency in asymptomatic adults and 57% in adults presenting at the medical outpatient departments in the USA [4]. In the USA, Vitamin D_3 deficiency is now recognized as an "epidemic" [5]. European population have similar prevalence of vitamin 25-hydroxyvitamin D_3 deficiency. A previous report from Australia reported 1 out of 3 showed the vitamin D_3 deficiency [6]. Previous studies from Pakistan have reported high prevalence of vitamin D_3 deficiency [7-9]. The problem of vitamin D_3 deficiency has reached an epidemic in the country and exact epidemiological data is lacking, but reported studies have found high prevalence [7-9]. The health problem of vitamin D_3 is highly overlooked by the health authorities. The problem of vitamin D_3 deficiency is further aggravated by lack of knowledge of public and poor awareness of the mass to handle the how to maintain required level of vitamin D_3 in the body [7-9]. Association of vitamin D_3 deficiency has been reported with disease process such as

the atherosclerosis [10], obesity [11], diabetes [12], hypertension [13, 14], myocardial infarction [15], and brain stroke [16]. Vitamin D_3 deficiency has been linked to the dyslipidemia which is an independent risk of atherosclerosis related cardiovascular and cerebrovascular disease [17, 18]. Few of recent studies [19, 20] have reported the association of vitamin D_3 deficiency and the dyslipidemia. The present study was conducted to estimate the burden of 25-hydroxyvitamin D_3 deficiency and association with dyslipidemia in type 2 diabetic subjects as very limited data are available in the country.

2. Subjects and Methods

A prospective case control study was conducted at the Department of Medicine, Isra University, and Hyderabad from January-July 2014. A sample of 310 subjects was selected through non-probability purposive sampling according to well delineated inclusion and exclusion criteria. Volunteer diagnosed type 2 diabetics of 20-50 years were included in the study protocol. Diabetics with renal failure, taking vitamin D_3 supplements and diuretic drug intake were excluded.

2.1. Vitamin D Levels

The normal, insufficiency and deficiency of Vitamin D_3 were defined as; normal levels (> 30ng/dl), vitamin D_3 insufficiency (20-30ng/dl) and vitamin D_3 deficiency (< 20ng/dl).

2.2. Systemic Hypertension

Hypertension was defined (Joint National Committee VII) as a systolic blood pressure > 140mmHg and/or a diastolic blood pressure > 90mmHg based on the average of 2 blood pressure measurements or a patient's self-reported history of hypertension or antihypertensive use. Patients with fasting plasma sugar more than 110mg/dL were considered as diabetic [21].

2.3. Dyslipidemia

Dyslipidemia was defined (ATP III) as one or more of the following: total cholesterol more than 200mg/dL, low density lipoprotein-cholesterol (LDL-C) more than 130mg/dL, high-density lipoprotein-cholesterol (HDL-C) below 40mg/dL, very low density lipoprotein-cholesterol (VLDL-C) more than 30mg/dL, and triglycerides more than 150mg/dL.

2.4. Lipid Estimation

The serum which was obtained was pipetted into a clean blood sample bottle and analyzed on the day of collection for serum sugar and lipid profile tests. Serum total cholesterol was determined by an enzymatic (CHOD-PAP) colorimetric method and triglycerides were determined by an enzymatic (GPO-PAP) method. HDL-Cholesterol was estimated by a precipitant method and LDL-Cholesterol by was estimated by using Friedewald's formula as; LDL-C = TC - HDL-C – (TG/5).

2.5. Glucose Estimation

Serum glucose was determined by using the glucose oxidase enzymatic method [22].

2.6. Vitamin D Estimation

The blood was centrifuged at 4000rpm for ten minutes and serum obtained was frozen at -20°C. The serum was used for estimation 25-hydroxyvitamin D_3. The vitamin D_3 was measured by ARCHITECT I 1000 system for estimation of 25-OH- D_3 tem from blood sera.

Alcoholics were defined as those in whom the alcohol consumption was > 50 g/day (equivalent to 500mL [2 drinks] of wine, 1000mLof beer, or more than 5 drinks [units] of spirits) [23]. Body mass index (BMI) values more than 30 kg/m^2 were considered as obese [24]. Smokers were defined as those reporting daily smoking. Non-smokers were defined as occasional smokers and ex-smokers [25]. Five ml of fasting venous blood sample was drawn from ante-cubital vein. Informed written consent was taken from the participants. Study was approved by the ethics committee of the institute. The data was recorded on a pre-structured proforma.

2.7. Statistical Analysis

Data was analyzed on SPSS version 22.0. Continuous and categorical variables were analyzed by student's t test and chi square test respectively. The associations of various lipid fractions with vitamin D_3 were analyzed by Pearson's correlation. The significant p-value was taken at ≤ 0.05.

3. Results

The present study was conducted at the Department of Medicine, Isra University Hyderabad, Sindh, Pakistan. A sample of 310 type 2 diabetics adults were selected and studied for 25-hydroxyvitamine D_3, dyslipidemia and their association. The demographic baseline characteristics of study population are shown in table 1. Mean ± S. D age of study subjects noted was 49 ± 9.7years. The mean ± S. D of 25-hydroxyvitamin D_3 was found at 31.20 ± 8.30 ng/dl (CI 24.90-39.41). The mean ± S. D values of normal, insufficient and deficient vitamin D_3 subjects are shown in table 2 (p-0.001). Overall reduced 25-hydroxyvitamin D_3 was observed in 84.1% (n = 261). The 25-hydroxyvitamin D_3 levels < 6 ng/dl were observed in the present study. The lipid profile status of subjects with normal and reduced 25-hydroxyvitamin D_3 showed significant differences as shown in table 3. Odds ratio analysis of 25-hydroxyvitamin D_3 with risk factors dyslipidemia, diabetes mellitus and hypertension are shown in table 4. Pearson's correlation showed strong association of triglyceride, total cholesterol, LDLc, VLDLc and low HDLc with 25-hydroxyvitamin D_3 deficiency, when compared to subjects with normal 25-hydroxyvitamin D_3 levels. Triglycerides, LDLc, VLDLc, and Cholesterols

exhibited an inverse correlation between 25 hydroxyvitamin D_3; however positive correlation was noted for HDL cholesterol. The correlation co-efficient and p-value are shown in table 5.

Table 1. *Demographic characteristics of type 2 diabetic study subjects (n = 310).*

Age	49 ± 9.7 years
Male	197 (63.5%)
Female	113 (36.4%)
Rural population	118 (38%)
Urban population	192 (61.9%)
Obesity	147 (47.4%)
Hypertension	231 (74.5%)
Dyslipidemia	215 (69.3%)
Smokers	119 (38.3%)
Postprandial blood glucose (mg/dl)	253 ± 61.5
BUN (mg/dl)	17 (5.4%)
Serum creatinine(mg/dl)	215 (69.3%)

Table 2. *25-hydroxyvitamin D_3 in type 2 diabetic subjects (n = 310).*

	Normal levels (>30ng/dl)	Insufficiency (20-30 ng/dl)	Deficiency (<20ng/dl)	p-value
No (%)	49 (15.8%)	60 (19.3%)	201 (64.8%)	0.001
Mean ± S. D	35.5 ± 0.9	25.17 ± 1.7	13.8 ± 5.7	0.0001

Table 3. *Lipid profile of type 2 diabetic subjects (n = 310).*

	Normal 25-OH-D_3	Reduced 25-OH-D_3	p-value
Triglycerides (mg/dl)	132.9 ± 45.7	214.1 ± 110.7	0.03
Total cholesterol (mg/dl)	158.3 ± 25.9	201.1 ± 44.9	0.001
HDLc (mg/dl)	39.9 ± 8.5	33.5 ± 9.47	0.035
LDLc (mg/dl)	96.3 ± 19.6	116.6 ± 39.3	0.001
VLDL (mg/dl)	41 ± 14	27 ± 9	0.001
Alkaline phosphatase (iu)	97.9 ± 11.9	119.7 ± 7.6	0.001
Serum calcium (mg/dl)	8.8 ± 1.9	7.1 ± 1.5	0.001
Serum phosphorus (mg/dl)	2.6 ± 0.9	2.4 ± 0.8	0.01
Postprandial blood glucose (mg/dl)	217.7 ± 45.9	251.9 ± 31.1	0.001

Table 4. *Odds ratio analysis of 25-hydroxyvitamin D_3 and risk factors.*

	Univariate analysis		Multivariate analysis	
Risk factors	OR*	95%CI	OR*	95%CI
Dyslipidemia	2.5	1.4-5.1	1.8	1.2-3.5
Diabetes mellitus	1.4	0.7-2.6	0.7	0.4-1.2
Hypertension	1.3	0.6-2.8	0.9	1.2-3.4

*Odds ratio

Table 5. *Correlation of 25-hydroxyvitamin D_3 with lipid fractions (n = 310).*

	Correlation co-efficient (r)	p-value
Triglycerides (mg/dl)	-0.36	0.03
Total cholesterol (mg/dl)	-0.40	0.002
HDLc (mg/dl)	0.405	0.03
LDLc (mg/dl)	-0.37	0.001
VLDL (mg/dl)	-0.29	0.001

4. Discussion

The Present study demonstrated overall reduced 25-hydroxyvitamin D_3 in 84.1% in type 2 diabetes mellitus which are consistent with previous report from Pakistan which has reported 77.5% vitamin D deficiency and additional 18% of insufficiency, but are contrary to other previous reports [26-28]. The study showed that 87% pregnant women were having Vitamin D_3 deficiency, 10% were having Vitamin D_3 insufficiency while only 3% had normal levels [29]. Another study from Karachi in 305 premenopausal females, showed 90.1% vitamin D_3 deficiency [30]. There are many factors which contribute to the vitamin D_3 deficiency in general population worldwide. These factors include reduced exposure to sunlight, age-linked reduction in sunlight induced skin synthesis, and intake of food with a reduced vitamin D_3 level. Vitamin D_3 deficiency is a new global epidemic among both children and adults [31, 32]. There are some evidences which confirm the association of vitamin D_3 deficiency with high possibility of other morbidities such as diabetes mellitus, cardiovascular illness, and malignancy, particularly of the intestine and prostate [33, 34]. Present study observed no significant relationship of low 25-hydroxyvitamin D levels with alcoholism, smoking and hypertension. The mean serum glucose level was significantly higher in subjects with low 25- hydroxyvitamin D. The Cigolini et al [35] reported that subjects with low 25-hydroxyvitamin D were more significantly associated with type 2 diabetes compared to controls as well as higher levels of HbA1c. Previous studies [13, 35, 36] have also found association of hypo 25-hydroxyvitamin D with impaired fasting glucose, risk of type 2 diabetes mellitus, and hypertension. The present study showed a similar frequency of deficiency of 25-

hydroxyvitamin D_3 in both male and female genders. Similar findings have been reported from Pakistan [37] and India [26]. However, controversial results are also reported which have shown higher frequency of vitamin D_3 deficiency in female [38]. The mean alkaline phosphatase was elevated (119.7 ± 7.6) in diabetic subjects with low 25-hydroxyvitamin D_3 levels, this parallels to the fact that as vitamin D3 decreases, the bone resorption in increases. The findings match with previous studies [1, 26, 39]. The present study observed significantly elevated total cholesterol levels in 25-hydroxyvitamin D deficient type 2 diabetics compared to those with normal levels, the finding is consistent with previous studies [26, 40, 41]. Similar are the observations of HDLc being positively associated with deficient 25-hydroxyvitamin D, the HDLc reduces with reduction in blood 25-hydroxyvitamin D_3, the findings are similar to reported studies [41- 45]. An inverse association of 25-Hydroxyvitamin D_3 levels of < 20 ng/ml was observed for the LDLc and serum triglycerides, findings are similar to previous reported studies [45- 48]. This deficiency raises the question why we do not have sufficient vitamin D_3 from sunlight? or the normal values have to be re-considered. In fact these ranges have been established for western population. The lack of awareness regarding healthy balanced diet and the overcooking of food are a few other contributing factors to the prevailing vitamin D_3 deficiency. A national programme on the supplementation of vitamin D_3 and a public awareness campaign may urgently be launched.

5. Conclusion

The present study reports high frequency of vitamin D_3 deficiency in type 2 diabetic subjects and deficiency was independently associated with dyslipidemia. The association endangers that the 25-hydroxyvitamine D_3 deficiency may add to the vascular complications due to dyslipidemia and vitamin D supplements may prevent them.

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