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Original Article

Correlational Study between Serum Vitamin-D Levels and Microvascular Complications in Diabetic Patients: A Tertiary Care Centre Experience from Western Uttar Pradesh

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Abstract
Background: *Role of Vitamin D in regulation of various important body functions has been well studied. Vitamin D deficiency is a risk factor for cardiovascular disease, hypertension, dementia and certain malignancies. Its role in increasing beta cell activity and insulin sensitivity is also under research and through this study we tried to assess the correlation between vitamin D levels and microvascular complications of diabetes.*
Methods: *200 patients of Type 2 diabetes were taken as cases while 200 healthy age and sex matched subjects were taken as controls. This observational study was conducted for 2 years in Endocrinology department of Lala Lajpat Rai Memorial Medical College, Meerut (UP). Relevant clinical examinations and investigations were done including serum 25-Hydoxy Vitamin D levels in all the subjects who were thereafter labeled as either Vitamin D sufficient, insufficient or deficient.*
Results: *In this study it was found that neuropathy was present in 100 cases (50%) with mean vitamin-D level 16.52 +/- 1.31 ng/mL and absent in rest 50% cases with vitamin-D levels of 17.66 +/- 1.18 ng/mL, which was significant(p= 0.002). Proliferative retinopathy was present in 52 cases with mean vitamin-D level 16.41 +/- 1.01 ng/mL and absent in 72 cases (36%) with mean vitamin-D 17.79 +/- 1.41 ng/mL, which was found to be significant(p = 0.012).*
Conclusions: *This study shows that the patients of diabetes in Western UP are deficient in vitamin-D as compared to non diabetics. As per individual complication is related, diabetic retino and neuropathy significantly correlates with vitamin-D deficiency/insufficiency.*
Keywords: *Diabetes Mellitus, Microvascular complications, Retinopathy, Neuropathy, Nephropathy, Vitamin-D.*

Introduction

Diabetes mellitus causes as a disease poses tremendous burden on individual and health care system around the globe .The world today is witnessing epidemic of diabetes mellitus.[1] The International Diabetes Federation estimated that by 2030, 8.4 % of India population will have diabetes and this figure will expected to go upto

10.1 million.[2] DM is a chronic disease with multiorgan involvement having many microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (coronary artery disease, cerebrovascular disease , peripheral artery disease) complications. Cardiovascular disease is the leading cause of death in individuals with DM.[3,4] If glycemic control is not achieved in earlier stages of the disease, the complications could be many in significant mortality and morbidity. Genetic and environmental factors such as sedentary lifestyle, high calorie diet, obesity etc. contribute to DM.[5] Of late many studies have demonstrated increased association of DM and vitamin-D deficiency.[6-10] Vitamin D is a secosteroid hormone that is synthesized in skin and sequentially metabolized in liver and kidneys in humans , has been well known for its function in maintaining calcium and phosphorous metabolism . However the ubiquitous distribution of intracellular vitamin-D receptor across diverse tissues and emerging evidence of increased risk of hypertension, cardiovascular disease, dementia and certain cancers associated with vitamin-D deficiency. Vitamin-D also exerts an indirect effect via regulation of extracellular calcium levels and calcium flux through the beta cells, there by promoting insulin secretion, which is a calcium dependent process. Evidence is also accumulating for a role of vitamin-D in maintaining normal glucose homeostasis. Vitamin-D deficiency is significantly related to insulin resistance and impaired insulin secretion. Moreover, a significant and strong association between vitamin-D deficiency and beta cell dysfunction has been reported in healthy, non diabetic or diabetic population. Furthermore, circulating form of vitamin-D (25-hydroxy-D) were significantly and inversely related to the risk for DM and related phenotypes in epidemiological studies.[11-13] A role of vitamin-D in pancreatic beta cell function might be mediated by the binding of circulating vitamin-D to beta cell vitamin-D receptor. Patients with type 2 DM have lower mean 25-hydroxy-D concentrations than non diabetic subjects. Vitamin-D lower levels may be significant risk factor for glucose intolerance and development of various complications. At least four prominent theories which are not mutually elusive have been proposed to explain how hyperglycemia might lead to the chronic complications of DM. An emerging hypothesis is that hyperglycemia leads to epigenetic changes in the affected cells. Vitamin-D deficiency underscores the pleiotropic effects of vitamin-D. It is also linked to an increased susceptibility to several chronic diseases.

Role of vitamin-D

1.Immunomodulation

Vitamin-D mediates immunological effects by binding to nuclear vitamin D receptors which are present n most immune cells types including both innate and adaptive immunity. Activation of the vitamin -D receptor has potent antiproliferative, pro-differentiative and immunomodulatory functions including both immune enhancing and immunosuppressive effects. [14,15] It also tend to increase susceptibility to various microbial infections.

2. Neoplasm

The anti-cancer activity of vitamin-D is thought to result from its role as a nuclear transcription factor that regulates cell growth, differentiation, apoptosis and a wide range of cellular mechanisms central to the development of cancer. These effects are mediated through vitamin-D receptors expressed in cancer cells. [16,17] Various mechanisms implicated in anticancer effects of vitamin-D involve cell cycle regulation , induction of apoptosis ,cell differentiation ,inhibition of angiogenesis, disruption of growth factors mediated cell survival signals.

3. Cardiovascular Disease

Research indicates that vitamin-D may play a role in preventing or reversing coronary disease. It is associated with an increase in blood pressure and cardiovascular risk.[18] The precise mechanism for cardiovascular regulation is still under investigation, possibilities include blood pressure

regulation through vitamin-D direct impact on heart and smooth muscles. There is high prevalence of cardiovascular risk in renal failure associated with lower levels of vitamin-D.

Vitamin-D and Type 2 DM

Type 2 DM is characterized by insulin resistance and altered insulin secretion.[20] Several studies have demonstrated a link between vitamin-D and the incidence of type 2 DM . Large cohort study from Finland indicated inverse association between serum vitamin levels and risk of developing type 2 DM. These results were consistent with the Nurses Health Study done in 2007 by Pittas et al.[19] Vitamin-D either directly stimulates expression of insulin receptors thereby enhancing insulin responsiveness for glucose transport by increased GLUT-4 activity on cells.[21]

Burden of Vitamin-D deficiency in India

It has been estimated that 1 billion people worldwide have vitamin-D deficiency or insufficiency.[23] There is widespread prevalence of varying degrees (50-90 %) of vitamin-D deficiency with low dietary calcium intake in Indian population according to various studies published earlier.[22] Vitamin-D deficiency is a common problem in India due to several factors discussed below

1) Changing food fads and food habits contribute to low dietary vitamin-D intake and lack of fortified foods.[26]
2) High fiber diet containing phosphates and phytates depletes vitamin-D stores of the body.[24]
3) Genetic polymorphism in vitamin-D receptors and its active metabolite action.
4) Modernization has lead to inadequate sun exposure especially in urban India.
5) Increased pollution can hamper the ultraviolet rays to adequately synthesize vitamin-D in skin.[25]
6) Cultural and traditional habits prevalent in certain religions like burqa and pardah system in muslims have been well known.

Definition of Hypovitaminosis-D:

1) Concentration of 25-Hydroxy-D more than or equal 30 ng/mL = Adequate or sufficient
2) Concentration of 25-Hydroxy-D between 20-29 ng/mL = Insufficient
3) Concentration of 25-Hydroxy-D 10-19 ng/mL = Mild deficiency
4) Concentration of 25-Hydroxy-D 5-9 ng/mL = Moderate deficiency
5) Concentration of 25-Hydroxy-D below 5 ng/mL = Severe deficiency

Materials And Methods

This study was an observational study done for a period of 2 years based on serum levels of vitamin-D and development of different microvascular complications in patients with long standing type 2 DM; conducted in our department of endocrinology ,Meerut which is a tertiary care centre of western Uttar Pradesh. Total 200 patients were taken as cases, aged between 40-70 years of both sexes. These cases do not had any associated comorbidities or any drug intake. Control group had 200 healthy subjects without any disease or drug history affecting vitamin-D levels.

Inclusion Criteria: Type 2 DM of age group 40 to 70 years. Symptoms of Type 2 DM were increased thirst, increased frequency and volume of micturition, weight loss, poor vision ,tingling and numbness in hand or feet or both , extreme fatiguability, pain in limb muscles .

Exclusion Criteria: patient with type 1 DM, history of chronic kidney/liver disease, on dialysis or renal transplant patients epilepsy, drugs which affect vitamin-D metabolism eg. phenytoin, glucocorticoids. Criteria for diagnosis of Diabetes Mellitus in patients was according to American Diabetic Association.

1. Fasting blood glucose more than equal to 126 mg/dL .Fasting means no calorie intake for atleast 8 hours. OR
2. Two hour post prandial blood glucose of more than equal to 200 mg/dL. Preferably done with

oral glucose tolerance test using 75 gm of anhydrous glucose taken with 200 ml of water.

OR

3. Random blood glucose of more than equal to 200 mg/dL in presence of symptoms of diabetes mellitus.

Quantitative determination of 25-hydroxy vitamin-D in human serum was done using chemiluminiscence microparticle immunoassay (CMIA) method. Vitamin-D present in the sample binds to antivitamin-D coated microparticles. After incubation a biotinylated vitamin-D,anti biotin acridinium labelled conjugate complex is added to the reaction mixture and binds to unoccupied binding sites of antivitamin-D coated microparticles. The subjects were classified as sufficient, insufficient and deficient on the basis of serum levels of vitamin-D. Statistical analysis was done using ANOVA method. Student t-test was used to compare differences between the case and the control subjects. Pearson coefficient was calculated for the correlation.

P value less than 0.05 was considered to be significant.

Observation and Result

In our study we found that various microvascular complications studied in 200 cases in which nephropathy was present in 164 cases (82%) mean vitamin-D was 17.08 +/- 1.37 ng/mL and absent in 36 cases (18%) with mean vitamin-D was 17.08 +/- 1.32 ng/mL, p = 0.946 was insignificant. Neuropathy was present in 100 cases (50%) with mean vitamin-D was 16.52 +/- 1.31 ng/mL and absent in rest 50% cases with their vitamin-D levels of 17.66 +/- 1.18 ng/mL, p= 0.002 which was significant. Nonproliferative Retinopathy was present in 76 cases (38%) with mean vitamin-D was 16.89 +/- 1.26 ng/mL. Proliferative Retinopathy was present in 52 cases (26%) with mean vitamin-D level was 16.41 +/- 1.01 ng/mL and absent in 72 cases (36%) with mean vitamin-D was 17.79 +/- 1.41 ng/mL, p = 0.012 which was significant.

Discussion

A novel association with diabetes that has considerable attention recently is vitamin-D deficiency. Consistent with the hypothesis that vitamin-D deficiency and diabetes are related areas with high prevalence of vitamin-D insufficiency and deficiency have been associated with a higher prevalence of diabetes and associated complications. There have been many reports that vitamin-D status is associate with insulin sensitivity, glucose tolerance and beta cell function. A low status of vitamin results in poor glycemic control and increased risk of complication and death in diabetic population compared to non diabetics. In this study the mean level of serum vitamin-D level in diabetics was 17.09 +/- 1.36 mg/mL with a vitamin-D deficiency prevalence of 98% as compared to control group serum vitamin-D level was 18.29 +/- 1.26 mg/mL with a vitamin-D deficiency prevalence of 90%. A student t-test was calculated and compared between these groups was significant with p value of 0.0001. The low serum vitamin-D were negatively correlated to the glycemia levels of cases as well as their microvascular complications .This study also shows that the population of western Uttar Pradesh is deficient in serum vitamin-D and is much low in cases compared to healthy controls. In this study correlation between duration of diabetes and serum vitamin-D levels was also found to be insignificant with p value of 0.514 And results further suggested that the control of blood glucose levels itself affect serum vitamin-D metabolism regardless of duration of diabetes. We analyzed the prevalence of diabetic microvascular complications and their association with serum 25-hydroxy-D, found cases with proliferative retinopathy had lower levels of serum vitamin-D than those with nonproliferative retinopathy and without retinopathy, p value 0.012 which was significant. As for nephropathy proteinuria more than 150 mg/day taken as abnormal, we found presence of nephropathy in 82% of cases while absence of nephropathy in 18 % of cases with

mean serum vitamin-D calculated in both groups was statistically insignificant, p value of 0.946. Similarly for neuropathy we found the patients with disease have lower serum concentration of vitamin-D than those who do not have it ,p value of 0.002, which was significant. Hence we found diabetic retinopathy and neuropathy, but not nephropathy are significantly associated with lower serum vitamin-D levels .Multiple regression analysis of the study showed that the number of complications was associated with decreased 25-hydroxy-D concentration, p value of 0.016 which was significant. This suggests that the progression of diabetic microvascular complications are associated with decrease vitamin-D concentration in blood.

Conclusion

In this study the mean level of serum vitamin-D in diabetic patients was 17.09 +/- 1.36 ng/mL as compared to control group serum levels of vitamin-D which was 18.29 +/- 1.26 ng/mL. Our study in this part of country shows that the population here are deficient in vitamin-D especially those who are suffering with DM compared to non diabetic population. As per individual complication is related, diabetic retino and neuropathy are significantly associated with patients who are vitamin-D deficient/insufficient. This reaffirms the previously reported findings that deficiency of vitamin-D could possibly play an important role in causation of the disease and its complication. Further interventional studies may be needed in future to decide upon the recommended daily allowances of vitamin-D to prevent the development of diabetes mellitus and its complications.

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