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Serum vitamin D and parathormone (PTH) concentrations as predictors of the development and severity of diabetic retinopathy

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KEYWORDS

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Abstract *Background:* Vitamin D is suggested to be an inhibitor of angiogenesis. The degree of severity of diabetic retinopathy (DR) may be related to serum vitamin D concentration.

Aim: Investigating vitamin D and parathormone (PTH) concentrations as predictors of the development and severity of diabetic retinopathy.

Methods: Two hundred diabetic patients presenting with suspected diabetic retinopathy were investigated, levels of vitamin D [25(OH) D3 and Calcitriol] and PTH were measured. Diabetic retinopathy was assessed using 7-field stereoscopic Fundus photography.

Results: Mean serum concentration of 1, 25 dihydroxy vitamin D 3 (1, 25(OH) 2 D3) was significantly lower in diabetic subjects with retinopathy than in diabetic subjects with no retinopathy and there is a significant negative correlation between the mean level of 1, 25(OH) 2 D3 and the degree of severity of retinopathy. Level of PTH was significantly higher in severe NPDR and PDR compared to patients with no retinopathy.

Conclusions: Low levels of vitamin D might be a risk marker of development or progression of diabetic retinopathy. It might be advisable that detailed ophthalmologic examination is needed

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for diabetics whose serum 1, 25(OH) 2D3 concentrations gradually decreased. The measurement of serum 1, 25(OH) 2 D3 concentrations could become a useful biochemical means to predict the severity of DR in patients with diabetes mellitus.

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1. Introduction

Diabetic retinopathy (DR) is one of the most common causes of blindness in individuals between the ages of 20 and 65 years. Neovascularization is the hallmark of proliferative diabetic retinopathy (PDR). Development and progression of diabetic microangiopathy in terms of retinopathy are known to be closely related to poor metabolic control, elevated arterial blood pressure, and other risk factors.^{1,2}

Vitamin D (VD) is necessary for normal insulin release and maintenance of glucose tolerance. It increases insulin sensitivity and insulin secretion.³

The β (beta) cell possesses specific receptors for the activated hormone 1, 25-dihydroxyvitamin D3 (1, 25(OH) 2 D3) and vitamin D-dependent calcium-binding proteins.⁴ Insulin secretion is impaired by vitamin D deficiency and restored by 1, 25(OH) 2 D3 administration.⁵

In addition to its osteocalcic effect, VD has immunomodulatory, anti-inflammatory, antioxidant, antiangiogenic, and antiproliferative functions in many kinds of cell. All of them are mediated by vitamin D receptors (VDR), a member of the nuclear receptor super family, which is extensively expressed in the retina.⁶

In a mouse model of ischemic retinopathy, 1, 25(OH) 2 D3 inhibited retinal neovascularization,⁷ while in cell culture, it inhibited endothelial cell proliferation.⁸ The antitumor activity of vitamin D compounds has been demonstrated against a variety of cancers, including retinoblastoma.^{9,10}

It also reduces corneal inflammation and neovascularization.¹¹⁻¹³ The reduced vascularity observed in many tumors treated with vitamin D compounds suggests tumor vasculature may be a target.⁷ Therefore, low serum levels of 1, 25(OH) 2 D3 may lead to increased, uncontrolled angiogenesis.¹⁴ And may be associated with endothelial dysfunction.¹⁵

Vitamin D deficiency is also associated with a high plasma PTH levels which is present in sub retinal fluids of the human eye. PTH excess can reduce glucose tolerance¹⁶ and induce inflammatory cytokines.¹⁷

Vitamin D may confer its actions via inhibition of inflammation, down regulation of the renin-angiotensin system, improved insulin secretion, and an antiproliferative effect on endothelial cells.¹⁸

In the present study, we investigate vitamin D and parathormone (PTH) concentrations as predictors of the development and severity of diabetic retinopathy.

2. Materials and methods

2.1. Patients

The present study is a cross sectional study with informed consent signed by all patients according to a protocol approved by the Ethics Committee of the Hospital.

Our study sample comprised 200 diabetic patients presenting with suspected diabetic retinopathy admitted to Alexandria and Kasr Al Eini hospital. Forty-three patients were insulin-dependent (type 1 diabetes) and 157 were noninsulin dependent (type 2 diabetes).

The duration of diabetes ranged from 11 to 28 years with a mean range of 19.6 ± 1.7 years. Fifty-two percentage were females while 48% were males with a mean age of 69 ± 2.6 years.

Therapy modalities for type 2 diabetes were diet therapy alone (5%), diet therapy plus oral antidiabetic drugs (74%) or diet therapy plus insulin therapy (21%).

History taking and complete clinical examination were done and recorded. Patients receiving Vit D therapy or similar drugs as mineral supplements or medications that are known to alter mineral metabolism (e.g., estrogen, thiazide diuretics, and anticonvulsants) were excluded from the study. Patients with major medical illness including renal failure, hepatic disease, and skeletal disease were also excluded.

2.2. Sampling

Blood samples were collected after an overnight fast. Serum was separated and stored frozen at 20° C. Routine blood examination, HbA (1c) were measured by using commercially available kits.

Levels of vitamin D [25(OH) D3 and Calcitriol] were determined by ELISA Kit from DRG International, Inc. – Biocompare Buyer's and PTH levels by ELISA immunodiagnostic system (IDS).

2.3. Ophthalmological examination

Assessment of visual acuity (Best Corrected Visual Acuity) (BCA) and anterior segment examination by slit lamp biomicroscopy were performed.

Diabetic retinopathy was assessed using 7-field stereoscopic fundus photography. Fundus fluorescein angiography was performed for all patients with retinopathy.

Levels of retinopathy were classified according to early treatment diabetic retinopathy study (ETDRS) into: No retinopathy (NR), mild nonproliferative diabetic retinopathy (mild NPDR), moderate nonproliferative diabetic retinopathy (moderate NPDR), severe nonproliferative diabetic retinopathy (severe NPDR) and proliferative diabetic retinopathy (PDR) Table 1.

(Twenty-one percentage) of our patients had NR, (19%) had mild NPDR, (17.5%) had moderate NPDR, (20.5%) had severe or very severe NPDR and 22% had PDR.

2.4. Statistical analysis

Data were collected, tabulated and then analyzed using SPSS Ver.17. Qualitative data were presented as numbers and per-

Table 1 Classification of diabetic retinopathy.

Nonproliferative Diabetic Retinopathy (NPDR)	
A. Mild NPDR	
• At least one microaneurysm	
B. Moderate NPDR	
• Hemorrhages or microaneurysms (H/Ma)	
• Soft exudates, Venous beading (VB), and intraretinal microvascular abnormalities (IRMAs) definitely present.	
C. Severe NPDR	
• H/Ma in all 4 quadrants	
• VB in 2 or more quadrants	
• IRMA in at least 1 quadrant	
D. Very Severe NPDR	
• Any two or more of C	
Proliferative Diabetic Retinopathy	
E. Early PDR	
• New vessels on the retina	
• Definition not met for F	
F. High-Risk PDR	
• New vessels on the disc (NVD) of 1/4 to 1/3 or more of the disc area or	
• Any NV and vitreous, preretinal or vitreous hemorrhage	

cent. Quantitative data were expressed as means and standard deviation. ANOVA test was used for comparison between the means of quantitative variables, with post hoc tests for paired comparisons. Spearman's correlation coefficient by rank was used to analyze correlations between different parameters. A 5% level was chosen as a level of significance in all statistical tests used in the study.

3. Results

Mean serum concentration of 1, 25 dihydroxy vitamin D 3 (1, 25(OH) 2 D3) was significantly lower in diabetic patients with

retinopathy than those with no retinopathy (NR) (51.4 ± 16.64 vs. 70.7 ± 15.56 pmol/L, $p < 0.001$). There was a significant negative correlation between the mean level of 1, 25(OH) 2 D3 and the degree of severity of retinopathy ($p < 0.001$). In mild nonproliferative diabetic retinopathy (mild NPDR), the level was 67.4 ± 13.7 pmol/L. In moderate nonproliferative diabetic retinopathy (moderate NPDR) the level was 59.3 ± 11.2 pmol/L. In severe nonproliferative diabetic retinopathy (severe NPDR) it was 45.7 ± 16.6 pmol/L and in proliferative diabetic retinopathy (PDR) it was 34.1 ± 17.2 pmol/L (Table 2).

There was a significant negative correlation between the Mean serum concentration of 1, 25 dihydroxy vitamin D 3 (1, 25(OH) 2 D3) and the age ($r = -0.154$, $p < 0.001$), duration of diabetes ($r = -0.342$, $p < 0.05$), and HbA1c ($r = -0.177$, $p < 0.001$). The latter 3 parameters showed a significant positive correlation with the degree of retinopathy ($r = 0.108$, $p = 0.016$) ($r = 0.217$, $p < 0.05$) and ($r = 0.365$, $p < 0.001$) respectively (Table 3). There was no correlation between serum level of 1, 25 dihydroxy vitamin D 3 (1, 25(OH) 2 D3) or the degree of retinopathy with the modality of treatment among different groups ($p > 0.05$).

The mean serum concentration of 25(OH) D was 31.6 ± 12.01 nmol/L. There was no correlation between serum 25(OH) D and mean serum level of 1, 25 dihydroxy vitamin D 3 or the degree of retinopathy ($p > 0.05$).

In diabetic patients with no retinopathy (NR), the mean serum concentration of PTH was 3.1 ± 0.45 , 3.2 ± 0.6 pmol/L in mild nonproliferative diabetic retinopathy (mild NPDR), 3.4 ± 0.17 pmol/L in moderate nonproliferative diabetic retinopathy (moderate NPDR), 5.4 ± 1.0 pmol/L in severe nonproliferative diabetic retinopathy (severe NPDR) and 6.0 ± 0.3 pmol/L in proliferative diabetic retinopathy (PDR).

There was no correlation between the mean serum concentration of PTH and the degree of retinopathy in NR, mild NPDR moderate NPDR ($p > 0.05$) while the level of PTH

Table 2 Correlation between the mean level of 1, 25(OH) 2 D3 and the degree of severity of retinopathy.

Degree of retinopathy	Mean level of 1, 25(OH) 2 D3 (pmol/L)	P value
Mild NPDR	67.4 ± 13.7	($p < 0.001$)
Moderate NPDR	59.3 ± 11.2	($p < 0.001$)
Severe NPDR	45.7 ± 16.6	($p < 0.001$)
PDR	34.1 ± 17.2	($p < 0.001$)

Mild NPDR): mild nonproliferative diabetic retinopathy.

(Moderate NPDR): moderate nonproliferative diabetic retinopathy.

(Severe NPDR): severe nonproliferative diabetic retinopathy.

(PDR): proliferative diabetic retinopathy.

p value < 0.05 is significant.

Table 3 Correlation between the Mean serum concentration of 1, 25 dihydroxy vitamin D 3 (1, 25(OH) 2 D3), the degree of retinopathy and different parameters.

	Age		Duration of diabetes		HbA1c	
	r	p	r	p	r	p
Mean serum concentration of (1, 25(OH) 2 D3)	-0.154	< 0.001	-0.342	< 0.05	-0.177	< 0.001
The degree of retinopathy	0.108	0.016	0.217	< 0.05	0.365	< 0.001

p value < 0.05 is significant.

was significantly higher in severe NPDR and PDR compared to patients with no retinopathy (NR) ($p < 0.001$).

4. Discussion

Calcitriol ($1\alpha, 25$ -dihydroxyvitamin D₃), the active hormonal form of vitamin D has a very important role, both pharmacological and physiological, at cellular level. It is a potent osteocalcic, immunomodulatory, anti-inflammatory and antioxidant factor in many kinds of cells. It also increases insulin sensitivity and insulin secretion.³

A majority of studies on the effect of $1, 25(\text{OH})_2\text{D}_3$ on cell growth and differentiation report an inhibition of proliferation coupled with an induction of differentiation.¹⁹

In addition to its effects on tumor cell proliferation and differentiation, it has a potent inhibitory effect on angiogenesis.¹⁰

Biological models support a causal role for VDD in proliferative retinopathy, which is characterized by neovascularization and angiogenesis. Higher serum $1, 25(\text{OH})_2\text{D}_3$ was associated with reduced angiogenesis in both a transgenic retinoblastoma model and ischemic retinopathy in mice.⁷

Mantell et al.¹⁹ demonstrated that the antiangiogenic properties of $1, 25(\text{OH})_2\text{D}_3$ are mediated by a direct effect on endothelial cells through inhibition of endothelial cell sprouting and morphogenesis, inhibition of VEGF-induced endothelial cell proliferation, inducing the regression of existing endothelial cell sprouts and elongated cells and inhibiting the formation of new blood vessels in tumor xenografts.

$1, 25(\text{OH})_2\text{D}_3$ also inhibits vascular endothelial growth factor (VEGF) induced endothelial cell proliferation,¹⁹ down-regulates the IGF-I pathway,²⁰ up-regulates the cellular transporters of sulfate²¹ which are negative regulators of angiogenesis,²² down-regulates the renin-angiotensin system,²³ stimulates the TGF β -1 (an antiproliferative and proapoptotic molecule),²⁴ and inhibits multiple proinflammatory and proangiogenic cytokines.¹¹⁻¹³ All of these molecules have been implicated in the pathogenesis of DR. On the other hand, calcium homeostasis and calcium-dependent signaling pathways have an important role in the development of retinal hypoxia, a major process in severe DR.⁶

Therefore, low serum levels of $1, 25(\text{OH})_2\text{D}_3$ may have an association with increased, uncontrolled angiogenesis with the progression of DR.²⁵

Our study showed that the Mean serum concentration of $1, 25$ dihydroxy vitamin D₃ ($1, 25(\text{OH})_2\text{D}_3$) was significantly lower in diabetic subjects with retinopathy than in diabetic subjects with no retinopathy (NR).

Also there was a significant negative correlation between the mean level of $1, 25(\text{OH})_2\text{D}_3$ and the severity of retinopathy being the lowest in proliferative diabetic retinopathy (PDR) group suggesting that neovascularization in the retina may involve a decrease in serum $1, 25(\text{OH})_2\text{D}_3$ concentrations in patients with DR.

These findings were in agreement with the study done in 2000 by Hulya et al.²⁵ who investigated whether there is a relationship between serum $1, 25$ dihydroxy vitamin D₃ [$1, 25(\text{OH})_2\text{D}_3$] and severity of diabetic retinopathy. They concluded that there was an inverse relationship between the severity of the retinopathy, i.e., neovascularization, and serum $1, 25(\text{OH})_2\text{D}_3$ concentrations, being the lowest in PDR and the highest in diabetic patients without retinopathy (NDR).

The current finding may suggest a permissive role of vitamin D deficiency in the pathogenesis of DR.

Our study revealed no correlation between the mean serum $25(\text{OH})\text{D}$ and the degree of retinopathy. These results are in agreement with Hülya Aksoy.²⁵ While a cross-sectional study of 581 type 2 diabetic patients shows a significant association between the existence of proliferative retinopathy and a decrease in $25(\text{OH})\text{D}_3$. Also, investigators found a decrease in $25(\text{OH})\text{D}_3$ according to the number of micro vascular complications present.^{26,27}

A clinic-based, cross-sectional study was conducted by Paynes and his colleagues in 2011 to assess the relationship between vitamin D status and diabetic retinopathy. They concluded that diabetic subjects, especially those with PDR, have lowered $25(\text{OH})\text{D}$ levels than those without diabetes.²⁸

The mean serum level of PTH in our study was significantly higher in severe NPDR and PDR compared to patients with no retinopathy (NR). These results are in agreement with the findings of previous studies.^{6,26,29}

This finding may be explained by a compensatory mechanism to the low serum $1, 25(\text{OH})_2\text{D}_3$ concentrations.

PTH excess can induce inflammatory cytokines which may play a role in the pathogenesis of proliferative DR.^{6,17}

From the results of the present study we can conclude that low levels of vitamin D might be a risk marker of development or progression of diabetic retinopathy. It might be advisable that detailed ophthalmologic examination is needed for diabetics whose serum $1, 25(\text{OH})_2\text{D}_3$ concentrations are diminished. The measurement of serum $1, 25(\text{OH})_2\text{D}_3$ concentrations could become a useful biochemical means to predict the severity of DR in patients with diabetes mellitus.

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