• Clinical Research •

Ocular findings of the patients with congenital leptin deficiency under long-term leptin replacement therapy

Ozlem Candan[1], *Sevde Nur Fırat*[2]

[1]Department of Ophthalmology, University of Health Sciences Ankara Training and Research Hospital, Ankara 06320, Türkiye
[2]Department of Endocrinology and Metabolism, University of Health Sciences Ankara Training and Research Hospital, Ankara 06320, Türkiye
Correspondence to: Ozlem Candan. Department of Ophthalmology, University of Health Sciences Ankara Training and Research Hospital, Ankara 06320, Türkiye. ozlem_aydnoglu@hotmail.com
Received: 2024-07-18 Accepted: 2025-06-03

Abstract

• **AIM:** To analyze the ocular findings of patients who received lifelong leptin therapy due to congenital leptin deficiency (CLD), an extremely rare condition.

• **METHODS:** A prospective, cross-sectional comparative study was performed on six patients with CLD and 13 healthy age- and sex-matched controls. The central corneal thickness (CCT), anterior chamber depth (ACD), axial length (AL), keratometry (K1, K2), optical coherence tomography (OCT), and OCT angiography parameters were compared between the leptin and control groups at the baseline visit. The change in these measurements in leptin patients over a two-year period was analyzed.

• **RESULTS:** CLD patients had lower mean AL, ACD, and CCT (P≤0.012 for all). Mean K1, K2 (P≤0.047 for both), choroidal thickness (P≤0.001), and central ganglion cell layer (GCL) thickness (P=0.029) were higher in the leptin group. Perifoveal superficial capillary plexus (SCP) density was decreased in all quadrants except the temporal region (P<0.05), and parafoveal deep capillary plexus (DCP) density was decreased in the superior hemisphere, temporal quadrant (P≤0.036 for both) and nasal quadrant (P=0.048) in the leptin group. During the two-year follow-up, no changes in anterior and posterior segment measurements were observed in the leptin patients, except for subfoveal choroidal thickness (P<0.001).

• **CONCLUSION:** CLD patients exhibit structural alterations in both the anterior and posterior segments of the eye, including notable changes in retinal and choroidal vasculature. However, there is limited evidence concerning the influence of leptin therapy on the eye.

• **KEYWORDS:** congenital leptin deficiency; leptin replacement treatment; ocular findings; axial length
DOI:10.18240/ijo.2025.10.19

Citation: Candan O, Fırat SN. Ocular findings of the patients with congenital leptin deficiency under long-term leptin replacement therapy. *Int J Ophthalmol* 2025;18(10):1949-1957

INTRODUCTION

Congenital leptin deficiency (CLD) is a rare inherited disorder causing marked hyperphagia and obesity in early childhood. Significant metabolic, endocrine, and immunological disorders have been observed in cases of congenital leptin deficiency, including glucose intolerance, insulin resistance, dyslipidemia, neuroendocrine dysfunction, and impaired immune function[1]. Treatment of CLD using a drug called metreleptin, a recombinant form of human leptin, reverses the symptoms of disease. Leptin is a peptide hormone consisting of 167 amino acids. Adipose tissue is responsible for the secretion of leptin that regulates energy homoeostasis. It shows pleiotropic impacts through binding and activating specific leptin receptors in the hypothalamus and other organs. Leptin also directly and indirectly affects tissues that are metabolically active, regulating various neuroendocrine axes[2]. Angiogenesis is essential in tissue homoeostasis and may lead to many pathological conditions; including the eye[3]. Studies have shown that leptin regulates normal and abnormal angiogenesis. *In vitro* studies detected the leptin receptor (ObR) in vascular endothelial cells, showing that leptin may cause angiogenic proliferation and differentiation in endothelial cells[4]. Research has indicated that diabetic patients exhibit elevated levels of leptin and leptin resistance[5]. Furthermore, studies have demonstrated that the vitreous of patients diagnosed with proliferative diabetic retinopathy contains increased levels of leptin, suggesting a role for this hormone in the promotion of angiogenesis. Conversely, an increasing number of studies in the literature demonstrate the effects of leptin on ageing, dementia, neurodegenerative diseases, age-related macular degeneration, and dry eye disease[6-13]. Furthermore, evidence has been found for the existence of

leptin receptors in the eye, including in the retinal ganglion cell layer (GCL)[14] and the retinal pigment epithelium[15]. According to these findings, congenital deficiency of leptin might play a part in developing vascular or structural pathology in the cornea, iris, anterior chamber, retina, and choroid. The use of metreleptin in the treatment of congenital leptin deficiency can reverse the symptoms associated with the condition. However, dose adjustment is based on clinical response, particularly in terms of weight control, and it remains uncertain whether the dose administered exceeds the physiological dose. In view of this, it would be beneficial to perform regular ophthalmological examinations in patients with congenital leptin deficiency to determine whether leptin replacement therapy has any proangiogenic or cumulative side effects on the retina, GCLs and vasculature of the eye.

Spectral-domain optical coherence tomography (SD-OCT) is a safe and effective imaging modality that is widely used in ophthalmology to investigate retinal thickness and morphology in normal and pathological eyes. Another noninvasive imagining technique, optical coherence tomography angiography (OCTA), enables the visualisation of retinal microvasculature with depth resolution. This technique allows for the quantitative analysis of the superficial (SCP) and deep retinal capillary plexus (DCP), in addition to the choroid. Both SD-OCT and OCTA can provide high-quality images of the retina and choroid, thus enabling a thorough assessment of microanatomy and pathological changes.

Since the number of patients with CLD is limited, there is no study in the literature analysing the ocular findings of CLD patients under leptin therapy. The present study aims to show the ocular findings of patients receiving leptin therapy for a long time. It is essential because it is the first study on this subject in this patient group.

PARTICIPANTS AND METHODS

Ethical Approval This comparative study, which had a cross-sectional and prospective design, was performed with the approval of the Ethics Committee of Ankara Training and Research Hospital (Ankara, Turkey, Ethics number: E-22-879). The researchers adhered to the tenets set forth in the Declaration of Helsinki. All participants or their legal representative provided written informed consent prior to their involvement in the study and consent for publication of the image.

Participants The study included six patients with a diagnosis of CLD receiving long-term leptin replacement therapy and 13 healthy controls of similar age and sex. CLD was diagnosed in patients who have had obesity since childhood based on having undetectable low plasma leptin levels and genetic detection of a mutation in the *LEP* gene. All case-patients are numbered 1-6. The phenotypic and genetic characteristics of each case were recorded and analysed.

Data Collection At the initial visit, a comprehensive ocular examination was conducted, encompassing intraocular pressure (IOP), best corrected visual acuity (BCVA, logMAR), slit-lamp examination, dilated fundus examination, measurement of anterior chamber depth (ACD), axial length (AL), central corneal thickness (CCT), and keratometry values (K1, K2) *via* optical low-coherence reflectometry (Lenstar 900; Haag-Streit Diagnostics, Switzerland). Spectralis-OCT (Heidelberg Engineering, Franklin, MA 02038, USA) and optical coherence tomography angiography (OCTA) examination (Optovue, RTVueXR Avanti Optovue Version 2017.1.0.151, Inc., Fremont, USA) were performed on all the participants. All of the above measurements were performed on leptin patients at the first- and second-year visits.

Spectral-domain Optical Coherence Tomography SD-OCT images of the fovea and optic disc were obtained. Retinal layer segmentation from each SD-OCT scan was carried out by automated software (Spectralis Software V6.16.8). The thickness maps were divided into subfields in line with the Early Treatment Diabetic Retinopathy Study using the built-in Spectralis application. The inner ring was divided into four quadrants. Average thickness and volume values of retinal and GCLs are reported in a numerical format in central, inferior inner, superior inner, temporal inner and inner nasal regions. Central macular thickness was defined as the mean of all points in the 1 mm radius inner circle. For the analysis of subfoveal choroidal thickness (SFCT) measurements (enhanced depth imaging optical coherence tomography; EDI-OCT), two choroidal borders (inner and outer) were determined. In addition, SFCT was measured manually using the software provided with the SD-OCT device after identification of two choroidal borders. The distance from the outer edge of the hyperreflective line corresponding to the retinal pigment epithelium to the inner surface of the sclera was defined as the SFCT. Retinal nerve fiber layer (RNFL) thickness was measured by an average of 16 consecutive circular B-scans of a 3.4-mm-diameter peripapillary circle centered on the optic disc.

Optical Coherence Tomography Angiography OCTA was performed based on the following protocol. Pupils were first dilated with 1% tropicamide with or without 2.5% phenylephrine eye drops in all leptin patients and healthy controls. Participants then underwent retinal OCTA imaging. A 6×6 mm^2 scan centered on the fovea was obtained from each subject. The superficial retinal capillary layer, which extends from 3 μm below the internal limiting membrane to 15 μm below the inner plexiform layer, and the deep retinal capillary layer, which extends from 15 to 70 μm below the inner plexiform layer, were automatically detected by the OCT instrument. Retinal capillary density was defined as the proportion of the measured area occupied by perfused vessels,

Table 1 The demographic characteristics of the CLD patients

Cases	Age (y)	Sex	Ages of diagnosis	BMI (kg/m^2)		Duration of metreleptin treatment (y)	Visual acuity (logMAR)		Refractive error	
				Baseline	Finally		OD	OS	OD	OS
Case 1	47	M	23	51.4	23.9	24	0.00	0.00	-	-
Case 2	59	F	35	46.7	34.1	24	0.00	0.00	-	-
Case 3	60	F	36	55.4	34.6	24	0.00	0.00	-	+0.50
Case 4	21	M	5	39.6	26.3	16	0.00	0.00	-0.25/ -0.50×160	-
Case 5	22	F	18	48.1	30.1	4	0.00	0.00	-0.50×140	-0.25×155
Case 6	18	M	14	38.5	22.6	4	0.00	0.00	-0.25×160	-0.50×180

CLD: Congenital leptin deficiency; BMI: Body mass index; OD: Right eye; OS: Left eye.

defined as pixels with a signal. Foveal avascular zone area was measured in the 3×3 mm^2 scan. Those with poor scan quality or obvious motion artifacts were excluded. Complete ophthalmic examination and analysis of the OCT and OCTA imaging were performed for all participants by the same opthalmologist, who is a retina specialist (Candan O).

Statistical Analysis Statistical analysis was performed using SPSS version 22.0 (IBM SPSS Inc., USA). The descriptive statistics were presented as median (minimum-maximum) or mean±standard deviation (SD) for continuous variables and frequency (%) for categorical variables. Due to the rarity of congenital leptin deficiency, data on these patients are limited, and no previous studies have evaluated ocular findings in this population. Therefore, the statistical analysis included both eyes of leptin patients and controls. Visual inspection (histograms and probability plots) and the Shapiro-Wilk test were used to evaluate the distribution of the data. The linear mixed model (LMM) was used to analyze patient and control group comparisons at baseline and longitudinal data of leptin patients between the initial visit and each time point[16]. For multiple comparisons, *P*-values were corrected for least significant difference (LSD). In a comparison of two groups using an LMM, the factor "Group" is designated as a fixed effect, while the factor "Person" is defined as a random effect. In the analysis of longitudinal data from leptin patients between baseline and each follow-up visit using LMM, the factors "Time" and "Eye" are designated as repeated measures. Additionally, "Time" is used as a fixed effect, while "Person" is selected as a random effect. $P \leq 0.05$ was accepted as the level of statistical significance.

RESULTS

Data from the scans of 38 eyes of six patients and 13 healthy controls were analysed. The leptin mutation was the same in all cases and they had the c.313C>T p.Arg105Trp mutation. The BCVA was 0.00 logMAR in both eyes, and IOPs were found to be normal in all patients. A thorough biomicroscopic and dilated fundus examination did not reveal any pathology.

The first 4 case-patients were from the same extended family. Case 1 and Case 2 were diagnosed in 1998 with severe obesity starting in early childhood, hypogonadotropic hypogonadism, and undetectable serum leptin levels. Case 3, an adult homozygous female, was severely obese and amenorrhoeic. She was diagnosed with leptin deficiency in 1999. Case 4 was a 5-year-old boy with severe obesity and he was diagnosed with leptin deficiency in 2006.

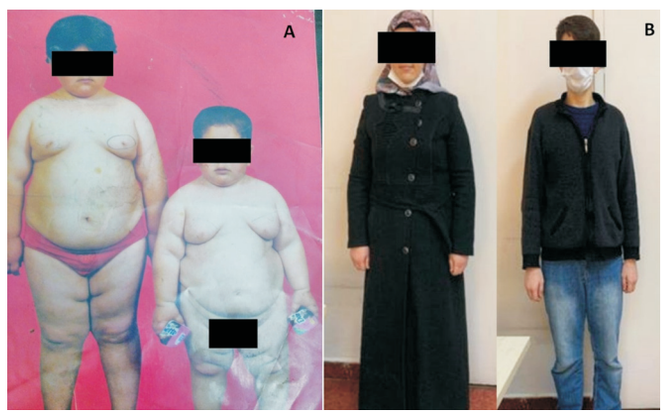

Figure 1 Phenotypic features of a patient before (A) and after (B) leptin replacement treatment.

Cases 5 and 6 were siblings from a different family. Case 5 presented to the out-patient endocrinology clinic at the age of 18y with the symptoms of hyperphagia, obesity, and primary amenorrhea. Case 6 was a 14-year-old boy who presented to the endocrinology outpatient clinic with a history of obesity and hyperphagia. Table 1 showed the patients' demographic characteristics, initial and post-treatment weights. Figure 1 showed the phenotypic features of a patient before and after leptin replacement treatment. Case 1 was operated on for bilateral cataracts at age 46, and case 2 at age 45. Age and sex of the CLD and control groups were not statistically significantly different (Table 1).

The values of the mean AL (22.64±0.52 *vs* 23.34±0.66 mm, *P*=0.012), ACD (3.08±0.14 *vs* 3.48±0.29 mm, *P*<0.01), and CCT (490.25±22.35 *vs* 540.53±16.45 μm, *P*<0.01) were statically significantly lower in the leptin group than in controls. The leptin group had higher K1 and K2 keratometry values, the differences in the mean K1 (*P*=0.022), and K2 (*P*=0.047) keratometry measurements were significant. Table 2 showed the anterior segment parameters.

Table 2 The anterior segment parameters in patients with CLD and control group

Parameters	CLD patients (*n*=6)	Control (*n*=13)	*P*[a]
AL (mm)	22.64±0.52 (21.84-23.47)	23.34±0.66 (22.07-24.42)	0.012
K1 (D)	43.86±1.38 (41.77-45.49)	42.664±0.81 (41.36-43.81)	0.022
K2 (D)	44.33±1.35 (42.08-45.92)	43.41±0.60 (42.50-44.50)	0.047
ACD (mm)	3.08±0.14 (2.9-3.26)	3.48±0.29 (3.00-3.99)	<0.01
CCT (μm)	490.25±22.35(443.0-514.0)	540.53±16.45(512.45-566.10)	<0.01

AL: Axial length; K1 and K2: Keratometry values; ACD: Anterior chamber depth; CCT: Central corneal thickness; CLD: Congenital leptin deficiency. [a]*P*<0.05 significantly different linear mixed model (LMM).

Table 3 Thickness of subfoveal choroidal, macular, retinal nerve fiber and ganglion cell layers in CLD patients and controls

Parameters	CLD patients (*n*=6)	Control (*n*=13)	*P*[a]
Subfoveal choroidal thickness (μm)	344.08±36.93 (291-410)	293.0±13.43 (252-321)	<0.01
Macular thickness (μm)			
Central	276.917±39.441 (164-327)	256.962±14.498 (236-281)	0.084
Superior	351.667±16.819 (327-381)	338.654±13.074 (317-357)	0.093
Inferior	333.333±57.381 (150-370)	338.577±14.181 (316-362)	0.693
Nasal	337.833±57.413 (160-382)	335.269±20.602 (251-359)	0.848
Temporal	335.5±18.333 (291-362)	327.308±12.312 (309-350)	0.271
Retinal nerve fiber layer thickness (μm)			
Central	104.083±4.518 (94-111)	100.769±8.868 (85-120)	0.413
Nasal superior	124.083±9.535 (111-145)	120.0±14.234 (77-146)	0.49
Temporal superior	139.917±7.365 (125-152)	135.346±28.432 (11-160)	0.638
Nasal	86.167±5.64 (79-100)	77.077±12.388 (61-110)	0.104
Temporal	71.0±10.392 (55-95)	72.808±5.968 (59-85)	0.63
Nasal inferior	118.083±14.734 (95-143)	114.962±21.725 (74-152)	0.754
Temporal Inferior	139.083±14.436 (111-155)	147.808±10.898 (120-160)	0.165
Macular ganglion cell layer thickness (μm)			
Central	18.91±8.61 (9-39)	14.07±3.1 (9-19)	0.029
Superior	55.75±3.7 (49-63)	55.692±4.68 (49-67)	0.98
Inferior	55.667±5.706 (46-65)	54.923±4.795 (50-65)	0.77
Nasal	55.667±5.359 (47-65)	55.154±4.897 (47-65)	0.846
Temporal	49.333±6.956 (30-60)	50.692±5.044 (41-61)	0.628

CLD: Congenital leptin deficiency. [a]*P*<0.05 significantly different linear mixed model (LMM).

Table 3 presented the measurements of the SFCT and RNFL thickness. Mean SFCT (344.08±36.93 *vs* 293±13.43 μm, *P*<0.01) and central GCL thickness (18.91±8.61 *vs* 14.07±3.1 μm, *P*=0.029) were both markedly increased in the leptin group. Figure 2 showed images of EDI measurement of two patients under leptin replacement treatment. Other OCT measurements including RNFL, GCL, and macular thickness were not significantly different.

Table 4 summarized the mean vessel density of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) in the parafoveal, perifoveal, and overall parafoveal and perifoveal quadrants and the area of the Foveal avascular zone (FAZ) in the leptin and control groups. The leptin and control groups showed significant differences in SCP vessel density in the perifoveal region, but not in the parafoveal region. The mean perifoveal SCP measurements in all regions, except the superficial perifoveal temporal region, were significantly decreased in the leptin group in comparison to the control group (*P*<0.05). DCP measurements in parafovea were statistically significantly different between the two groups. DCP parafoveal vessel density measurements in the superior hemisphere, nasal and temporal quadrants were lower in the leptin group. FAZ area was not different between leptin and control groups (*P*=0.898). Vessel density images of the SCP and DCP of two patients on leptin replacement therapy were shown in Figure 3.

At the 12 and 24mo visits, there were no significant changes in the measurements of K1, K2, ACD, AL, CCT, and OCT and OCTA parameters. Interestingly, SFCT showed an increase at month 12 and a slight decrease at month 24, but SFCT measurements were increased at both months 12 and 24 compared to baseline (Table 5).

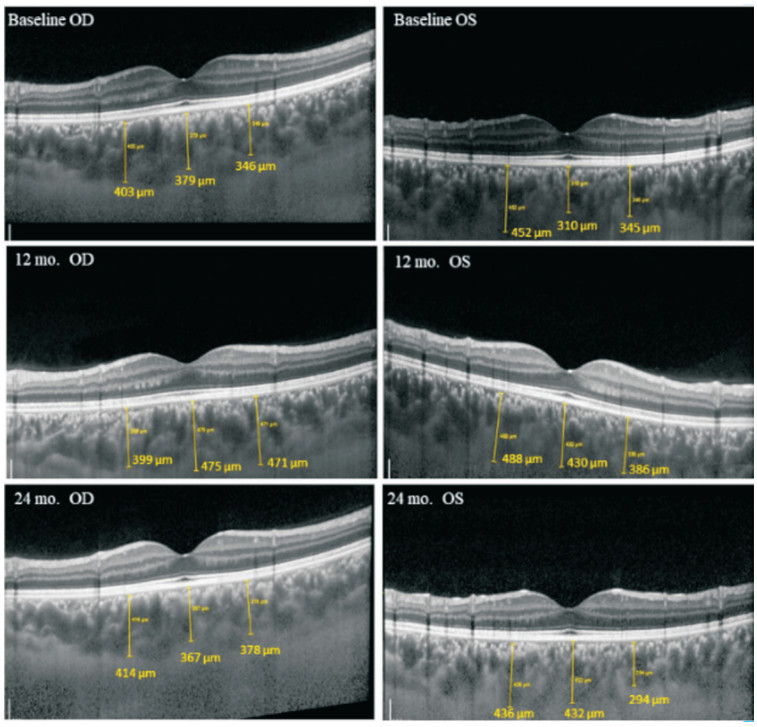

Figure 2 Images of EDI-OCT measurements of a patient under leptin replacement treatment during 2y of follow up EDI-OCT: Enhanced depth imaging optical coherence tomography.

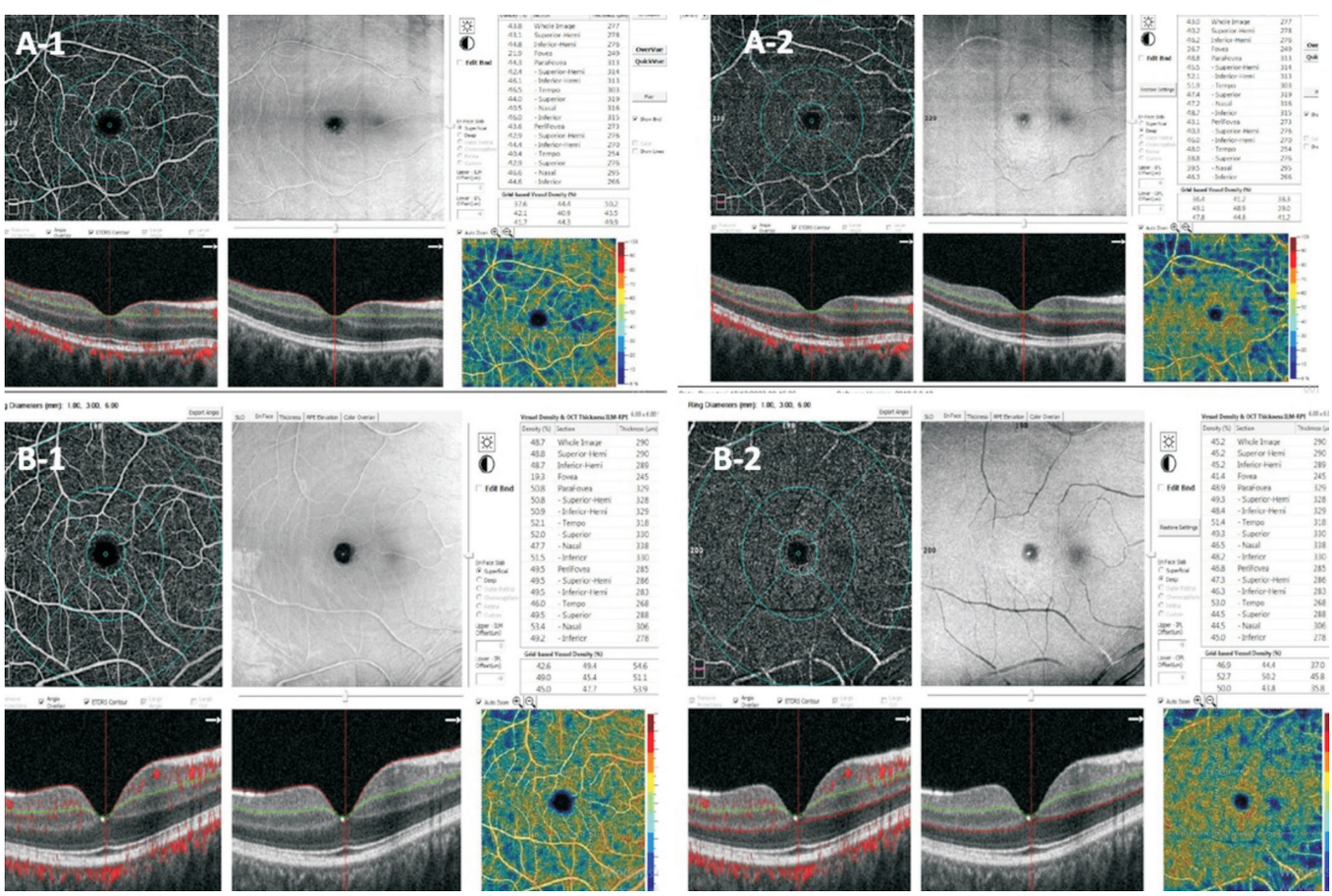

Figure 3 Images of vessel density of the SCP and DCP of two patients under leptin replacement treatment A1-A2: OCTA images of vessel density of the SCP and DCP of a patient under leptin replacement treatment for less than five years (A1: An image of vessel density of the SCP; A2: An image of vessel density of the DCP); B1-B2: OCTA images of vessel density of the SCP and DCP of a patient under leptin replacement treatment for more than five years (B1: An image of vessel density of the SCP; B2: An image of vessel density of the DCP). SCP: Superficial capillary plexus; DCP: Deep capillary plexus; OCTA: Optical coherence tomography angiography.

Table 4 The mean vessel density of the SCP and DCP at fovea and area of the FAZ in CLD patients and controls

Parameters	CLD patients (*n*=6)	Control (*n*=13)	*P*[a]
FAZ	0.24±0.05 (0.17-0.33)	0.24±0.05 (0.11-0.37)	0.898
Superficial capillary plexus vessel density (%)			
Superficial-whole	44.45±3.17 (39.3-48.7)	47.60±3.63 (39.7-52.9)	0.031
Superficial-superior hemisphere	44.08±3.09 (38.5-48.8)	47.36±3.49 (40.0-52.6)	0.024
Fovea central density	19.2±6.21 (3.3-27.3)	17.66±6.18 (5.9-29.7)	0.61
Parafovea central density	45.93±4.54 (38.2-51.7)	48.52±5.50 (36.1-55.0)	0.202
Parafovea temporal	46.83±5.81 (32.7-53.1)	49.84±6.48 (33.2-58.6)	0.203
Parafovea superior	46.91±4.21 (38.7-52.0)	49.04±6.67 (33.7-57.3)	0.361
Parafovea nasal	42.38±5.14 (30.2-49.1)	45.61±4.76 (32.0-52.4)	0.119
Parafovea inferior	47.66±4.77 (37.6-53.4)	49.66±5.64 (37.9-56.9)	0.308
Perifovea central density	45.02±2.98 (40.7-49.5)	48.44±3.54 (40.5-53.7)	0.026
Superficial perifovea superior hemisphere	44.54±3.19 (38.5-49.5)	48.21±3.30 (41.3-53.5)	0.016
Superficial perifovea inferior hemisphere	45.51±3.12 (39.7-49.5)	48.86±3.73 (40.3-53.9)	0.025
Perifovea temporal	41.47±3.63 (34.3-46.0)	44.44±4.03 (35.9-49.8)	0.063
Perifovea superior	44.34±3.21 (38.3-49.5)	48.16±3.50 (41.0-53.4)	0.014
Perifovea nasal	49.05±3.06 (44.5-53.4)	52.75±3.23 (45.4-57.3)	0.011
Perifovea inferior	45.26±3.15 (40.7-49.9)	48.83±3.88 (40.6-55.3)	0.031
Deep capillary plexus vessel density (%)			
Fovea central density	38.76±5.12 (28.9-47.3)	37.14±7.52 (28.7-53.6)	0.65
Parafovea central density	51.03±3.50 (46.3-55.8)	52.63±3.56 (45.6-60.4)	0.25
Deep parafovea superior hemisphere	50.40±4.76 (38.8-56.9)	53.66±2.63 (48.9-60.8)	0.021
Deep parafovea inferior hemisphere	51.65±3.72 (44.6-55.4)	52.73±3.52 (45.9-60.1)	0.469
Parafovea temporal	52.65±2.25 (48.1-56.1)	55.30±3.12 (47.8-61.2)	0.036
Parafovea superior	49.98±6.09 (33.8-56.3)	52.57±3.19 (46.7-61.8)	0.103
Parafovea nasal	50.14±4.51 (44.0-58.1)	52.93±2.87 (47.8-60.0)	0.048
Parafovea inferior	51.33±3.85 (44.4-56.8)	52.78±4.00 (42.5-59.5)	0.313
Perifovea central density	47.41±3.66 (38.9-51.8)	48.65±4.47 (41.2-60.8)	0.494
Perifovea temporal	51.08±3.98 (41.0-55.7)	52.56±3.68 (44.9-61.3)	0.356
Perifovea superior	43.65±6.39 (26.3-50.9)	47.51±4.71 (40.9-61.5)	0.075
Perifovea nasal	46.89±5.08 (36.1-53.9)	47.03±4.75 (40.5-60.0)	0.936
Perifovea inferior	48.10±3.50 (40.1-51.4)	48.56±5.44 (40.2-61.3)	0.838

FAZ: Foveal avascular zone; CLD: Congenital leptin deficiency. [a]*P*<0.05 significantly different linear mixed model (LMM).

DISCUSSION

The current study represents the first in the literature to evaluate the ocular findings in patients with congenital leptin deficiency and the impact of long-term leptin replacement therapy on ocular structures. Our data showed that long-term leptin therapy does not affect anterior segment parameters, OCT and OCTA findings, but congenital leptin deficiency does.

CLD is a very rare disease, affecting one case in 4.4 million[17], and characterised by undetectable or very low levels of leptin. Leptin replacement therapy is the only available treatment option. To date, the total number of patients reported in the literature was only 165[1] and, in addition, there is no study in the literature analysing the ocular findings of CLD patients under leptin therapy. In the current study, we found that the mean AL and ACD measurements of the patients with CLD were significantly decreased. Previous studies reported that leptin levels decreased when growth hormone levels were insufficient[18] Similarly, Hwang *et al*[19] reported that the gene polymorphism of leptin and leptin receptor genes was related to growth hormone deficiency pathogenesis, and the decreased levels of leptin were correlated with short status. One exciting finding by Pereira and Allemann[20] was that they found a correlation between AL, ACD, vitreous cavity depth, and height in an average population. They found that each 10 cm increase in height was associated with 0.32 mm of increase in AL, 0.07 mm of ACD, and 0.50 D of keratometry flattening. Their results might explain why the mean AL and ACD measurements are decreased in our leptin patients. According to the present study, the mean CCT measurements were thinner in the leptin group than in the controls. Several ocular and non-ocular conditions lead to decreased CCT,

Table 5 Anterior and posterior segment measurements of CLD patients at month 12 and 24 compared to baseline

Parameters	Baseline	Month 12	Month 24	*P*
AL[b]	22.642±0.523 (21.84-23.47)	22.639±0.537 (21.83-23.5)	22.647±0.559 (21.82-23.59)	0.634
K1[b]	43.865±1.38 (41.77-45.49)	43.827±1.389 (41.72-45.51)	43.824±1.407 (41.72-45.67)	0.402
K2[b]	44.336±1.355 (42.08-45.92)	44.368±1.385 (42.1-46.0)	44.431±1.376 (42.19-46.11)	0.198
ACD[b]	3.082±0.141 (2.9-3.26)	3.064±0.134 (2.87-3.25)	3.056±0.135 (2.86-3.24)	0.081
CCT[b]	490.25±22.354 (443-514)	490.0±22.642 (442-514)	490.667±23.088 (442-513)	0.332
Subfoveal choroidal thickness (μm)	344.083±36.931 (291-410)	408.5±53.804 (352-518)	387.0±65.819 (313-511)	<0.001
Macular ganglion cell layer thickness central (μm)[b]	18.917±8.616 (9-39)	20.917±8.401 (13-38)	20.417±7.729 (13-37)	0.423
Macular thickness central (μm)	276.917±39.441 (164-327)	289.167±21.051 (265-329)	288.0±21.134 (265-325)	0.215
Retinal nerve fiber layer thickness central (μm)	104.083±4.518 (94-111)	104.417±5.155 (92-111)	104.417±5.951 (91-111)	0.903
Superficial capillary plexus vessel density (%)				
Superficial-whole[b]	44.458±3.173 (39.3-48.7)	46.217±2.532 (40.9-51.2)	46.033±2.162 (42.1-48.3)	0.147
Superior hemisphere[b]	44.083±3.098 (38.5-48.8)	45.75±2.572 (41.1-51.2)	45.825±2.878 (41.0-50.2)	0.14
Fovea	19.2±6.21 (3.3-27.3)	19.558±3.708 (12.5-25.2)	20.758±6.042 (9.7-31.4)	0.431
Parafovea	45.933±4.543 (38.2-51.7)	46.992±4.64 (35.3-52.0)	46.333±3.646 (39.3-51.7)	0.696
Perifovea[a]	45.025±2.989 (40.7-49.5)	46.783±2.557 (41.5-51.6)	46.575±1.976 (43.2-49.7)	0.14
Perifovea superior hemisphere[b]	44.542±3.192 (38.5-49.5)	46.342±2.92 (41.1-51.8)	46.575±2.918 (40.8-52.9)	0.139
Perifovea inferior hemisphere[b]	45.517±3.129 (39.7-49.5)	47.192±2.497 (41.9-51.4)	46.6±1.658 (43.9-49.4)	0.228
Perifovea superior[b]	44.342±3.21 (38.3-49.5)	45.617±2.992 (41.3-51.3)	46.008±3.32 (40.5-53.3)	0.349
Perifovea nasal	49.05±3.067 (44.5-53.4)	51.442±2.422 (46.9-54.9)	51.375±2.194 (47.8-56.7)	0.025
Perifovea inferior[b]	45.267±3.152 (40.7-49.9)	47.133±2.614 (42.2-51.7)	46.083±2.186 (42.7-50.3)	0.196
FAZ	0.24±0.051 (0.173-0.338)	0.249±0.052 (0.173-0.364)	0.24±0.055 (0.157-0.354)	0.224
Deep capillary plexus vessel density (%)				
Fovea central density	38.767±5.122 (28.9-47.3)	37.833±4.819 (29.4-44.5)	38.6±6.038 (29.5-49.3)	0.53
Parafovea central density	51.033±3.504 (46.3-55.8)	50.158±5.109 (43.7-58.6)	50.533±4.828 (44.1-61.2)	0.89
Parafovea superior hemisphere[b]	50.408±4.764 (38.8-56.9)	50.325±4.68 (45.4-58.7)	51.458±4.264 (46.1-61.2)	0.792
Parafovea temporal[a]	52.658±2.255 (48.1-56.1)	52.642±4.264 (43.9-59.1)	53.067±4.352 (47.4-62.2)	0.955
Parafovea nasal[a]	50.142±4.519 (44.0-58.1)	49.375±5.129 (42.0-58.3)	50.608±3.593 (45.3-60.1)	0.786

AL: Axial length; K1 and K2: Keratometry values; ACD: Anterior chamber depth; CCT: Central corneal thickness; FAZ: Foveal avascular zone; CLD: Congenital leptin deficiency. [a]*P*<0.05 significantly different linear mixed model (LMM); [b]Parameters showing significant difference from controls and no difference during 2y of follow-up.

including ethnicity, genetic factors, dry eye, neurodegenerative movement disorders (Parkinson's disease), chronic hypoxia, and obstructive sleep apnoea syndrome[21-26]. Previous studies have reported leptin's role in stimulating angiogenesis and maintaining a fenestrated endothelium in adipose tissue and endocrine organs[3-5]. Similarly, some studies showed leptin might have dual roles in stimulating angiogenesis and maintaining appropriate vascular structure in the placenta[27]. Leptin patients' mean CCT values were lower than controls. The probable explanation for our results may be the consequent chronic hypoxia resulting from the inappropriate vascular anatomy and impaired angiogenesis due to leptin deficiency.

In our study, mean SFCT measurements were significantly higher in leptin patients than controls. Gonul *et al*[28] studied choroidal thickness changes in morbidly obese patients after bariatric surgery. They suggested that there was a positive correlation between choroidal thickness and body mass index (BMI), and that choroidal thickness levels were progressively lower as BMI decreased. Before starting leptin treatment, all of our patients had extreme obesity but they experienced dramatic weight loss after treatment. Increased choroidal thickness in our leptin patients compared to controls was not related with BMI. A likely explanation for this difference is that previous studies on the role of leptin in promoting angiogenesis have shown that leptin promotes neovascularization in the cornea, retina, and choroid and synergizes with fibroblast growth factor (FGF-2) and vascular endothelial growth factor (VEGF) in stimulating angiogenesis[27,29-32]. Moreover, it has been documented that leptin-induced endothelial dysfunction may play a contributory role in the development of gestational hypertension in female patients[33]. Replacement of leptin for patients with CLD may promote angiogenesis, induce vascular permeability, and thus increase choroidal thickness measurements. Interestingly, SFCT showed an increase at

12mo and a slight decrease at 24mo, but SFCT was still increased compared to baseline measurements. This may again support the effect of leptin treatment in inducing vascular permeability in the choroidal vasculature.

On the other hand, our data show a significant increase in the measurements of thickness of central GCL measurements. Matochik *et al*[34] showed that the concentration of grey matter tissue in the brains of the three adults with genetic leptin deficiency increased after leptin replacement therapy. Similarly, according to Gupta[12], leptin may be utilised as a possible neuroprotective agent in glaucoma management by reducing apoptosis, oxidative stress, and excitotoxicity. The increased central GCL measurements in our leptin patients compared to the controls, may suggest that leptin therapy may influence the retinal GCL. However, no significant differences were observed when it came to measuring RNFL and macular thickness. In addition, there are no changes in any of the anterior and posterior segment measurements in the leptin patients at 12 and 24mo. Therefore, more evidence is needed to show that leptin treatment has a neuroprotective effect.

We found that SCP vessel density in the perifovea region significantly was diminished in leptin patients compared to the controls. Likewise, statistically significant difference was detected in the mean DCP parafoveal vessel density measurements in the superior hemisphere, nasal and temporal quadrants. Even though the leptin patients have decreased vessel densities of SCP and DCP compared to the controls, no significant differences were demonstrated during the two years follow-up. As previously stated, leptin is critical in stimulating angiogenesis and maintaining an appropriate vascular structure. Thus, it can be suggested that not leptin therapy itself but the lack or low levels of leptin may have contributed to a decline in vessel densities of the SCP and DCP in patients with CLD.

This study bears several limitations. These include the small sample size due to CLD being a rare disease, the use of a cross-sectional study design that resulted in anterior segment, OCT, and OCTA being measured at different times during treatment, and the lack of pretreatment measurements. Moreover, we did not perform fundus fluorescein angiography (FFA), as FFA is a gold standard but an invasive diagnostic procedure for our patients, who did not have any complaints of ocular symptoms or retinal pathology.

In conclusion, the present study provides the first detailed assessment of ocular findings in patients with CLD and how long-term leptin replacement therapy affects the anterior and posterior segments of their eyes. This study demonstrates that patients with congenital leptin deficiency may have developmental changes in the anterior and posterior segments of their eyes. In addition, leptin replacement therapy increased choroidal thickness during 2y of follow-up and may have an effect on the choroidal vasculature. However, the two-year longitudinal data of our study show that there is no effect of leptin replacement on anterior segment parameters and retinal vasculature. OCT will be essential for the follow-up of these patients. The use of EDI-OCT in detecting alterations in the choroidal circulation prior to the onset of decompensation renders it a valuable tool for ongoing monitoring. Further longitudinal studies with greater sample sizes are needed to determine the full impact of congenital leptin deficiency and long-term replacement therapy on ocular structures.

ACKNOWLEDGEMENTS

Authors' Contributions: Conceived and/or designed the work that led to the submission, acquired data, and/or played an important role in interpreting the results: Candan O and Fırat SN; Drafted or revised the manuscript: Candan O and Fırat SN; Approved the final version: Candan O and Fırat SN; Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Candan O and Fırat SN.

Conflicts of Interest: Candan O, None; **Fırat SN,** None.

REFERENCES

1 Besci Ö, Fırat SN, Özen S, *et al*. A national multicenter study of leptin and leptin receptor deficiency and systematic review. *J Clin Endocrinol Metab* 2023;108(9):2371-2388.

2 Obradovic M, Sudar-Milovanovic E, Soskic S, *et al*. Leptin and obesity: role and clinical implication. *Front Endocrinol* 2021;12:585887.

3 Lee P, Wang CC, Adamis AP. Ocular neovascularization: an epidemiologic review. *Surv Ophthalmol* 1998;43(3):245-269.

4 Wang Y, Hu C. Leptin and asthma: what are the interactive correlations? *Biomolecules* 2022;12(12):1780.

5 Vilariño-García T, Polonio-González ML, Pérez-Pérez A, *et al*. Role of leptin in obesity, cardiovascular disease, and type 2 diabetes. *Int J Mol Sci* 2024;25(4):2338.

6 Katagiri M, Shoji J, Inada N, *et al*. Evaluation of vitreous levels of advanced glycation end products and angiogenic factors as biomarkers for severity of diabetic retinopathy. *Int Ophthalmol* 2018;38(2):607-615.

7 Flores-Cordero JA, Pérez-Pérez A, Jiménez-Cortegana C, *et al*. Obesity as a risk factor for dementia and Alzheimer's disease: the role of leptin. *Int J Mol Sci* 2022;23(9):5202.

8 Harvey J. Novel leptin-based therapeutic strategies to limit synaptic dysfunction in Alzheimer's disease. *Int J Mol Sci* 2024;25(13):7352.

9 Charisis S, Short MI, Bernal R, *et al*. Leptin bioavailability and markers of brain atrophy and vascular injury in the middle age. *Alzheimers Dement* 2024;20(9):5849-5860.

10 Evereklioglu C, Doganay S, Er H, *et al*. Serum leptin concentrations are decreased and correlated with disease severity in age-related macular degeneration: a preliminary study. *Eye* (*Lond*) 2003;17(3):350-355.

11 Seshasai S, Liao J, Toh QC, *et al*. Serum leptin and age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2015;56(3):1880-1886.

12 Gupta A. Leptin as a neuroprotective agent in glaucoma. *Med Hypotheses* 2013;81(5):797-802.

13 Pei X, Ba M, Yang T, *et al*. Leptin receptor deficiency-associated diabetes disrupts lacrimal gland circadian rhythms and contributes to dry eye syndrome. *Invest Ophthalmol Vis Sci* 2025;66(1):19.

14 Suganami E, Takagi H, Ohashi H, *et al*. Leptin stimulates ischemia-induced retinal neovascularization: possible role of vascular endothelial growth factor expressed in retinal endothelial cells. *Diabetes* 2004;53(9):2443-2448.

15 Maberley D, Cui JZ, Matsubara JA. Vitreous leptin levels in retinal disease. *Eye* (*Lond*) 2006;20(7):801-804.

16 Herber R, Graehlert X, Raiskup F, *et al*. Statistical evaluation of correlated measurement data in longitudinal setting based on bilateral corneal cross-linking. *Curr Eye Res* 2022;47(7):995-1002.

17 Salum KCR, Rolando JM, Zembrzuski VM, *et al*. When leptin is not there: a review of what nonsyndromic monogenic obesity cases tell us and the benefits of exogenous leptin. *Front Endocrinol* 2021;12:722441.

18 Florkowski CM, Collier GR, Zimmet PZ, *et al*. Low-dose growth hormone replacement lowers plasma leptin and fat stores without affecting body mass index in adults with growth hormone deficiency. *Clin Endocrinol* 1996;45(6):769-773.

19 Hwang IT, Kim M, Kim NY, *et al*. Gene polymorphisms in leptin and its receptor and the response to growth hormone treatment in patients with idiopathic growth hormone deficiency. *Endocr J* 2021;68(8):889-895.

20 Pereira GC, Allemann N. Ocular biometry, refractive error and correlation with height, age, gender and years of formal education. *Arq Bras Oftalmol* 2007;70(3):487-493.

21 Biousse V, Skibell BC, Watts RL, *et al*. Ophthalmologic features of Parkinson's disease. *Neurology* 2004;62(2):177-180.

22 Ulusoy EK, Ulusoy DM. Evaluation of corneal sublayers thickness and corneal parameters in patients with Parkinson's disease. *Int J Neurosci* 2021;131(10):939-945.

23 Bergmanson JP, Chu LW. Corneal response to rigid contact lens wear. *Br J Ophthalmol* 1982;66(10):667-675.

24 Chalkiadaki E, Andreanos K, Florou C, *et al*. Corneal endothelial morphology and thickness alterations in patients with severe obstructive sleep apnea-hypopnea syndrome. *Cornea* 2021;40(1):73-77.

25 Chalkiadaki E, Andreanos K, Karmiris E, *et al*. Effects of continuous positive airway pressure treatment for obstructive sleep apnea-hypopnea syndrome on corneal morphological characteristics. *Cornea* 2021;40(8):988-994.

26 Dimasi DP, Burdon KP, Craig JE. The genetics of central corneal thickness. *Br J Ophthalmol* 2010;94(8):971-976.

27 Cao R, Brakenhielm E, Wahlestedt C, *et al*. Leptin induces vascular permeability and synergistically stimulates angiogenesis with FGF-2 and VEGF. *Proc Natl Acad Sci U S A* 2001;98(11):6390-6395.

28 Gonul S, Yilmaz H, Gedik S, *et al*. Evaluation of the choroidal thickness and retinal nerve fiber layer and visual fields in morbid obesity: does bariatric surgery affect retinal structure and function? *Indian J Ophthalmol* 2021;69(2):301-306.

29 Hao R, Liu Y, Li XM. Leptin's concentration in tears and dry eye: a clinical observational study. *Int J Ophthalmol* 2021;14(1):83-88.

30 Zhang Y, Chua S Jr. Leptin function and regulation. *Compr Physiol* 2018;8(1):351-369.

31 Maurya R, Bhattacharya P, Ismail N, *et al*. Differential role of leptin as an immunomodulator in controlling visceral leishmaniasis in normal and leptin-deficient mice. *Am J Trop Med Hyg* 2016;95(1):109-119.

32 Wang Z, Huang X, Ye X, *et al*. Roles of leptin on the key effector cells of rheumatoid arthritis. *Immunol Lett* 2021;233:92-96.

33 Mellott E, Faulkner JL. Mechanisms of leptin-induced endothelial dysfunction. *Curr Opin Nephrol Hypertens* 2023;32(2):118-123.

34 Matochik JA, London ED, Yildiz BO, *et al*. Effect of leptin replacement on brain structure in genetically leptin-deficient adults. *J Clin Endocrinol Metab* 2005;90(5):2851-2854.