Effect of low 25-Hydroxyvitamin D Levels on Retinal Nerve Fiber Layer Thickness

Düşük Serum 25-Hydroxyvitamin D Düzeylerinin Retina Sinir Lifi Kalınlığına Etkisi

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ABSTRACT

Purpose: To compare the retinal nerve fiber layer (RNFL) thickness of patients with low serum 25-hydroxyvitamin D (25OHD) with those of healthy controls.

Materials and Methods: Forty eyes of 40 premenopausal women with low serum 25OHD (patient group) and 40 eyes of 40 age- and sex-matched healthy subjects (control group) were included in the study. Disc area (DA), rim area (RA), central subfield thickness (CST), cube volume (CV), cube average thickness (CAT), average RNFL thickness, and peripapillary RNFL thicknesses of temporal, nasal, inferior, and superior quadrants were determined by Cirrus HD spectral-domain optical coherence tomography (OCT) in each participant.

Results: Although CST and CAT were thinner in the patient group than in the control group, the difference did not reach statistical significance (p1=0.019 and p2=0.025, respectively). On the other hand, CST had a significant correlation with serum 25OHD levels (r1=0.371, p1<0.001).

Conclusions: We demonstrated that although low serum 25OHD levels caused CST and CAT thinning, this thinning was not statistically significant. However, there was a relationship between the CST and serum 25OHD levels. Further studies with larger sample sizes are warranted.

Key Words: 25-Hydroxyvitamin D, spectral-domain, optical coherence tomography.

ÖZ

Amaç: Serum 25-Hydroxyvitamin D (25OHD) düzeyi düşük hastaların retina sinir lifi tabakası (RSLT) kalınlıklarını sağlıklı insanlarınkiyle karşılaştırmak.

Gereç ve Yöntem: Serum 25OHD düzeyi düşük 40 premenopozal kadının 40 gözü (hasta grubu) ile yaş ve cinsiyetleri aynı olarak seçilen 40 sağlıklı gönüllünün 40 gözü (kontrol grubu) çalışma kapsamına alındı. Her katılımcının disk alanı (DA), rim alanı (RA), santral fovea kalınlığı (SFK), foveal hacim (FH), ortalama foveal kalınlık (OFK) ile ortalama, temporal, nazal, inferior ve superior kadran peripapiller RSLT kalınlıkları Cirrus HD spektral-domain OKT ile ölçüldü.

Bulgular: Hasta grubunda SFK ve OFK değerleri kontrol grubuna göre daha inceydi fakat aradaki fark istatistiksel olarak anlamlı değildi (p1=0.019 and p2=0.025, sırasıyla). Ancak SFK değerleri ile serum 25OHD değerleri arasında anlamlı bir korelasyon mevcuttu (r1=0.371, p1<0.001).

Sonuç: Bu çalışmada düşük serum 25OHD düzeylerinin SFK ve OFK değerlerinde incelmeye sebep olduğunu, ancak bu incelmenin istatistiksel olarak anlamlı olmadığını gösterdik. Fakat SFK değerleri ile serum 25OHD değerleri arasında bir ilişki mevcuttu. Bu konuda daha fazla katılımcıdan oluşan daha fazla sayıda çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: 25-Hidroksivitamin D, spektral-domain, optik koherens tomografi.

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INTRODUCTION

Vitamin D is a steroid hormone with multiple biological functions.[1,2] Low serum 25-hydroxyvitamin D (25OHD) levels have been demonstrated to be frequent in the elderly, with a prevalence of 90%, and have been shown to be related to several adverse health results in addition to bone defects.[1-3] It has been displayed that low serum 25OHD levels were associated with early age-related macular degeneration (AMD).4 In addition, high serum levels of vitamin D have been recognized as a factor reducing the risk of AMD.[4,5]

The pathogenesis of AMD is not well-known, but it is well established that angiogenesis plays a main role in the development and progression of AMD.6 In addition, inflammation has been described as a potential risk factor for AMD.[7,8] Previous studies have suggested an anti-inflammatory role for vitamin D.[9]

Due to the potential causative role of inflammation in AMD, it is possible that vitamin D may protect against the occurrence and progression of AMD via its anti-inflammatory properties. Further, it was recently displayed that vitamin D is a potent inhibitor of angiogenesis.[10-12] Therefore, we hypothesized that in patients with vitamin D deficiency there might be the signs of early AMD and accordingly, the macular findings of optical coherence tomography (OCT) might be different from healthy controls.

To our best knowledge, there is no study investigating the effect of low serum 25- 25OHD concentrations on retinal nerve fiber layer thickness. Therefore, in the present study we aimed to compare retinal nerve fiber layer (RNFL) thicknesses of patients with low serum 25-hydroxyvitamin D (25OHD) with those of healthy controls by spectral-domain OCT.

MATERIALS AND METHODS

Forty eyes of 40 premenopausal women with low serum 25OHD (patient group) and 40 eyes of 40 age- and sex-matched healthy subjects (control group) were consecutively included in this cross-sectional study. The patients were diagnosed in Department of Physical Medicine and Rehabilitation. The control subjects were chosen from the hospital staff and family members of patients. Control subjects had had no systemic disease which could affect the OCT parameters (i.e. diabetes mellitus or hypertension) and they all had normal serum 25OHD levels. Fasting early-morning venous blood was collected from subjects for measurement of serum 25OHD. Serum concentrations of 25OHD were measured using radioimmunoassay (Incstar Corp., Stillwater, MN). A cutoff point of 30 ng/mL was used to define the vitamin D status.[2] Subjects with <30 ng/mL serum 25OHD levels including both patients with vitamin D deficiency (with serum 25OHD concentrations less than 10 ng/mL) and patients with vitamin D insufficiency (with serum 25OHD concentrations of 10-30 ng/mL) were enrolled to the patient group.[13] All control subjects had serum 25 OHD levels of ≥30 ng/mL. All patients were informed about the study procedure and consented to participate. This study followed the Tenets of the Declaration of Helsinki and was approved by the Local Ethics Committee.

A standard ophthalmological examination including evaluation of visual acuity (by Snellen charts), slit-lamp biomicroscopic examination, measurement of intraocular pressure (by Goldmann applanation tonometry), central corneal thickness measurement, perimetry, and funduscopy was performed for each subject. Exclusion criteria included glaucoma or an intraocular pressure higher than 21 mmHg (cup/disc ratio abnormalities or glaucomatous visual field defects), corneal abnormalities, retinal diseases, pseudoexfoliation syndrome, optic disc disorders, neurological diseases, a previous history of ophthalmic surgery or ocular trauma, myopia or hyperopia >3.0 diopters, AMD, and use of steroids or antiglaucomatous drugs. Peripapillary RNFL thickness was measured by the same blinded investigator using Cirrus HD spectral-domain OCT (Carl Zeiss Meditec, Dublin, CA). Disc area (DA), rim area (RA), central subfield thickness (CST), cube volume (CV), cube average thickness (CAT), average peripapillary RNFL thickness, and peripapillary RNFL thicknesses of temporal, nasal, inferior, and superior quadrants were determined with optic disc 200×200 cube scan protocol, along a circle with a diameter of 3.45 mm around the center of the disc. Scans with signal strengths lower than 7 were excluded from the study.

Statistical Analysis

Statistical analysis was performed using SPSS version 16.0. Sex was compared using the chi-square test. All variables were checked with the Kolmogorov-Smirnov test. The paired t-test was used to compare the groups. Pearson correlation coefficients were calculated to evaluate relations between the OCT parameters and 25OHD. Bonferroni's test was used for adjustment of multiple comparisons. Statistical significance was set at 0.05/10=0.005.

RESULTS

The demographic and clinical characteristics of the groups are given in the table. The groups were similar concerning axial length ($p>0.05$), whereas they were significantly different regarding serum 25OHD levels ($p<0.001$).

Table: *The demographic and clinical characteristics of the groups (mean±SD).*

Characteristic	Patient group (n=40)	Control group (n=40)	P
Age (years)	35.0±7.5	35.0±7.5	
Sex (male/female)	22/18	22/18	
Axial length (mm)	24.0±1.0	24.2±1.2	0.860
25O HD (ng/mL)	12.4±3.7	27.9±9.2	**<0.001**
CST (µm)	242.9±18.6	252.8±19.6	0.019
CV (mm3)	9.4±0.6	9.5±0.8	0.393
CAT (µm)	278.2±8.8	282.9±9.7	0.025
DA (mm2)	1.8±0.2	1.9±0.3	0.833
RA (mm2)	1.3±0.2	1.3±0.2	0.677
Peripapillary RNFL thickness (µm)			
Average	93.0±8.0	92.6±6.6	0.822
Temporal quadrant	62.8±7.9	65.7±10.7	0.165
Superior quadrant	116.7±14.9	112.9±17.5	0.284
Nasal quadrant	73.7±8.6	72.8±11.9	0.699
Inferior quadrant	118.1±17.0	116.1±17.4	0.605

25OHD; 25-hydroxyvitamin D, CAV; Cube Average Thickness, CST; Central Subfield Thickness, CV; Cube Volume, DA; Disc Area, RA; Rim Area, RNFL; Retinal Nerve Fiber Layer, Patient group; group that included patients with low 25OHD Statistical significance was set at 0.05 / 10=0.005.

None of the patients had ocular hypertension, glaucoma or any visual field defect. Although CST and CAT were thinner in the patient group than in the control group the difference did not reach statistical significance after Bonferroni adjustment (p1=0.019 and p2=0.025, respectively). In addition, there were no significant differences between the groups concerning CV, DA, RA, average peripapillary RNFL thickness and peripapillary RNFL thicknesses of all four quadrants. CST had a significant correlation with serum 25OHD levels (r1=0.371, p1<0.001). However, CAT, CV, DA, RA, average peripapillary RNFL thickness, and peripapillary RNFL thicknesses of all four quadrants had no correlation with serum 25OHD levels.

DISCUSSION

The present study displayed that although CST and CAT were thinner in premenopausal women with low serum 25OHD than in healthy controls according to measurements performed by Cirrus HD spectral-domain OCT, the differences did not reach statistical significance. Further, there was no significant difference between the groups regarding CV, DA, RA, average peripapillary RNFL thickness, and peripapillary RNFL thicknesses of all four quadrants.

On the other hand, CST had a significant correlation with serum 25OHD levels. Vitamin D is thought to have a possible role in ocular functioning as its receptors have been found in vertebrate retinal tissue.[14,15] Further, it is expressed in human cultured retinal endothelial cells.[16] Vitamin D has been revealed to reduce angiogenesis in cultured endothelial cells, the retinas of retinoblastoma animal models, and oxygen-induced ischemic retinopathy.[10,11,17] The pathogenesis of AMD includes a complex interaction of multiple factors including light damage, oxidative stress, inflammation, possible disturbance in the choroidal blood vessels, and genetic predisposition.[18-22] Immunological changes seem to be associated with early pathological changes in the retinal pigment epithelium and drusen formation. Immune components, including immunoglobulins, complement factors and fibrinogen, have been observed to be entrapped within drusen.[23-25] Evidence of inflammatory cell involvement in the later stages of AMD includes the presence of multinucleated giant cells and leukocytes in the choroid of AMD eyes and in excised choroidal neovascularization.[26-28] It has been shown that vitamin D reduces the proliferation of cells of the immune system, and that there is an inverse relationship between vitamin D levels and several chronic conditions associated with inflammation.[29-34]

In addition, it has been shown that vitamin D is a potent inhibitor of angiogenesis by its influence on endothelial cells and by interrupting signaling pathways which are key to angiogenesis.[10-12] In the present study, we could not find a significant difference between the foveal thicknesses of the groups. However, our results showed that there was a relationship between the central foveal thickness and serum 25OHD levels.

Parekh et al.,4 using fundus photography analysis, investigated the relationship between serum 25OHD levels and AMD in a cross-sectional study. They displayed that serum 25OHD levels were conversely related with early AMD but not with advanced AMD. However, visual function was not assessed in the study population. The pathognomonic signs of early AMD are the presence of pigmentary changes and drusen which is extracellular deposition of abnormal material in the macula.[35] The pigmentary changes occur at the level of the retinal pigmented epithelial cells, and are thought to reflect a dysfunction or partial loss of these cells.[12] Schuman et al.,[36] investigated changes in the neurosensory retina over drusens in subjects with non-neovascular AMD by using spectral-domain OCT, and noted thinning of the photoreceptor layer overlying these drusen. In addition, Curcio et al.,37 reported a correlation between the presence of drusen and photoreceptor cell death in the retinas of eyes diagnosed with AMD. Focal loss of photoreceptors was not recorded over specific drusen; however, the photoreceptor loss did appear more widespread than noted in study by Schuman et al. In the present study, we failed to find foveal thinning in patients with low serum 25OHD levels. This might have been caused by the small sample size of our study. We believe that larger series will be more informative.

Measurement of macular thickness is important for the diagnosis, treatment, and follow-up of several ocular diseases. The introduction of OCT has allowed ophthalmologists to reliably notice small changes in macular thickness and to quantitatively assess the efficacy of different therapeutic modalities. In this study, we used spectral-domain OCT which is a recent technique imaging of ocular structures with higher resolution and faster scan rate compared with the previous version of this technology.[38,39] As far as we are aware, we are the first to investigate the association between low serum 25OHD and spectral-domain OCT parameters.

In conclusion, we demonstrated that although low serum 25OHD levels caused CST and CAT thinning, this thinning was not statistically significant. On the other hand, CST had a significant correlation with serum 25OHD levels. Further studies with larger sample sizes are warranted.

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