JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/13872

An examination of retinal findings with optical coherence tomography in hypothyroidism patients with vitamin D deficiency: A comparative study

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Received: 2023-09-17.
Accepted: 2023-10-18

J Clin Med Kaz 2023; 20(6):36-40

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Abstract

Aim: This study aimed to examine the retinal layer before and after treatment in patients with hypothyroidism with vitamin D deficiency, since the vitamin also protects the retinal cells against inflammatory damage.

Material and methods: The free T3, free T4, and vitamin D levels of 104 patients with no ocular disease were first measured. Ophthalmological examinations of these patients, who were divided into three groups, were performed by specialist ophthalmologists, while retinal findings were examined using optical coherence tomography (OCT) and recorded. The first group was given vitamin D for three months, the second levothyroxine, and the third vitamin D + levothyroxine. After three months repeat OCT was performed, and the results were compared with the previous values.

Results: The thickness of the left inner nuclear cell layer of the patients in the vitamin D group increased significantly compared to pre-treatment. Post-treatment right central macular thickness, right nerve fiber layer, right outer nuclear cell layer, right pigment epithelial layer, left central macular, and left inner nuclear cell layer thicknesses were all significantly higher compared to pre-treatment in the patients in the levothyroxine + vitamin D group, while right outer retinal layer and left retinal nerve fiber thicknesses decreased ($p<0.05$).

Conclusion: A greater increase in cell layer thickness was observed in the group using vitamin D and levothyroxine together compared to those in which vitamin D and levothyroxine were employed alone. However, further studies on the effect of vitamin D on retinal cell development and protection against injury are now needed.

Keywords: Hashimoto's thyroiditis, hypothyroidism, optical coherence tomography, retina, vitamin D

Introduction

The most frequent cause of hypothyroidism, a disease caused by insufficient synthesis and/or release of thyroid hormones, is Hashimoto's thyroiditis (HT). This was first described in 1912 and is the most frequently encountered autoimmune thyroiditis in the general population. The disease emerges through the interaction of environmental (30%) and genetic (70%) factors [1]. Genetic factors include immune regulator genes, major histocompatibility genes (HLA), and thyroid-specific genes (Tg and TSHR) [2]. Environmental factors include smoking, alcohol use, iodine intake through diet, stress, selenium and Vitamin D deficiency, bacterial and viral infections, pregnancy, and medications [1,2]. Although HT is generally asymptomatic, some patients describe a sensation of heat, tightness, and pain in the neck [3]. Hypothyroidism is present in approximately 20% of patients at the time of diagnosis [4]. In contrast to other vitamins, Vitamin D is regarded as a hormone since it is synthetized in the body. It is known to affect bone

metabolism and Ca balance in the body. Studies have maintained that vitamin D can exhibit potentially protective effects in several human diseases, including various types of cancer, cardiovascular diseases, kidney and muscle diseases, hypertension, and type 2 diabetes mellitus [5-12]. Vitamin D exhibits neuroprotective and neuromodulatory effects, and is associated with several diseases that affect the central nervous system, such as Alzheimer's [13].The effects on the retina of vitamin D deficiency and hypothyroidism have been investigated separately in several studies [14,15]. However, we encountered no previous studies evaluating retinal findings with optic coherence tomography (OCT) in patients with hypothyroidism accompanying vitamin D deficiency and the relationship between these findings and vitamin D deficiency.

The purpose of this study was to investigate ophthalmological examination findings and retinal findings determined using optical coherence tomography, and the effect of the addition of vitamin D to hypothyroidism treatment on retinal cell layers in hypothyroid patients with vitamin D deficiency detected at the internal medicine clinic.

Material and methods

Setting and participants

One hundred four patients meeting the inclusion criteria between 01.06.2021 and 01.12.2021 were included in the study. Patients aged over 18 and meeting the inclusion criteria, with hypothyroidism and vitamin D deficiency, with no chronic disease, not receiving Vitamin D therapy, with no retinal disease, and with no corneal, lens, or vitreous opacity that might prevent OCT being performed were referred to the eye diseases clinic once their free T3, free T4, TSH, and vitamin D levels had been measured and recorded. The patients were divided into three groups, one receiving levothyroxine alone, one receiving vitamin D alone, and a third receiving combined levothyroxine and vitamin D. Routine ophthalmological examinations and visual acuity evaluations were performed by specialist ophthalmologists in the eye diseases clinic, and biomicroscopic examinations were also performed. Retinal images were than captured in a non-interventional manner using a Spectralis-OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) device in the eye diseases clinic. Ophthalmological findings and retinal layer thicknesses calculated from images obtained using an ACT device were recorded. The three groups were invited to attend check-ups after three months of treatment. Full participation was achieved, and no patient loss occurred. Retinal layer thicknesses were again recorded using OCT.

Statistical analysis

The research data were analyzed on SPSS (Statistical Package for the Social Sciences) version 23.0 software. In addition to descriptive methods such as number and percentage calculations and arithmetic mean, the Kolmogorov-Smirnov test was applied to evaluate normality of distribution. The paired t test and One-Way ANOVA (Tukey's test for post hoc) were used to compare normally distributed variables between the groups. The results were expressed at a 95% confidence interval, with p values <0.05 being regarded as statistically significant.

Results

The participants' descriptive characteristics

The mean age of the patients in the study was 48.46±11.57 years (min 22, max 73), 68.3% were women, 33.7% had a chronic disease, and 34.6% used levothyroxine + vitamin D therapy. Fifty percent of patients had severely low vitamin D levels (Table 1).

Table 1 The participants' descriptive characteristics (n=104)

Characteristic	n	%
Sex		
Female	71	68.3
Male	33	31.7
Chronic disease		
Yes	35	33.7
No	69	66.3
Vitamin D level		
Severely low	52	50.0
Moderately low	52	50.2
Group		
Levothyroxine	33	31.7
Vitamin D	35	33.7
Levothyroxine+Vitamin D	36	34.6
Age (Mean±SD)	48.46±11.57 (min. 22, max. 73)	

Retinal cell layer values before and after treatment in the study groups

No statistically significant associations were observed between retinal cell layer measurements and T3 levels among the different treatment groups (p>0.005). However, T3 levels differed significantly depending on the type of treatment (p<0.001). Advanced analysis performed to identify the group in which this difference appeared revealed significantly higher T3 levels in the levothyroxine group than in the other two groups. Examination of TSH levels in terms of type of treatment revealed significantly higher values in the levothyroxine + vitamin D group compared to the levothyroxine only group.

Right outer retinal cell layer thicknesses in the levothyroxine group decreased significantly compare to pre-treatment.

In the vitamin D group, left inner plexiform layer and left retinal nerve fiber thicknesses decreased compared to pre-treatment, while a significant increase was determined in left inner nuclear cell layer thickness compared to pre-treatment.

Significant increases were determined post-treatment in terms of right central macular thickness, right nerve fiber layer, right outer nuclear cell layer, right pigment epithelial layer, left central macular thickness, and left inner nuclear cell layer thickness compared to pre-treatment values in patients in the levothyroxine +vitamin D group, while right outer retinal layer and left retinal nerve fiber thicknesses decreased (p<0.005) (Table 2).

A comparison of the patients' pre- and post-treatment Vitamin D levels

Significant differences were determined between the levothyroxine, Vitamin D, and levothyroxine+ Vitamin D groups' pre-treatment Vitamin D levels (p<0.001) (Table 3).

A comparison of the patients' pre- and post-treatment Vitamin D levels in the study groups

Post-hoc analysis applied to identify the group from which the difference derived showed that pre-treatment Vitamin D levels were significantly higher in the levothyroxine group than in the other two study groups. However, no significant variation in post-treatment Vitamin D levels was observed among the groups.

Vitamin D levels increased significantly after treatment compared to pre-treatment levels in the levothyroxine, Vitamin D, and levothyroxine+ Vitamin D groups (p<0.001) (Table 4).

Table 2 Retinal cell layer values before and after treatment in the study groups

	Levothyroxine groupa Mean±SD	Vitamin D groupb Mean±SD	Levothyroxine+ vitamin D groupc Mean±SD	p*
Right central macular thickness (Before) Right central macular thickness (After) p**	271.51±31.02 273.45±25.84 0,319	266.14±25.91 268.28±22.95 0.106	266.70±26.00 269.03±23.09 0.012	0.382 0.374
Right nerve fiber layers (Before) Right nerve fiber layers (After) p**	11.54±3.44 12.18±2.05 0.321	11.80±3.35 12.42±2.67 0.104	11.47±2.76 12.55±2.48 0.029	0.903 0.799
Right ganglion cell layer (Before) Right ganglion cell layer (After) p**	14.72±8.04 13.66±3.75 0.497	15.22±9.17 14.37±6.44 0.491	13.33±4.54 13.19±2.61 0.858	0.555 0.552
Right inner plexiform cell layer (Before) Right inner plexiform cell layer (After) p**	19.06±6.48 19.12±3.22 0.958	19.85±6.47 20.00±4.70 0.882	17.86±3.97 19.38±3.04 0.071	0.340 0.609
Right inner nuclear cell layer (Before) Right inner nuclear cell layer (After) p**	19.66±8.05 19.87±3.45 0.878	19.40±7.47 18.74±4.03 0.586	17.52±5.34 18.44±3.78 0.362	0.383 0.259
Right outer plexiform cell layer (Before) Right outer plexiform cell layer (After) p**	26.76±9.24 25.78±3.58 0.546	26.94±6.66 27.42±5.62 0.697	26.19±7.99 26.05±5.20 0.919	0.919 0.333
Right outer nuclear cell layer (Before) Right outer nuclear cell layer (After) p**	87.87±11.71 93.06±8.03 0.019	86.74±13.71 89.28±9.90 0.205	87.16±13.53 91.61±8.72 0.040	0.937 0.217
Right pigment epithelial layer (Before) Right pigment epithelial layer (After) p**	16.60±4.28 16.66±1.45 0.941	15.54±2.63 16.31±1.45 0.086	15.27±1.56 16.22±1.74 0.011	0.161 0.466
Right inner retinal layer (Before) Right inner retinal layer (After) p**	182.72±33.92 181.36±13.91 0.830	179.42±29.02 178.31±19.30 0.794	175.25±21.19 181.19±14.22 0.100	0.549 0.673
Right outer retinal layer (Before) Right outer retinal layer (After) p**	87.72±4.77 85.30±4.23 0.041	85.94±4.69 85.40±3.92 0.592	86.69±3.83 85.05±4.30 0.042	0.257 0.937
Right retinal nerve fiber thickness (Before) Right retinal nerve fiber thickness (After) p**	99.06±11.56 100.96±10.61 0.261	101.54±7.64 99.40±6.48 0.061	98.94±9.17 97.44±8.52 0.248	0.442 0.243
Left central macular thickness (Before) Left central macular thickness (After) p**	269.87±28.45 273.60±10.70 0.463	263.65±19.83 269.71±16.14 0.052	261.58±17.13 269.72±12.80 0.020	0.279 0.394
Left nerve fiber layer (Before) Left nerve fiber layer (After) p**	13.15±7.83 12.09±1.89 0.469	11.68±2.17 11.77±2.17 0.812	12.16±2.22 11.50±2.14 0.319	0.406 0.501
Left ganglion cell layer (Before) Left ganglion cell layer (After) p**	13.66±4.78 12.63±1.98 0.249	12.91±3.39 13.08±2.79 0.726	13.18±3.75 12.55±3.29 0.499	0.721 0.688
Left inner plexiform layer (Before) Left inner plexiform layer (After) p**	19.60±6.87 17.48±2.20 0.106	18.80±3.23 17.82±2.99 0.040	18.00±3.65 17.36±2.88 0.363	0.386 0.759
Left inner nuclear cell layer (Before) Left inner nuclear cell layer (After) p**	19.78±7.18 21.24±4.23 0.305	17.40±4.62 20.34±4.53 0.001	18.33±5.67 21.61±4.53 0.009	0.249 0.470
Left outer plexiform cell layer (Before) Left outer plexiform cell layer (After) p**	27.51±8.41 27.12±3.58 0.801	26.14±6.24 27.20±3.76 0.275	26.77±6.69 26.16±4.74 0.679	0.732 0.497
Left outer nuclear cell layer (Before) Left outer nuclear cell layer (After) p**	89.00±12.30 92.87±10.91 0.136	91.20±11.07 92.28±11.26 0.646	85.72±11.39 93.02±11.52 0.001	0.139 0.958
Left pigment epithelial layer (Before) Left pigment epithelial layer (After) p**	16.96±6.89 15.30±2.44 0.218	16.34±5.15 15.48±2.20 0.337	15.52±1.64 15.41±2.23 0.818	0.487 0.947
Left inner retinal layer (Before) Left inner retinal layer (After) p**	181.45±27.46 182.42±15.67 0.842	176.91±20.14 180.68±15.67 0.233	174.11±17.49 179.63±13.77 0.081	0.380 0.703
Left outer retinal layer (Before) Left outer retinal layer (After) p**	86.51±7.50 84.63±4.32 0.247	86.31±4.95 85.31±5.20 0.364	85.83±3.68 85.63±4.03 0.817	0.870 0.651
Left retinal nerve fiber thickness (Before) Left retinal nerve fiber thickness (After) p**	96.12±14.08 95.15±9.41 0.647	100.14±8.02 96.31±7.05 0.007	97.02±10.87 93.63±9.12 0.025	0.299 0.423
T3	3.86±0.87	3.12±0.55	3.16±0.77	<0.001 a>b, a>c
T4	10.75±3.16	9.85±1.84	9.57±2.00	0.112
TSH	7.86±3.89	10.97±5.94	11.58±6.39	0.015 c>a

* One-way ANOVA, ** paired t test

Table 3 A comparison of the patients' pre- and post-treatment Vitamin D levels

Vitamin D	Mean±SD	p
Pre-treatment	13.92±5.84 (min.0, max.24)	<0.001
Post-treatment (3-months)	29.89±8.79 (min.13, max.88	

Table 4 A comparison of the patients' pre- and post-treatment Vitamin D levels in the study groups

	Levothyroxine groupa	Vitamin D groupb	Levothyroxine+ Vitamin D groupc	p
Pre-treatment	20.27±2.62	11.25±4.88	10.71±3.90	<0.001* a>b, a>c
Post-treatment	30.08±5.42	28.94±11.80	30.65±7.98	0.713*
P	<0.001**	<0.001**	<0.001**	

* One-way ANOVA, ** paired t test

Discussion

One of the environmental factors involved in the etiology of hypothyroidism is vitamin D deficiency [2]. Vitamin D has been shown to suppress the inflammatory cascade in the region between the retinal pigment epithelium and the choroid and to protect the retinal cells against inflammatory injury [16]. Decreased central retinal thickness measured using OCT in individuals with no disease has been found in subjects with vitamin D deficiency. In addition, an association has been found between vitamin D deficiency and decreased vision [17]. The findings of the present study suggest that vitamin D deficiency can give rise to thinning in specific retinal cell layers in hypothyroid patients. However, a significant increase was observed after treatment, particularly in the group receiving combined levothyroxine and vitamin D.

All members of the patient group in this study were hypothyroid, and thinning was determined in specific layers at initial examination. TSH levels were higher in the group using levothyroxine+vitamin. Ulas et al. compared the blood values and OCT findings of patients with chorioretinitis and a control group and determined high TSH values and a thinner choroid and retinal cell layer at OCT in the group with chorioretinitis. They therefore concluded that that thinning occurs in the cell layer in individuals with hypothyroidism [18].

Right outer retinal layer thicknesses in this study decreased significantly in the patients in the levothyroxine group compared to pre-treatment. Ozturk et al. examined the OCT findings of patients with primary hypothyroidism at one, three, and six months and reported no significant change in the thickness of the retinal nerve fiber layer after treatment compared to pre-treatment [19]. Yu et al. compared patients with thyroid-related ophthalmopathy and healthy volunteers and determined a thinner retinal nerve fiber layer in the ophthalmopathy group [20].

The thicknesses of the left inner plexiform layer and left retinal nerve fibers in this study decreased in the vitamin D group compared to pre-treatment, while left inner nuclear cell layer thickness increased significantly compared to pre-treatment. Fjeldstad et al. also determined no association between decreased retinal nerve fiber layer thickness or macular volume and Vitamin D deficiency in multiple sclerosis patients with no findings of optic neuritis [21]. These findings may be due to sampling differences.

Epidemiological studies recently showed an association between low 25-hydroxyvitamin D (25-OH-D) concentrations and impairment of visual acuity [22]. A positive association has also been reported between Vitamin D deficiency and age-related macular dysfunction [23-26].

Ozturk and Cankaya (2020) compared a group with vitamin D deficiency and a group with normal vitamin D levels and observed that deficiency produced adverse effects on contrast sensitivity function and also a difference in thickness in some segments of the retinal layers [27].

Statistically significant post-treatment increases in right central macular thickness, right nerve fiber layer, right outer nuclear cell layer, right pigment epithelial layer, left central macular, and left inner nuclear cell thicknesses compared to pre-treatment were observed in the group receiving levothyroxine + vitamin D. However, no significant increase was observed in the cell layers in the group receiving levothyroxine only. Link et al. examined the OCT retinal findings and visual acuity of a patient with vitamin D, vitamin A, and vitamin B6 deficiency before and after treatment and determined severe pre-treatment thinning in the inner plexiform layer and the ganglion cell layer, and vision impairment. However, an improvement in vision and increased thickness in the cell layers were determined after treatment [28].

Left inner nuclear cell layer thickness increased significantly in the present study in the group receiving vitamin D only. Another study involving a quantitative evaluation of retinal structure parameters in children with vitamin D deficiency compared retinal nerve fiber layer, central macula, retinal layer, and choroid thicknesses and structural retinal parameters including the central retinal artery and central retinal vein between the vitamin D deficiency group and healthy volunteers. The findings revealed choroidal thinning, a decreased central retinal artery diameter, and an increased central retinal vein diameter in the vitamin D deficiency group [29].

Robredo et al. investigated the effect of vitamin D against oxidative stress and inflammation in retinal pigment epithelium and retinal endothelial cell series and determined a decrease in proinflammatory cytokine and interleukin levels with the addition of vitamin D to treatment. This also suggests that Vitamin D exhibits anti-inflammatory effects [30]. In another study, Ekinci et al. showed that vitamin D3 [1.25 (OH) 2] exhibited an ameliorating effect against oxidative damage in retinal cell layers. At the same time, those authors reported that vitamin D represented an effective therapeutic alternative in the prevention of age-related macular degeneration [31].

Conclusion

The findings of this study suggest that changes occur in the retinal cell layers of hypothyroid patients. This research investigated the development of hypothyroidism, a condition mostly of autoimmune origin, as a result of vitamin D deficiency deriving from environmental factors and the relationship between vitamin D deficiency and retinal cell damage. The increase in the thickness in some retinal cell layers in the group receiving vitamin D therapy only was found to be statistically significant. However, an increase in thickness was observed in more cell layers in the group using vitamin D and levothyroxine in combination. This suggests that vitamin D levels should be measured in hypothyroid patients, and that appropriate doses and lengths of treatment should be administered in cases in which these levels are low. The number of studies on this subject is limited. However, we think that more significant results can be obtained with longer follow-up and treatment and larger sample numbers in the future.

Research limitations: One particular limitation of the study is that it was conducted in a single center.

Ethics approval and consent to participate: Kirklareli University Health Sciences Institute Ethical Committee, Turkey, in March 2021 (no. E-69456409-199-7279).

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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