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Original Research Article

ROLE OF VITAMIN D IN ENDOTHELIAL CELL OF RETINA

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Abstract

Vitamin D deficiency is a common health problem worldwide. Many parts of the human eye, including the epithelium of the cornea, lens, ciliary body, and retinal pigment epithelium, as well as the corneal endothelium, ganglion cell layer, and retinal photoreceptors, contain vitamin D receptor. Physiological effects of vitamin D From an ocular point of view, the role in macular and retinal health had been advanced, as well as the involvement in corneal inflammatory response, wound healing, and dry eye disease. The most important effect of vitamin D is on, phosphorus, calcium metabolism and on bone mineralization. Recently, it was observed that vitamin D deficiency and insufficiency are related with common cancers, cardiovascular diseases, metabolic syndromes, infectious, and many chronic diseases including autoimmune disease. Benefits of vitamin D may be amplified through synergistic interaction with topical corticosteroids which accelerates improvement in corneal shape and optics, substantially benefiting the control of ocular surface disease and dry eye symptoms. Aqueous humour is the primary source responsible for the feeding of corneal endothelial layer hence endothelial abnormalities can be expected due to accumulated inflammatory cytokines and multiple toxic products in the aqueous humour of the patients with vitamin D deficiency.

MATERIAL AND METHODS: Subjects were selected with vitamin D deficiency in the age group of 20–55 years. 50 patients having serum vitamin D levels <15 ng/ml were included in the study. Serum vitamin D levels of <15 ng/ml were included in the control group. Vitamin D levels in tear fluid were measured by direct competitive chemiluminescent enzyme linked immunoassay. A complete ophthalmic evaluation was performed in all participants which includes assessment of visual acuity, anterior segment evaluation and posterior segment evaluation. Specular microscopy was performed on the eyes of the patients with vitamin D deficiency and healthy control group individuals. Corneal endothelial cell density (CD) and central corneal thickness (CCT) values were calculated automatically using the software of the specular microscope.

RESULTS: The study group included 23 male and 27 female subjects while study group included 24 male and 26 female. Mean age of male in study group was 46.4 ± 12.56 and female was 45.6 ± 11.77. In control group mean male age was 48.5 ± 9.25 and female age was 49.56 ± 12.55. In study group Mean Corneal endothelial cell density (CD) was observed as 2632.89 ± 189.25 cells/mm ^{2} and Mean central corneal thickness (CCT) was 587.2 ± 25.89 µ. In control group Mean Corneal endothelial cell density (CD) was observed as 2954.97 ± 116.89 cells/mm ^{2} and Mean central corneal thickness (CCT)

was 546.0 ± 36.22 µ. Vitamin D levels of Tears in study group was 8.4 ± 1.7 ng/ml and in control group it was 16.2 ± 2.3 ng/ml.

CONCLUSION: It has been observed that there is statistically significant difference in the corneal endothelial cell density (CD) and central corneal thickness (CCT) in patients with vitamin D deficiency. It was observed that Vitamin D is present in tear fluid and there is significant difference in the levels of vitamin D in study and control group.

Introduction:

Vitamin D deficiency is a common health problem worldwide. Many parts of the human eye, including the epithelium of the cornea, lens, ciliary body, and retinal pigment epithelium, as well as the corneal endothelium, ganglion cell layer, and retinal photoreceptors, contain vitamin D receptor (VDR) [1]. Physiological effects of vitamin D From an ocular point of view, the role in macular and retinal health had been advanced, as well as the involvement in corneal inflammatory response, wound healing, and dry eye disease [2].Vitamin D is a group of fat-soluble vitamin which can be synthesized by the body under appropriate biological conditions. It includes vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). In the liver hepatocytes, vitamin D3 is converted to calcidiol (calcifediol) 25-hydroxyvitamin D3 (25[OH] D3) and vitamin D2 is converted to 25-hydroxyergocalciferol (25[OH] D2) by the 25-hydroxylase. 25(OH)D3 is converted to 1,25-dihydroxycholecalciferol (1,25[OH]2D3-calcitriol), the active form of vitamin D3 by 1α hydroxylase in the kidneys and many tissues. To determine the vitamin D status in serum, these two vitamin D metabolites are measured [3].

The most important effect of vitamin D is on, phosphorus, calcium metabolism and on bone mineralization. Recently, it was observed that vitamin D deficiency and insufficiency are related with common cancers, cardiovascular diseases, metabolic syndromes, infectious, and many chronic diseases including autoimmune diseases [4]. Vitamin D3 increases the production of anti-inflammatory cytokines and reduces the production of pro-inflammatory cytokines thus playing important role in inflammatory process [5, 6]. Aqueous humor is the primary source responsible for the feeding of corneal endothelial layer hence endothelial abnormalities can be expected due to accumulated inflammatory cytokines and multiple toxic products in the aqueous humor of the patients with vitamin D deficiency.

The receptors for Vitamin D receptor (VDR) are expressed in the cornea, lens, ciliary body, retina, and retinal pigment epithelium and polymorphisms in the receptor and its start codon have been linked to myopia of the eye [7, 8, 9]. The keratoconus and other forms of keratoectasia, following refractive surgery, can be significantly improved by adequate vitamin D supplementation. Also benefits of vitamin D may be amplified through synergistic interaction with topical corticosteroids which accelerates improvement in corneal shape and optics, substantially benefiting the control of ocular surface disease and dry eye symptoms [10].

Our aim of the study was to see whether corneal endothelium is affected by the vitamin D deficiency as it causes inflammation, oxidation, and apoptosis.

MATERIAL AND METHODS

The present study was carried out in Dept. of Ophthalmology at K. M. Medical College and Hospital, Mathura (UP). The present study was approved by the institutional review board. 50 subjects were selected with vitamin D deficiency in the age group of 20–55 years. 50 patients having serum vitamin D levels <15 ng/ml were included in the study. Serum vitamin D levels of <15 ng/ml were included in the control group. Written informed consent was obtained from all the participants in study group and control group. Subjects were excluded if they had any

significant history of ocular disease, refractive surgery, corneal reshaping, bifocals or the use of atropine. Also systemic disease such as diabetes mellitus and hypertension, previous ocular surgery or laser therapy, history of any corneal disorder, trauma history, and glaucoma were excluded from the study. Vitamin D levels in tear fluid were measured by direct competitive chemiluminescent enzyme linked immunoassay.

A complete ophthalmic evaluation was performed in all participants which includes assessment of visual acuity, anterior segment evaluation and posterior segment evaluation after dilating pupils by +90D bio-microscopy to rule out certain posterior segment conditions such as glaucoma.

Specular microscopy was performed on the eyes of the patients with vitamin D deficiency and healthy control group individuals. Corneal endothelial cell density (CD) and central corneal thickness (CCT) values were calculated automatically using the software of the specular microscope

Statistical analysis was done with SPSS software. The mean or median value of the individual groups was reported as Mean ± SEM or median (along with the range). Two-tailed $p < 0.05$ was considered to be statistically significant.

OBSERVATIONS AND RESULTS

The study group included 23 male and 27 female subjects while study group included 24 male and 26 female.

Table 1: Study and control group

Group	Male	Female	Mean age Male	Mean age Female
Study group	23	27	46.4 ± 12.56	45.6 ± 11.77
Control group	24	26	48.5 ± 9.25	49.56 ± 12.55

Mean age of male in study group was 46.4 ± 12.56 and female was 45.6 ± 11.77. In control group mean male age was 48.5 ± 9.25 and female age was 49.56 ± 12.55.

Table2: Vitamin D level study and control group

Group	Male	Female	Total
Study group	7.56 ± 3.25	5.23±2.21	6.26±3.10
Control group	48.55 ± 9.56	46.22 ± 10.22	47.22±9.98
P value	P < 0.0001	P < 0.0001	P < 0.0001

Intraocular pressure, anterior segment bio microscopic examinations, and posterior segment findings were normal in study as well as in control groups. Corneal endothelial cell density (CD), and central corneal thickness (CCT) values were calculated.

Table 3: Corneal endothelial cell density (CD), and central corneal thickness (CCT)

Group	Mean Corneal endothelial cell density (CD)	Mean central corneal thickness (CCT)	Vitamin D level in Tears
Study group	2632.89 ± 189.25 cells/mm ^{2}	587.2 ± 25.89 µ	8.4 ± 1.7 ng/ml
Control group	2954.97 ± 116.89 cells/mm ^{2}	546.0 ± 36.22 µ	16.2 ± 2.3 ng/ml
Difference	322.080	-41.200	7.800
Standard error	31.458	6.296	0.404
95% CI (Confidence Interval)	259.6535 to 384.5065	-53.6948 to -28.7052	6.9973 to 8.6027
t-statistic	10.239	-6.544	19.284
DF	98	98	98
Significance level	P < 0.0001	P < 0.0001	P < 0.0001

In study group Mean Corneal endothelial cell density (CD) was observed as 2632.89 ± 189.25 cells/mm ^{2} and Mean central corneal thickness (CCT) was 587.2 ± 25.89 µ. In control group Mean Corneal endothelial cell density (CD) was observed as 2954.97 ± 116.89 cells/mm ^{2} and Mean central corneal thickness (CCT) was 546.0 ± 36.22 µ. Vitamin D level of Tears in study group was 8.4 ± 1.7 ng/ml and in control group it was 16.2 ± 2.3 ng/ml. Statistically significant difference was observed in study group as well as in control group in regard to Mean Corneal endothelial cell density (CD), Mean central corneal thickness (CCT) and Vitamin D levels of Tears.

DISCUSSION AND CONCLUSION

Blood levels of vitamin D has been related to the dietary variables. There is positive association between increased calcium in the diet and increased vitamin D levels in the blood [11]. Lower levels of vitamin D have been found in the obese [12]. Vitamin D deficiency has been linked to dry eye [8]. There is a protective role for vitamin D for macular degeneration [13]. In an observation it is found that beneficial responses are usually only seen when the serum 25(OH)D3 level rises above 50 ng/cc and optimal response begins around 70-80 ng/cc [14]. Vitamin D is known for modulating the expression of various inflammatory cytokines in various cells which includes corneal epithelial cells [15] and correction of vitamin D deficiency reversed symptoms in a case of corneal neuralgia [16]. Vitamin D (both 25-hydroxyvitamin D_3 and 1, 25-dihydroxyvitamin D_3) was shown to influence corneal epithelial barrier function by regulating expression of occluding [17].

In our study Vitamin D was measured in human tears by competitive chemiluminescent immunoassay and it was found that a vitamin D level in serum of study group was 6.26±3.10 and in control group was 47.22±9.98. This was statistically significant. In tears vitamin D levels were 8.4 ± 1.7 ng/ml in study group and 16.2 ± 2.3 ng/ml in control group. In a study it was found that the 25-hydroxyvitamin D level was significantly higher in the tears than in the serum [18]. Also in, another study reported significantly higher 25-hydroxyvitamin D levels in tears (71.8 ± 6.2 ng/ml) compared to serum (21.8 ± 11.3 ng/ml) in children (12.5 ± 2.5 years) using electro chemiluminescent immunoassay [19].

Oxidation, inflammation, and angiogenesis in the ocular tissues may lead to dysfunction and cell loss and vitamin D inhibits the production of pro-inflammatory cytokines, including interleukin (IL)-2, IL-12, interferon-γ, and tumor necrosis factor-α [20]. In a study by Codoner-Franch et. al. [21], demonstrated that lower vitamin D levels have association with higher levels of oxidative stress biomarkers including plasma malondialdehyde and nitrotyrosine concentrations in obese children. In our study significant difference was observed in Mean Corneal endothelial cell density (CD), Mean central corneal thickness (CCT) and Vitamin D level of Tears of vitamin D deficiency patients and control group. It has been demonstrated that vitamin D is able to regulate proliferation and cell differentiation, apoptosis, angiogenesis, and gene regulation. Also in animal studies it has been demonstrated that the exposure of vitamin D to lymphocytes results in decreased cell proliferation and apoptosis [22]. In our study endothelial indices such as CD and CCT were abnormal in study group showing **corneal endothelial layer being affected**. As the sample size is small we cannot conclude the study but in our study it has been observed that there is statistically significant difference in the **corneal endothelial cell density (CD) and central corneal thickness (CCT) in patients with vitamin D deficiency**. It was observed that **Vitamin D is present in tear fluid and there is significant difference in the levels of vitamin D in study and control group**.

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