Association of serum vitamin D and parathormone levels in patients of type 2 diabetes mellitus with diabetic retinopathy

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Abstract

The present study was aimed to evaluate the association of serum 25-hydroxy vitamin D and parathormone in 46 patients of type 2 diabetes mellitus with diabetic retinopathy [non-proliferative, (n=27); proliferative (n=19)]. Twenty one diabetic patients without retinopathy were taken as control. Serum 25-hydroxy vitamin D and intact parathyroid hormone were measured by chemiluminescence microparticle immunoassay. Concentration of 25-hydroxy vitamin D differed significantly among groups (p=0.018) and it was significantly lower in proliferative diabetic retinopathy than no diabetic retinopathy (p=0.003). Logistic regression analysis revealed that vitamin D deficiency [25-hydroxy vitamin D <20 ng/mL] was independently associated with development of diabetic retinopathy (p=0.007, OR 20.90, 95%CI 2.33-187.23). In conclusion, vitamin D deficiency is associated with diabetic retinopathy complicating type 2 diabetes mellitus.

Introduction

Vitamin D deficiency is a major concern worldwide. It has been estimated that almost one billion people in the world suffer from vitamin D deficiency or insufficiency.[1] Even in tropical regions where the risk of vitamin D deficiency was previously assumed to be low, has become a global public health concern now-a-days.[2] Even a study shows that deficiency in vitamin D is observed in Bangladesh female garment workers.[3]

Much evidence have suggested that vitamin D deficiency is involved in the development of various diseases including type 1 and type 2 diabetes,[4] cardiovascular disease,[5] cancer[6] and autoimmune diseases.[7] In fact, in addition to its classical role in bone and mineral homeostasis, recent studies have shown that vitamin D has inhibitory effects on inflammation and proliferation of endothelial cells and angiogenesis which are involved in the development of diabetic retinopathy.[8, 9]

The cause of diabetic retinopathy is not clear. The retinopathy may develop not only in diabetes but also in neonate.[10]

Several studies have also shown that vitamin D receptor is expressed in retina and vitamin D has direct inhibitory effects on the development of diabetic retinopathy in experimental animal models. Some studies revealed that vitamin D inhibits retinal neovascularization in a mouse oxygen-induced ischemic retinopathy model.[11, 12] Further studies revealed that vitamin D has protective effects on diabetic retinopathy by inhibiting vascular endothelial growth factor (VEGF) and transforming growth factor-β_1 (TGF-β_1) in the retinas of diabetic rats.[13] In addition, some human genetic studies have shown that polymorphisms of vitamin D receptor gene are associated with diabetic retinopathy.[14, 15] All these suggest a role of vitamin D in the pathogenesis of the development of diabetic retinopathy.

Vitamin D deficiency may also be associated with a high plasma parathormone level, subsequently which may present in subretinal fluid of the human eye. It is shown through different studies that parathormone excess can reduce glucose tolerance[16] and induce inflammatory cytokines like IL-6 and its soluble receptor (IL-6sR)[17] and thereby may contribute to development and progression of diabetic retinopathy.

The potential role of vitamin D deficiency and associated high parathormone in the development of diabetic retinopathy has been a matter of specific interest in recent years. That is why, we designed a study which was aimed to evaluate the association of serum vitamin D and

parathormone with diabetic retinopathy in type 2 diabetic patients.

Materials and Methods

This study was conducted from March 2015 to February 2016 after receiving Institutional Review Board approval. By convenient and purposive sampling, a total of 67 type 2 diabetic individuals of both sex, age between 35 to 65 years, attending in retina clinic and outdoor of Ophthalmology Department of Bangabandhu Sheikh Mujib Medical University and National Institute of Ophthalmology for fundoscopic examinations, were enrolled in this study. The subjects with type 1 diabetes mellitus or specific types of diabetes, acute complications of diabetes, major illness (renal failure, hepatic disease, skeletal disease or malignancy), hypertensive retinopathy or retinopathy due to other cause, acute or chronic infection, pregnancy or subjects using of vitamin D and/or calcium supplements or medications that are known to alter metabolism (estrogen, thiazide diuretics, anticonvulsants etc.) were excluded from this study. After enrollment, they were grouped on the basis of fundoscopic examination as non-proliferative diabetic retinopathy (n=27) and proliferative diabetic retinopathy (n=19), both were considered as cases and no diabetic retinopathy (n=21), was considered as control. Informed written consents were taken and with all aseptic precaution, blood samples were collected from each study subject. Fasting plasma glucose and 2 hours postprandial plasma glucose were measured using glucose oxidase methods (Siemens Healthcare Diagnostics Inc., Germany). Serum creatinine was measured by modified kinetic Jaffe assay (Siemens Healthcare Diagnostics Inc., Germany). Serum calcium and albumin were measured by dye-binding methods (CI 4100 ARCHITECT, USA) and serum vitamin D [25(OH) D] and parathormone (iPTH) were measured by chemiluminescence microparticle immunoassay (CI 4100 ARCHITECT, USA). Vitamin D deficiency was defined as a serum 25(OH)D level below 20 ng/mL and insufficiency as a serum 25(OH)D level 21-29 ng/mL in accordance with the generally accepted standard.[18] Serum parathormone >65 pg/mL was considered as high.[19]

The statistical analysis was carried out using the SPSS version 22. Quantitative data were expressed as means and standard deviation (mean ± SD). Differences among the groups were analyzed using the Kruskal–Wallis test or ANOVA test as appropriate for measurement of data, as well as the Chi-Square test for categorical values. Differences between groups were assessed by means of Mann-Whitney U test or Bonferroni post hoq test as adequate. Multinomial logistic regression analysis was performed to evaluate the relationships between presence of diabetic retinopathy and the serum 25 (OH)D concentration and also to evaluate the odds ratio (OR), controlling for covariates. Spearman's correlation coefficient by rank was used to analyze correlations between vitamin D and diabetic retinopathy. A p value <0.05 was considered significant.

Table I

Baseline characteristics of study subjects

Parameters	Diabetes mellitus			p value
	With retinopathy		Without retinopathy	
	Proliferative	Non-proliferative		
No. of cases (male/female)	16/3	20/7	13/8	0.28[b]
Age (years)	52.8 ± 10.2	53.2 ± 7.7	54.9 ± 11.2	0.755
Hypertension (%)	63.2	44.4	38.1	0.258[b]
Duration of diabetes (year)	10.3 ± 7.6	9.4 ± 8.1	9.5 ± 9.4	0.789[a]
Systolic BP (mm Hg)	131.6 ± 17.1	125.5 ± 14.8	122.4 ± 11.3	0.136
Diastolic BP (mm Hg)	84.7 ± 9.04	83.7 ± 9.7	80.2 ± 8.1	0.252
BMI (Kg/m^2)	24.02 ± 2.9	24.8 ± 3.5	26.0 ± 4.1	0.217
FPG (mmol/L)	7.8 ± 2.5	8.3 ± 2.9	7.7 ± 2.1	0.692[a]
PPG (mmol/L)	11.5 ± 5.1	11.6 ± 3.1	11.2 ± 4.7	0.614[a]
Serum creatinine (mg/dL)	0.9 ± 0.2	1.0 ± 0.2	0.9 ± 0.1	0.589
eGFR (mL/min/1.72 m^2)	92.2 ± 21.9	82.1 ± 18.7	82.5 ± 21.8	0.207
Serum adjusted calcium (mg/dL)	8.04 ± 0.9	8.5 ± 1.2	8.8 ± 0.9	0.087

Continuous variables reported as mean ± SD and categorical variables as absolute or relative frequencies; One way ANOVA test was done to find out the level of significance; [a]Kruskal-Wallis test was done to find out the level of significance; [b]Chi-Square test was done to find out the level of significance

Results

There were no significant differences among groups in terms of overall baseline demographic, paraclinical and clinical characteristics (Table I).

The concentration of serum vitamin D (in ng/mL) differed significantly among groups (p=0.018) and it was significantly lower in proliferative retinopathy group compared to non-retinopathy group (p=0.003). However, the concentration of parathormone among groups did not differ significantly (p=0.752) (Table II).

Spearman's correlation test revealed that there was a significant negative correlation between serum

Table II

Comparison of serum vitamin D and parathormone among groups

Parameter		Diabetes mellitus			p value
		With retinopathy		Without retinopathy	
		Proliferative	Non-proliferative		
Serum 25-hydroxy vitamin D (ng/mL)	Median	19.4[a]	22.9	25.2	0.018
	IQR	16.2–30.2	17.8–36.5	22.0–40.0	
Serum intact parathyroid hormone (pg/mL)	Median	43.8	43.5	41.9	0.752
	IQR	30.4–59.7	34.3–72.3	36.8–52.95	

Kruskal-Wallis test was done to find out the level of significance; [a]p=0.003 between proliferative diabetic retinopathy and no diabetic retinopathy group which was revealed by Mann-Whitney U test

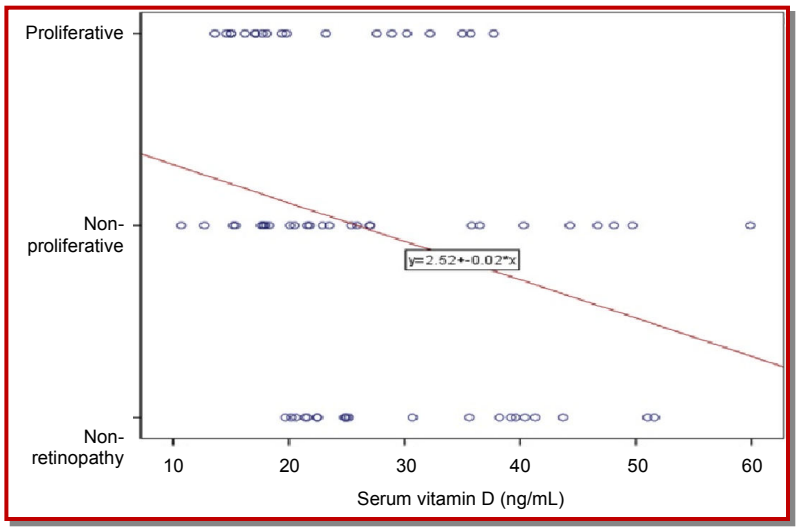

Figure 1: Correlation of serum vitamin D with diabetic retinopathy

vitamin D level and diabetic retinopathy (r= -0.348 and p=0.004) (Figure 1).

Multinomial logistic regression analysis of serum vitamin D, duration of diabetes, hypertension, serum parathormone and adjusted calcium in relation to diabetic retinopathy, revealed that vitamin D deficiency (<20 ng/mL) was independently associated with the development of diabetic retinopathy (Wald=6.828, p=0.009, OR 19.141, 95% CI 2.091 to 175.183) irrespective of the diabetes duration, hypertension, serum parathormone and adjusted calcium (Table III).

Discussion

This study was aimed to evaluate the association of serum vitamin D and parathormone concentrations with diabetic retinopathy in type 2 diabetic patients.

Serum vitamin D concentration differed significantly among groups and there was a downward trend in average vitamin D level with increased stages of diabetic retinopathy. The concentration was significantly lower in proliferative diabetic retinopathy group than no diabetic retinopathy group. However, the concentration of parathormone among three groups did not differ significantly. Alcubierre et al., 2015,[20] conducted a case-control study to explore the association of vitamin D and diabetic retinopathy. When the authors compared the biochemical characteristics of type 2 diabetic patients with and without retinopathy, they found lower level of vitamin D in retinopathy group than in no retinopathy group and it was significantly lower in Grade 2-4 DR group than no diabetic retinopathy group which were consistent with our findings. Similar to the findings of our study, the authors did not find any significant difference of parathormone level.

Table III

Logistic regression analysis in relation to diabetic retinopathy

Parameters		Wald	p value	OR	95% CI for OR	95% CI for OR
					Lower	Upper
Serum 25-hydroxy vitamin D	(<20 ng/mL)	6.8	0.009	19.1	2.1	175.2
Duration of diabetes	(>5 years)	1.7	0.192	2.3	0.6	8.3
Hypertension	Yes	0.1	0.784	1.2	0.3	1.0
Serum intact parathyroid hormone	(>65 pg/mL)	0.2	0.651	1.4	0.3	7.2
Serum adjusted Ca	(<8.5 mg/dL)	1.3	0.254	2.0	0.6	6.6

Nonetheless, we found a study that was inconsistent with the results of our study and study by Alcubierre et al. (2015) regarding parathormone concentration. Reheem et al. (2012)[21] did a cross-sectional study and checked parathormone level in both type 1 and type 2 diabetic patients. The authors found significantly higher level of parathormone in severe NPDR and PDR group than in no retinopathy group.

We also did the Spearman's correlation test which showed significant negative correlation between serum vitamin D level and diabetic retinopathy but the finding was not compatible with that of the study by Reheem et al. (2012).[21] The authors found no correlation between serum vitamin D level and the degree of retinopathy. However, we did not find any other study to compare our finding in this regard.

Finally, we did multinomial logistic regression analysis which showed that low level of serum vitamin D (<20 ng/mL) was independently associated with the development of diabetic retinopathy. This result suggested that vitamin D deficiency is the sole contributing factor in developing diabetic retinopathy in type 2 diabetic patients irrespective of the duration of diabetes, hypertension, serum parathormone and adjusted calcium. Our study result, however, was not coherent with the findings of He et al. (2014)[22] who conducted a large cross-sectional study of type 2 diabetes mellitus patients. Multiple logistic regression analysis of their study concluded that along with low serum vitamin D level, serum calcium, duration of diabetes and systolic blood pressure were also independent risk factors for diabetic retinopathy. Another cross-sectional study of type 2 diabetic patients conducted by Zoppini et al. (2015) [23] also supported the findings of He et al. (2014) and thus, conflicted with our study result. According to the study by Zoppini et al. (2015), the multiple logistic regression analysis showed that there were significant association of high vitamin D with reduced risk of diabetic retinopathy and that of longer duration of diabetes with increased risk of diabetic retinopathy. The dissimilarities of these two study results with our study findings indicate that a multi-institutional large sample case-control study is needed to be conducted.

Conclusion

Vitamin D deficiency is independently associated with diabetic retinopathy in patients with type 2 diabetes mellitus. However, the relationship between vitamin D and parathormone and/or parathormone and diabetic retinopathy still remains inconclusive.

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