High prevalence of vitamin D deficiency among newly diagnosed youth-onset diabetes mellitus in north India

Alta prevalência de deficiência de vitamina D entre casos de diabetes de início na juventude recém-diagnosticada no norte da Índia

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ABSTRACT

Objectives: Vitamin D deficiency is common at all ages, and low levels of vitamin D have been associated with high incidence of type 1 diabetes. Similar results are not consistent for type 2 diabetes. The aim of the present study was to estimate vitamin D status in newly detected youth-onset diabetes in north India. Subjects and methods: This was a prospective case control study at a tertiary care hospital in north India. Seventy two newly detected youth-onset diabetes subjects (age < 25 years), and 41 age- and gender-matched healthy controls were studied. In addition to basic information and management regarding their diabetes, metabolic parameters and serum 25(OH)D were measured in both the groups. Results: Vitamin D deficiency was seen in 91.1% of the subjects with diabetes, and 58.5% of the healthy controls. Mean ±SD 25(OH)D was significantly low, 7.88 ± 1.20 ng/mL in subjects with diabetes against 16.64 ± 7.83 ng/mL in controls. Sixty percent of cases had severe Vitamin D deficiency compared with 8.3% in controls. Levels of vitamin D did not correlate with clinical parameters, such as gender, body mass index; or with biochemical parameters, such as serum calcium, phosphorus, alkaline phosphatase, fasting plasma glucose, and HbA1C. Conclusion: Vitamin D deficiency is common in people with youth-onset diabetes.

Keywords
Vitamin D deficiency; youth-onset diabetes; type 2 diabetes; 25(OH)D

RESUMO

Objetivos: A deficiência de vitamina D é comum em todas as idades, e baixas concentrações de vitamina D estão associadas à alta incidência de diabetes tipo 1. Entretanto, resultados similares não são consistentes para o diabetes tipo 2. O objetivo do presente estudo foi estimar a condição dos pacientes com relação à vitamina D em casos de diabetes de início na juventude recém-diagnosticada no norte da Índia. Sujeitos e métodos: Este foi um estudo prospectivo controlado em um hospital de cuidados terciários no norte da Índia. Setenta e dois pacientes com diabetes de início na juventude recém-diagnosticada (idade < 25 anos) e 41 controles saudáveis, sem diabetes, pareados por idade e sexo, foram estudados. Além das informações básicas e controle do diabetes, parâmetros metabólicos e a 25(OH)D sérica foram avaliados em ambos os grupos. Resultados: A deficiência de vitamina D foi observada em 91,1% dos pacientes com diabetes e em 58,5% dos controles saudáveis. A média ± DP de 25(OH)D foi significativamente baixa, 7,88 ± 1,20 ng/mL nos pacientes com diabetes contra 16,64 ± 7,83 ng/mL nos controles. Sessenta por cento dos pacientes com diabetes apresentaram deficiência grave de vitamina D, contra 8,3% dos controles. As concentrações de vitamina D se correlacionaram com os parâmetros clínicos, como sexo, índice de massa corporal, ou com parâmetros bioquímicos, como cálcio e fósforo séricos, fosfatase alcalina, glicemia de jejum e HbA1C. Conclusão: A deficiência de vitamina D é comum em pacientes com diabetes de início na juventude.

Descritores
Deficiência de vitamina D; diabetes de início na juventude; diabetes tipo 2; 25(OH)D
INTRODUCTION

Vitamin D deficiency (VDD) is presently a major health problem in both adults and children across the globe, and it is more so in the Indian subcontinent (1-4). Many studies that focused on pediatric age have demonstrated high prevalence of VDD in normal children and adolescents (5,6). In the past decade, interest in diabetes mellitus and vitamin D metabolism has grown. Many epidemiological studies have found high prevalence of VDD in children with type 1 diabetes mellitus (T1DM), suggesting an association between the two (7-10). Type 1 DM is an autoimmune disease with contribution from environmental insults in its causation (11). In susceptible persons, cytokine production and lymphocyte proliferation has been postulated to be decreased by immunomodulatory actions of vitamin D, thus preventing destruction of beta-cells and subsequent development of T1DM (12). These observations are supported by many clinical studies where it has been shown that supplementation of vitamin D during early childhood helps preventing T1DM (13). There have also been many suggestions about the association of VDD and the incidence of type 2 diabetes mellitus (T2DM). Studies have suggested an inverse relationship between low intake of total vitamin D and risk of T2DM (14,15). Similarly, supplementation of vitamin D in high risk groups, such as in patients with impaired fasting blood glucose levels, resulted in decreased rise in fasting plasma glucose and insulin resistance after three years, compared with the placebo group (16).

Kashmir valley is situated at an altitude of 1,574-5,425 feet above the sea level at latitudes 32° 0-34° 50' N and longitude 73° 45'-75° 35' E, in the Northern mountainous regions of India, with cold temperatures during six months of the year. However, the exposure to sunlight and consumption of dairy products are acceptable. The area has a high prevalence of diabetes across different age groups (17,18). The prevalence of VDD is quite common in the adult population (19). The aim of the present study was to assess vitamin D status in the young population with diabetes and age- and gender-matched controls.

SUBJECTS AND METHODS

The present prospective case control study was conducted at a tertiary care hospital in north India over a period of two years. This study included 72 cases of youth-onset diabetes mellitus (age of onset of diabetes < 25 years), and 41 age- and sex-matched healthy control subjects. Cases with new onset diabetes aged below twenty five years of age were recruited and classified during the two years of observation. Subjects were classified as T1DM, if they had an episode of ketoacidosis; as T2DM if they had no episode of ketoacidosis and were controlled on oral antidiabetic drugs for more than a year after diagnosis; and as fibrocalkulative pancreatopathy (FCPP) if they had pancreatic calcification on abdominal X-ray in addition to diabetes (17). Age-, sex- and body mass index-matched healthy subjects below 25 years of age were identified and included as controls. Informed consent was obtained from all the subjects and controls after explaining the study to them in their local language. The study was approved by the review board of the institution.

Detailed history focusing on the presentation of diabetes mellitus (osmotic symptoms, ketoacidosis, or others), family history of diabetes, occupation, socioeconomic status, drug intake, menstrual history, and history of any systemic illness was recorded.

Direct sunlight exposure was assessed by average daily duration of exposure and percentage of body surface area exposed (20). Nutritional status of the patients and controls was assessed by a trained dietician based on the average composition of their daily diet in terms of energy, carbohydrate, protein, fat, and calcium content using a semi-quantitative food-frequency questionnaire (21,22), and published data on nutrient composition of Indian food (23).

Examination of the subjects included recording of height, weight, body mass index (BMI), waist and hip circumference, and measurement of waist-to-hip ratio. BMI was calculated by the formula: body weight in kg/ height in m².

After overnight fasting, a venous blood sample was drawn for analysis of glucose, lipids, creatinine, calcium, phosphorus, and alkaline phosphatase. These biochemical measurements were determined by an automatic colorimetric method. HbA1c was measured with high performance liquid chromatography (HPLC) standardized for the DCCT assay (reference range, 4-6%). The blood sample for estimation of 25(OH)D was allowed to clot at room temperature (15-25 °C) and centrifuged for 15 minutes to obtain hemolysis-free serum. Serum was then collected into separate plastic tubes and stored at -20 °C. After rapid extraction from serum with acetonitrile, 25(OH)D was estimated by radioimmunoassay (RIA) procedure (catalogue no. 68100, Dia Sorin, Stillwater, Minnesota USA). The intra- and inter assay coefficients of variation ranged...
between 11.7-12.5% and 9.4-11%, respectively. Samples were collected throughout the study duration with equal representations in winter and summer. The criteria used to define vitamin D status were: sufficiency (25OHD levels, 30-100 ng/mL), insufficiency (25OHD, 20 to 30 ng/mL), and deficiency (25OHD, < 20 ng/mL) (1).

**Statistics**

Statistical analysis was performed using SPSS for Windows (version 11). Results were expressed as means ±SD. A simple factorial analysis was used to find the correlation of between vitamin D status and the other clinical and biochemical parameters, after adjusting for age. An independent samples t test was used to compare mean ±SD values between cases and controls; p-value less than 0.05 was considered as significant.

**RESULTS**

Seventy two patients of youth-onset diabetes mellitus were studied with a mean ±SD age of 16.72 ± 0.68 years. There were 33 males (45.8%) and 39 females (54.2%). Fifty eight (86.4%) patients had type 2 DM (26 were males and 32 were female), 13 (18.1%) had type 1 DM (6 males and 7 females) and one patient was classified as having FCPP. As seen in Table 1, both cases and controls were comparable in age and BMI.

Overall plasma 25(OH)D levels were significantly lower in the patients (mean ±SD of 7.88 ± 1.20 ng/mL) than in the control subjects (mean ±SD of 16.64 ± 7.83 ng/mL; p = 0.000). A high percentage of cases (94.4%) as well as controls (58.5%), had vitamin D deficiency. Mild and moderate VDD was seen more in controls than in cases, but severe VDD was seen more in patients with diabetes (60%) compared with 8.3% in the controls (Table 1). Overall plasma levels of vitamin D did not reveal any correlation with sex, BMI, serum calcium, alkaline phosphate, and HbA1C (Table 2). Mean ±SD plasma 25(OH)D levels were marginally lower in the group with T1DM (11.36 ± 4.74 ng/mL) compared with T2DM (7.34 ± 1.19 ng/mL); but the difference was not statistically significant (p = 0.260). Although T2DM was a larger group (n = 58) compared with T1DM (n = 13), an uniformly high percentage of patients (92.3% in T1DM and 98.3% in T2DM) had vitamin D deficiency (Table 3).

**DISCUSSION**

Vitamin D deficiency is now regarded as pandemic in all age groups in humans (4,24). High prevalence of VDD has been seen in normal healthy children at different ages. The main aim of the present study was to assess vitamin D status in new onset diabetes in the younger age group (< 25 years), and in age- and gender-matched controls without diabetes.
Using a serum vitamin D cutoff value of less than 20 ng/mL, high prevalence of VDD was seen in both groups of people with or without diabetes. VDD was seen in 58.5% of healthy controls in the age group of < 25 years, and 39% of them had 25(OH)D in the range of 5-10 ng/mL, indicating moderate VDD. In a similar population of similar age, VDD was seen in 55% of normal subjects (5). The high percentage of VDD in the present study was attributed to decreased vitamin D intake, dark complexion, and winter months. A recent study has revealed VDD in as high as 85% of normal children in the age group < 16 years, using a cutoff value of < 30 ng/mL (6). The high percentage of VDD in that study was explained by decreased sunshine exposure, limited outdoor activities, and decreased awareness about fortification with vitamin D. Similarly, vitamin D concentration of < 9 ng/mL was found in 35.7% of normal children in the age group of 10-18 years (24). Our study revealed a greater percentage of normal people (58.5%) having VDD. Although sunshine exposure is good in India, it is limited to only few months, and fortification of food with vitamin D is not routine in the country.

Our main focus was to estimate vitamin D status in newly diagnosed youth-onset diabetes. We found that VDD was found in 94.4% of people with diabetes, compared with 58.5% of age- and sex-matched healthy controls. VDD was more prevalent in girls (65%) compared with boys (52.4%) in the healthy controls, and this gender difference was not seen in the diabetes group.

Some recent studies have focused on the prevalence of VDD in people with T1DM. Prevalence varied from as high as 90.60% with a vitamin D cutoff value of < 30 ng/mL in Qatar (6), to as low as 15% with a vitamin D cutoff value of < 20 ng/mL at Joslin's diabetes center (9), and intermediate prevalence of 54% with a vitamin D cutoff value of < 32 ng/mL in DIASS study (8). In one north Indian study, 58% children with T1DM aged between 6 and 12 year were vitamin D-deficient as compared with only 32% in the control group (25). In our study 25(OH)D was significantly lower (mean ± SD of 7.88 ± 1.20 ng/mL) in patients, compared with 16.64 ± 7.83 ng/mL in the controls. Many recently published studies have found significantly lower levels of 25(OH)D in patients with diabetes compared with controls (6,8,10,26).

The universal findings of low vitamin D in people with T1DM have implications in its pathogenesis. As early as 1980, it was found that VDD in rabbits inhibited pancreatic insulin secretion (27). There is evidence that vitamin D regulates beta-cell function by either influencing insulin secretion, inhibiting beta-cell apoptosis, or by increasing beta-cell replication (28). In the context of T1DM, vitamin D has a significant role in altering self-immunity leading to diabetes (29). Assessing the data on the incidence of T1DM in children < 14 years in 51 regions across the globe, incidence rate of T1DM approached zero in regions with high UVB irradiance (30). The association of adequate vitamin D and incidence of T1DM is also reflected by seasonal variations in the incidence of T1DM. It has been observed that children born in the spring are associated with increasing likelihood of T1DM (31). The association of hypovitaminosis D and T1DM is further strengthened by laboratory studies. An association between vitamin D receptor (VDR) polymorphism and T1DM was reported in Indian, German, and Taiwan populations (32-34). Also, polymorphism in CYP 27B1 gene has been shown to decrease the local expression of 1-alpha-hydroxylase, and subsequent decreased conversion of 25(OH)D to 1:25(OH)2D, increasing the predisposition to T1DM.

In the present study, high prevalance of hypovitaminosis D in people with diabetes could point to an association between the two disorders in our community. Type 2 DM is a disorder resulting from defects in insulin sensitivity and secretion. The disorder is more common in obese individuals with sedentary lifestyle and higher levels of inflammatory cytokines (35). Many studies have suggested that vitamin D could have a role in improving beta-cell function and increasing insulin sensitivity. The National Health and Nutrition Examination Survey (NHANES) showed an inverse correlation between 25(OH)D and the incidence of T2DM/insulin resistance. (36). A similar inverse relationship between 25(OH)D and glycemic status was found in other studies (37,38). In the present study, serum 25(OH)D was also significantly lower in patients with T2DM when compared with healthy controls. The direct clinical evidence of the association between hypovitaminosis D and diabetes has come from interventional studies; these studies are more robust for T1DM. The use of cod liver oil during the first year of life was associated with lower risk of T1DM (39). A reduction as high as 29% in the risk of T1DM was seen in infants supplemented with vitamin D compared with controls in the meta-analysis of four studies (40). In the EURODIAB study, a reduction as high as 30% in the risk of T1DM was seen with vitamin D supplementation early in life (13).

Clinical intervention studies with T2DM are less consistent. In Nurses’ Health Study which followed a large cohort of women over 20 years, a combined intake of > 800 U of vitamin D was associated with a decrease of 33% in the risk of T2DM compared with the intake of < 600 mgs
of calcium and 400 U of vitamin D (41). These results have not been reproduced yet. In the Women’s Health Initiative Study, calcium in low doses and 400 IU of vitamin D per day were not shown to be protective. Similarly, in one study, no improvement in glucose tolerance has been seen with vitamin D supplementation in vitamin D sufficient individuals (42). Genetic background, baseline vitamin D, and the vitamin D dose given may be important determinants in such discrepancy. The present study also revealed that vitamin D levels were significantly low in patients with T2DM compared with controls. It could be postulated that either hypovitaminosis D has increased insulin resistance or impaired beta-cell function, or both, but that was not the aim of the study.

There are several limitations of our study: we separated patients in type 1 and type 2 diabetes on the basis of hard evidence of diabetic ketoacidosis in favor of T1DM. Although maturity-onset diabetes of young (MODY) is common among Indians (43), we could not classify any patient in MODY, as all of them required insulin from the beginning, and continue to be on insulin. We did not measure their beta-cell reserve, nor did we estimate their islet cell antibodies, but we believe that absence of these investigations did not affect the results, as we had the broader aim of -finding vitamin D status in youth-onset diabetes.

In summary, the aim of the current prospective study was to find vitamin D status in seventy two newly detected youth-onset diabetes, both type 1 and T2 DM (age < 25 years) and 41 age- and gender-matched controls. Both cases and controls were vitamin D deficient. The mean serum 25(OH)D was significantly low in people with diabetes compared with controls. Levels of 25(OH)D did not correlate with age, sex, BMI, nutritional calcium intake, plasma glucose, and HbA1C. Whether vitamin D status in patients with diabetes has a role in the pathogenesis of diabetes mellitus in younger patients needs to be elucidated in future studies.

Disclosure: no potential conflict of interest relevant to this article was reported.

REFERENCES


Vitamin D deficiency in early onset diabetes


