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Original Research Article

Study of 25 (OH) Vitamin D_3 with Reference to Magnesium and Calcium Status in Type 2 Diabetes Mellitus

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Abstract

Vitamin D (1, 25-dihydroxycholecalciferol, Calcitriol) plays a role in calcium metabolism. Calcium is a recognized second messenger implicated in insulin secretion This explains the indirect role of Vitamin D in insulin secretion and insulin sensitivity. Hence, low Vitamin D levels are implicated in decreased insulin secretion and increased insulin resistance. In this study, we tried to find out the probable association of Vitamin D_3, calcium and magnesium in type 2 diabetes mellitus (T2DM) cases. The levels of 25(OH) Vitamin D_3 in 50 T2DM subjects with 30 age and sex matched healthy controls. Data obtained were statically analysed and the *p*-value was calculated. *p*-value less than 0.05 was considered as significant. The results showed that the levels of 25 (OH) Vitamin-D_3 was significantly low among T2DM cases (13.29±2.42 ng/ml) in comparison to healthy controls (21.55±0.50 ng/ml) ($p<0.001$). The levels of calcium and magnesium were also significantly low in T2DM cases as compared to healthy controls ($p<0.001$). From the present study, it is concluded that there is significant low level of 25 (OH) Vitamin-D_3, calcium and magnesium levels in T2DM.

Keywords

Vitamin D_3
Calcium
Magnesium
Diabetes mellitus

Introduction

Vitamin D is a fat soluble vitamin. Vitamin D (1, 25-dihydroxycholecalciferol; Calcitriol) is essential for normal growth and development. Cholesterol is converted ultimately to 1, 25 Dihydroxychole-calciferol (1, 25 DHCC; Calcitriol). 25-Hydroxy cholecalciferol (25 (OH) Vitamin D3) formed in the liver reflects total Vitamin D status. Vitamin D is also called as "Sunshine vitamin" (Samanek et al., 2006), 7- Dehydrocholesterol is the precursor of Vitamin D which is present in the skin. Upon exposure to UV radiations present in sunlight, cholecalciferol is formed. Vitamin D acts like a hormone and its action is mainly on three target tissues namely kidney, intestine and bone. Vitamin D plays an important role in calcium metabolism and in addition, it has a role in cell differentiation, immune regulation and prevention of neoplastic transformation (Szkandera et al., 2013). These

variegated effects of Vitamin D are attributed to the Vitamin D receptors present on different types of tissues (Vinh Qu et al., 2013). Lesser degree of deficiency or insufficiency may have important implications (Gradinaru et al., 2012).Vitamin D deficiency causes growth retardation, muscle weakness and skeletal deformities and rickets in children is an extreme consequence of Vitamin D deficiency (Nassar et al., 2012).

Low Vitamin D is indicated with higher rates of increased insulin resistance, weight and BMI (body mass index) (Wright et al., 2013). Vitamin D deficiency/insufficiency is a global phenomenon; the deficiency can be found in all age group and ethnicities. While sunlight is an excellent source of Vitamin D, it must be noted that sunscreen, clothing, winter season and skin pigmentation reduces sun exposure of skin to UV rays and ultimately affects Vitamin D synthesis in skin (Engelsen, 2010; Webb, 2006). Vitamin D synthesis requires specific wavelength of sunlight UVB rays (290-310 nm) which is predominantly more during morning hours and in summer days (Guillemant et al., 2001).

Evidences are becoming increasingly available in adults suggesting Vitamin D deficiency in adulthood might be associated with chronic disorders including type 2 diabetes mellitus (T2DM). Calcium is important for insulin secretion and Vitamin D has a role in calcium metabolism (Cangoz et al., 2013). This explains the indirect role of Vitamin D in insulin secretion. Certain experimental studies have depicted that Vitamin D is responsible for glucose induced insulin secretion and improve insulin sensitivity, and exerts anti-inflammatory effect (Talaei et al., 2013). Previous studies have already established an inverse association among Vitamin D status, impaired glucose level and T2DM (Mata-Granados et al., 2008). Low Vitamin D levels are a risk factor for impaired glucose tolerance and T2DM (Wilmot et al., 2013). However, there are limited studies, which have been performed in the region of Puducherry (Southern India), which reflects the Vitamin D status and insulin resistance observed in T2DM.

Hence, in the present study, we evaluated the Vitamin D levels in T2DM subjects and normal healthy controls and examined the association of serum Vitamin D, calcium and magnesium levels.

Materials and methods

This study was conducted at Geetanjali medical college and hospital, Udaipur from may 2014 to November 2014 that included 50 freshly diagnosed cases of T2DM who had visited the outpatient clinics of Geetanjali hospital, Udaipur. The patients were not on any treatment which can affect Vitamin D, magnesium or calcium status. 30 healthy age and sex matched controls were selected from the same population, but without diabetes mellitus, hypertension, cardiovascular, cerebrovascular disorders, hepatic and renal disorders.

Subjects with Vitamin D, calcium or magnesium supplementation or those using sunscreen were excluded from the study. Subjects with renal, hepatic or cerebrovascular disorders or endocrinal disorders, females on estrogen therapy, chronic disorders such as tuberculosis, type 1 diabetes mellitus were also excluded from the study. After considering all exclusion and inclusion criteria, thirty T2DM cases and an equal number of healthy controls were selected for this study.

Biochemical analysis of cardio-metabolic risk factors

Four ml of venous blood sample (fasting) was collected under aseptic precautions from the subjects and controls, following period of overnight fast. Biochemical parameters were analyzed as follows: fasting plasma glucose (analyzed by glucose oxidase and peroxidase method GOD-POD) in Roche cobas c 311 instrument, serum triacylglycerols (Glycerol kinase method), 25(OH) Vitamin D (analyzed by CLIA method by automated chemiluminiscence), serum calcium (by Orthocresolpthalein complexone, OCPC method) and alkaline phosphatase (paranitro phenyl phosphate PAPP method).

Magnesium in serum was assayed by Calmagite indicator method. All the above mentioned biochemical parameters were estimated in roche cobas c 311 fully automated analyzer and roche cobas e 411 immunoassay system instrument.All above samples are analysed along with randox quality control sera. As per ADA criteria, T2DM is confirmed in those having fasting blood glucose above 126mg/dl and postprandial above 200mg/dl,

as performed on two different occasions (Moreno-Pérez et al., 2013). Hypovitaminosis D is defined as that, wherein the levels of 25(OH) Vitamin D3 are below 25ng/ml 25(OH) D3 were measured by automated chemiluminescence (CLIA) method (Wright et al., 2013), BMI was calculated by using formula wt (kg)/ht(m^2). Statistical analysis was done by using online student *t* test calculator. Test of significance was calculated by unpaired student's *t* test between cases and controls. Value $p<0.05$ was considered statistically significant.

Results and discussion

The results of the variables, namely Vitamin D levels, calcium, and magnesium in normal and diabetic cases are shown in (Table 1). 25 (OH) Vitamin D_3 level was significantly low among T2DM cases than healthy controls ($p<0.001$). There is hypovitaminosis D among T2DM cases than healthy controls.

Calcium and magnesium levels were also significantly low in T2DM cases as compared to healthy controls ($p<0.001$) (Tables 1 and 2). Similarly fasting glucose were significantly high among T2DM cases than healthy controls ($p<0.001$), as shown in (Tables 1 and 2).

In our study, Vitamin D level was significantly low among T2DM than healthy controls ($p<0.001$). There is hypovitaminosis D among T2DM cases than healthy controls. Vitamin D affects the insulin level as well as insulin sensitivity. The presence of Vitamin D receptors on different tissues explains its diversity of action (Gradinaru et al., 2012).

Table 1. Vitamin D, calcium, and magnesium levels in case group (n=50) and control group (n=30).

Parameters	T2DM cases (n=50)	Healthy controls (n=30)
Vit.D level [25 (OH) D_3] (ng/ml)	13.29 ± 2.42	21.55 ± 0.50
Calcium (mg/dl)	8.0 ± 0.77	10.31 ± 0.79
Magnesium (mg/dl)	1.90 ± 0.49	4.41 ± 0.15
Glucose fasting (mg/dl)	115.80 ± 19.60	87.90 ± 1.60

Table 2. Comparison of various parameter between case group (n=50) and control group (n=30).

Parameter	Pair compared	Group	Subjects (No.)	Average	*p*-value
Vit. D level [25 (OH) D_3] (ng/ml)	T2DM cases Vs Healthy controls	T2DM cases	50	13.29	<0.001
		Healthy controls	30	21.55	
Calcium (mg/dl)	T2DM cases Vs Healthy controls	T2DM cases	50	8.0	<0.001
		Healthy controls	30	10.31	
Magnesium (mg/dl)	T2DM cases Vs Healthy controls	T2DM cases	50	1.90	<0.001
		Healthy controls	30	4.41	
Glucose fasting (mg/dl)	T2DM cases Vs Healthy controls	T2DM cases	50	115.80	<0.001
		Healthy controls	30	87.90	

Hence, reduced levels of Vitamin D are associated with insulin resistance and may thus be linked to poor glucose control observed in T2DM patients (George et al., 2012; Ayesha et al., 2001). Our results are consistent with previous reports that depicted the fact that hypovitaminosis D in adults may influence the risk of developing diabetes and metabolic syndrome (Wortsman et al., 2000; Palomer et al., 2008). Vitamin D deficiency as a predisposing factor in the pathogenesis of diabetes mellitus and cardiovascular diseases (Davidson et al., 2013). It is believed that future studies will be really helpful to determine the long term adverse effects of Vitamin D deficiency including poor outcome as observed in diabetic management.

In this study, we obtained a significant negative association between Vitamin D level and DM, independent of other parameters, as obesity and adiposity. We included individuals with only normal BMI (BMI lesser than 30). High BMI and adiposity may affect the levels of Vitamin D by the partly

sequestering action enforced by the adipose tissue (Diaz et al., 2011). Vitamin D is stored in inactive form in liver and adipose tissue. The activation of Vitamin D (hydroxylation reaction) occurs in liver and kidneys and finally gets activated to calcitriol (1,25 DHCC) (Barengolts, 2010). In healthy subjects, Vitamin D deficiency occurs mainly because of low dietary intake and less exposure to sunlight. Low or decreased exposure to sunlight (specifically UV-rays in 290-310 nm wavelength), clothing, decreased outdoor activities, and use of sunscreens also affect the Vitamin D status (Webb, 2006) Seasonal variation also affects the Vitamin D status, mainly in winter (Niranjan et al., 2013; Paolisso et al., 1990).

Certain other causes such as mal-absorption, liver or kidney disorder and obesity also increase the risk for development of Vitamin D deficiency. Obesity is common among T2DM subjects and Vitamin D stored in adipose tissue causes decreased bioavailability (Diaz et al., 2011). This puts obese T2DM subjects at greater risk of developing Vitamin D deficiency (Moreno-Pérez et al., 2013). However, in this study we selected T2DM cases as well as healthy controls with normal BMI. We also observed low magnesium levels in T2DM subjects, as compared to healthy controls.

According to this finding, Vitamin D levels can also affects the magnesium status (Chaudhary et al., 2010). There are already well established facts that low magnesium levels affects glucose metabolism (Rice et al., 2011; Mangukiya and Neha, 2014). Low magnesium levels are related to obesity (Rodriguez and Guerrero, 2011). Obesity is associated with increased oxidative stress and insulin resistance (Guerrero and Rodriguez, 2011). Such a nexus, connecting Vitamin D status in the light of magnesium levels as related to obesity, insulin resistance, and oxidative stress is interesting. Very few reports are available from Southern India and future work needs to be carried out by highlighting the molecular mechanism of Calcitriol action (vis-a-vis) with Vitamin D status (25 hydroxychole-calciferol (Van Meijl et al., 2008)

The isolated reports available in the literature, very few talk about calcitriol role in obesity and insulin resistance with reference to magnesium status (Guerrero and Rodríguez, 2011; Van Meijl et al., 2008). Magnesium is involved in several facet carbohydrate metabolisms including on insulin release and action (Van Meijl et al., 2008). Earlier reports point out that the role of magnesium on insulin resistance is either cause or effect relationship (Chaudhary et al., 2010)

The present study acquired a significant negative correlation between Vitamin D levels and fasting glucose in T2DM subjects. Proper mechanisms linking hypovitaminosis D with increased blood glucose level remains unclear, but there are some supporting studies which indicate that Vitamin D may directly affect pancreatic β-cell secretory functions through nuclear Vitamin D receptors and may affect the insulin sensitivity through insulin receptor expression regulation of intracellular receptors (Cangoz et al., 2013; Talaei et al., 2013; Mata-Granados et al., 2008). In a few animal studies, administration of calcitriol (activated form of Vitamin D) has been shown to prolong the onset of Type 1 Diabetes mellitus, mainly through immune regulation (Palomer et al., 2008; Van Meijl et al., 2008). This is mainly because of effect of Vitamin D on inflammatory pathway (Gradinaru et al., 2012; Palomer et al., 2008).

Type 2 diabetic patients had reduced levels of Vitamin D than normal individuals. The insulin resistance is more in Vitamin D deficiency. Hence, Vitamin D plays an important role in maintaining normoglycemic condition by influencing insulin secretion. In deficiency state of Vitamin D, there is decreased insulin sensitivity and increased insulin resistance (Mangukiya and Neha, 2014). Chronic Vitamin D deficiency may be a predisposing factor for type 2 diabetes mellitus as per our study. So, in tropical countries like India where there is an abundance of sunlight, still Vitamin D deficiency is quite common. But, Vitamin D deficiency can be avoided by early diagnosis and dietary fortification as well as dietary supplementation of Vitamin D (Van Meijl et al., 2008).

It is suggested in the present study that the inclusion of serum magnesium estimation in obese individual may be made compulsory so that it could be used as a predictor of obesity induced insulin resistance that would eventually predisposes to diabetes mellitus and future micro, and macro vascular complications.

We further suggest that magnesium supplementation (diet rich in green leafy vegetables) would help enable the obese individuals to delay the onset of T2DM.

Fortification of foods with Vitamin D can be the proposed treatment for prevention of Vitamin D deficiency (Niranjan et al., 2013), High risk population should be screened thoroughly and must be placed on Vitamin D supplements. Irradiation of milk with UV rays causes enrichment of milk with Vitamin D (Van Meijl et al., 2008). Irradiated milk will acts as a rich source of Vitamin D. It may be noted that irradiated milk is a poor source of vitamin A. As per our observation, it is advised to T2DM patients to take Vitamin D and calcium regularly in consultation with the physician. Those who are using sunscreen with high SPF (sun protection factor) should receive supplements of Vitamin D and calcium.

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