Duration-dependent Effects of Growth Hormone on Retinal Microvascular Parameters in Pediatric Congenital Idiopathic Growth Hormone Deficiency: An OCT-A Based Study

Ebru Cömert Hamzaoğlu[1], Fırat Selen[1], Dilek Çiçek[2], Duygu Düzcan Kilimci[2], Ali Tunç[3]

ABSTRACT

Purpose: The aim of this study was to compare optical coherence tomography anjiography (OCT-A) measurements across three pediatric congenital idiopathic growth hormone deficiency (IGHD) groups defined by recombined GH (rhGH) treatment status and duration: no prior GH treatment, 4 months of GH treatment, and at least 1 year of GH treatment.

Materials and Methods: A total of 47 right eyes from 47 pediatric IGHD patients were included in the study. We divided the patients into three groups. The first group consisted of children who had not yet started rhGH therapy (n=16), the second group included children who had received treatment for 4 months (n=14), and the third group comprised children who had been receiving treatment for at least 12 months (n=17). Retinal microvascular structure were evaluated with recorded OCT-A images via OCTAVA (OCT-A Vascular Analyzer) image analysis software in terms of the parameters vessel area density, vessel length density, vessel length, vessel diameter, branchpoint density, tortuosity, and metrics characterising the foveal avascular zone (FAZ) including FAZ area, p, circularity, acircularity index, axis ratio, and vessel density within a 300-µm width ring surrounding the FAZ.

Results: The groups were not different in terms of age, height and weight of the patients. The median treatment duration was 0 month in group 1, 4 months in group 2 and 12 months (min 12- max 36 months) in group 3. ($p < 0.001$) No significant difference was detected in the OCT-A parameters among the three study groups (p>0,05).

Conclusion: The analysis revealed no statistically significant

Keywords: Congenital idiopathic growth hormone deficiency, recombinant growth hormone, retinal microvasculature, OCT-A, OCTAVA.

INTRODUCTION

Growth hormone (GH) is produced by somatotroph cells of the anterior pituitary gland and plays a critical role in the neural and vascular maturation. Congenital idiopathic growth hormone deficiency (IGHD), resulting from insufficient GH secretion, is an endocrine disease in childhood, which is diagnosed with the assessment of bone age by radiographic methods to detect impaired linear growth and delayed skeletal maturation, measurement of insulin-like growth factor-1 (IGF-1) levels, stimulation tests to evaluate GH secretion, and cranial magnetic resonance imaging to assess pituitary anatomy [1-3]. Early treatment with recombinant human growth hormone (rhGH) is necessary to reach a normal growing pattern during childhood.

1 Mersin City Training and Research Hospital, Ophthalmology, Mersin, Türkiye

2 Mersin City Training and Research Hospital, Pediatric Endocrinology, Mersin, Türkiye

3 Mersin City Training and Research Hospital, Pediatry, Mersin, Türkiye

Received: 02.05.2026
Accepted: 05.08.2026

J Ret-Vit 2026; 35: 256-263

DOI:10.37845/ret.vit.2026.35.32

Correspondence author:
Ebru Cömert Hamzaoğlu
Email: dr.ebrucomert@gmail.com

Copyright © 2026 The author(s). This is an open-access article under the terms of the Creative Commons Attribution License (CC BY) which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is properly cited.

GHD can manifest with a variety of ocular sequelae, impacting fundamental structures and functions of the eye. A noticeable consequence in affected individuals, particularly children, is an observed reduction in retinal vascularization. Specifically, analyses have revealed a decreased number of retinal vascular branching points, indicating potentially suboptimal development of the retinal blood supply compared to healthy cohorts [4-8]. Interestingly, the administration of growth hormone (GH) replacement therapy, while systemically beneficial, does not consistently lead to a significant amelioration of these specific retinal vascular phenotypes or other quantifiable retinal neural parameters [9].

Furthermore, individuals with GHD may present with structural alterations in the choroid. Studies have indicated a propensity for choroidal thinning, particularly pronounced in sub foveal and temporal regions [10]. Despite this, therapeutic intervention with GH does not appear to exert a substantial influence on the developmental trajectory or thickness of this choroidal layer in pediatric patients [10].

Optical coherence tomography angiography (OCT-A) provides detailed visualization of the retinal vascular network by obtaining contrast from the movement of red blood cells within the vessels. It uses sequential OCT scans of a specific retinal area. Unlike fundus fluorescence angiography (FFA), this angiography method does not use any dye injection and is therefore non-invasive [11]. While FFA imaging is limited to the superficial capillary plexus (SCP) of the retina, OCT-A can be used in the diagnosis of diseases that may affect the deep capillary plexus (DCP) [12].

We aimed to compare the OCTA measurements of IGHD patients who have not received GH treatment with those of IGHD patients who have been undergoing GH treatment for 4 months and those who have been receiving GH treatment for at least 1 year.

MATERIALS AND METHODS

The present study was designed as a retrospective, single-center investigation. We reviewed the data of the patients who have the diagnosis of IGHD and were referred from the pediatric endocrinology unit of the pediatrics department of Mersin City Training and Research Hospital, between January 2024 and September 2025.The local institutional review board and ethics committee of the faculty of medicine of Mersin University approved the study protocol (1095/10/2025).

The patients who were equal to or less than 16 years old, had no history of any ocular disease or had no additional systemic disease other than IGHD and were not receiving any therapy other than rhGH for the consulted group, were assessed in the study. The patients were excluded from the study if they had a history of preterm or small-for-gestational-age at birth, a diagnosis of systemic or ocular diseases such as hepatic or renal disease, hypertension, cardiovascular disease, thyroid disease, high refractive errors, glaucoma, uveitis.

We divided the patients into three groups. The first group consisted of children who had not yet started rhGH therapy, the second group included children who had received rhGH treatment for 4 months, and the third group comprised children who had been receiving rhGH treatment for at least 12 months.

Pubertal status was determined according to Tanner criteria, using breast maturation in girls and genital maturation in boys. [13] All participants underwent a comprehensive clinical and laboratory evaluation, including complete blood count, routine biochemical analyses, thyroid function tests, and measurement of serum tissue transglutaminase antibodies to exclude other causes of growth impairment. Skeletal maturation was assessed by bone age determination using the Greulich–Pyle reference atlas. Cranial magnetic resonance imaging focusing on the hypothalamic–pituitary region was performed in all patients to identify possible structural abnormalities. Growth hormone secretion was evaluated by two pharmacological stimulation tests employing L-dopa and clonidine. Serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) concentrations were also assessed. A diagnosis of growth hormone deficiency was established when the peak GH concentration remained below 10 µg/L in both stimulation tests, together with compatible clinical findings, auxological parameters, and biochemical results, in accordance with established Growth Hormone Research Society recommendations. [14] Initially dose of 0.025 mg/kg/day of rhGH was started in patients of group 2 and group 3. Data of the patients, who were asked to attend follow-up visits at the endocrinology and ophthalmology

clinics, were obtained by scanning the patients' folders, retrospectively.

Visual acuity, anterior segment, and fundus findings were obtained from ophthalmological examination records. Retinal microvasculature evaluated with OCT-A (Heidelberg OCT II Spectralis) images via OCTAVA (OCT-A Vascular Analyzer) image analysis software. OCTAVA is an open-source toolbox that can analyze retinal OCT-A image. OCTAVA graphical user interface with added metrics for retinal analysis was given in Fig 1. [15] OCT-A analyses were performed by a single analyst who was masked to group assignment.

We set frangi at 4, twig size at 8 and image size at 2.9 for optimizing image processing. The toolbox delivers microvascular metrics including vessel area density (VAD), vessel length density (VLD), total, mean, and median vessel length (VL), mean and median vessel diameter, branchpoint density (BD), tortuosity for the whole image and metrics characterizing the foveal avascular zone (FAZ), including FAZ area, circularity, acircularity index, axis ratio, and vessel density (VD) within a 300-µm width ring surrounding the FAZ (FD-300).

As the aim of the study, we compared OCTAVA measurements among three groups.

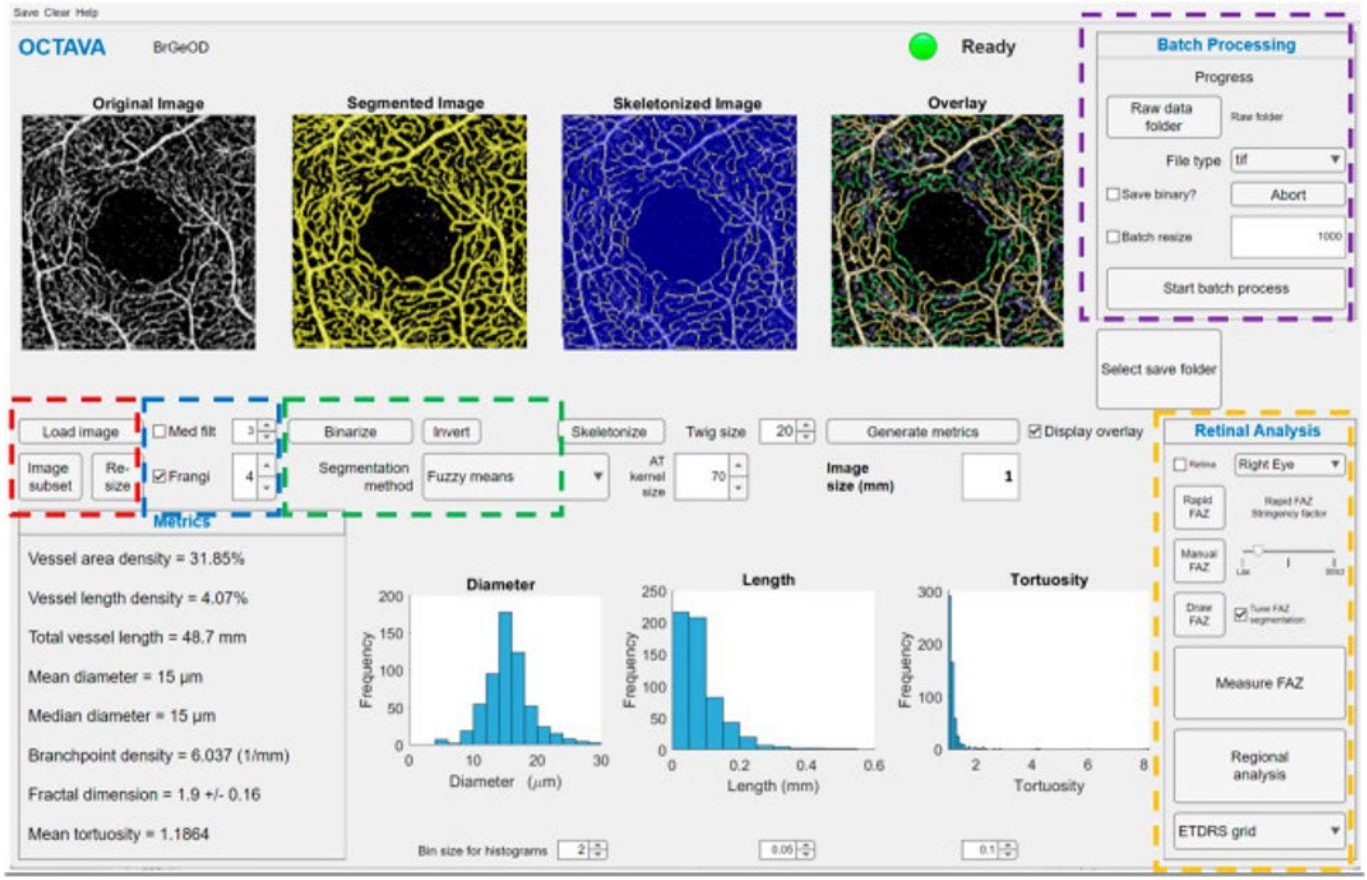

Figure 1. *Screenshot of OCTAVA analysis page. After uploading the original image, binarization is applied to obtain vessel parameters and FAZ parameters*

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Data normality was assessed using the Shapiro–Wilk test. Comparisons of OCTA parameters according to treatment groups were performed using the Kruskal–Wallis test. When the Kruskal–Wallis test indicated a statistically significant difference, post-hoc pairwise comparisons were conducted using the Mann–Whitney U test with Bonferroni correction. For comparisons among the three treatment groups, the Bonferroni-adjusted significance threshold was set at $p < 0.0167$. Effect sizes for significant pairwise Mann–Whitney U comparisons were calculated as $r = |Z|/\sqrt{N}$, where N represents the total number of observations in the two compared groups. Post-hoc power analysis was performed for OCTA parameters to evaluate whether non-significant findings might be related to limited statistical power. To account for the non-parametric nature of the data, statistical power for the Kruskal–Wallis test was calculated using the non-parametric eta-squared (η^2) effect size index, defined as $\eta^2 = (\chi^2 - k + 1)/(N - k)$, where χ^2 represents the Kruskal–Wallis test statistic, k is the number of groups, and N is the total sample size (N = 47 eyes). The non-centrality parameter ($\Lambda = N \times \eta^2$), together with the corresponding degrees of freedom, was used to estimate the achieved statistical power for nominally significant and non-significant parameters. The distribution of Tanner stages among the study groups was compared using Fisher's exact test because the assumptions for Pearson's chi-square test were not met due to small expected cell counts. All statistical tests were two-sided. A p value < 0.05 was considered statistically significant for overall Kruskal–Wallis comparisons. For post-hoc pairwise comparisons, Bonferroni-adjusted significance thresholds were applied as described above.

RESULTS

Demographic data

A total of 47 eyes from 47 patients were included in the study. To avoid potential inter-eye correlation and ensure statistical independence of the observations, only the right eye of each participant was selected for analysis. Among the 47 participants included in the study, 16 were assigned to Group 1, 14 to Group 2, and 17 to Group 3. Considering follow-up durations, nine patients were followed for 12–24 months, whereas eight patients had follow-up longer than 24 months, in group 3. Demographic data was given in ***Table 1***.

Thirty-two patients (68.1%) were male and fifteen patients (31.9%) were female. The mean age was 11.67 ± 2.94 years (range: 5.50-16 years). The 47 analyzed eyes were distributed across Tanner stages as follows: 14 eyes (29.8%) in Tanner stage 1, 9 eyes (19.1%) in stage 2, 15 eyes (31.9%) in stage 3, 5 eyes (10.6%) in stage 4, and 4 eyes (8.6%) in stage 5. The distribution of Tanner stages differed significantly among the three study groups (***Table 2***). Stage 1 was observed predominantly in Groups 2 and 3, whereas stages 4 and 5 were mainly represented in Group 3.

Treatment duration differed significantly among the three groups. Post-hoc pairwise comparisons showed significantly higher treatment duration in group 2 compared with group 1 ($p< 0.001$, $r = 0.98$), in group 3 compared with group 1 ($p< 0.001$, $r = 0.88$), and in group 3 compared with group 2 ($p< 0.001$, $r = 0.86$).

Assessment of OCTA parameters

Changes in the parameters according to the study groups were shown in ***Table 3***. Comparison of OCTA parameters among the three study groups revealed a statistically non-significant difference in all parameters. ($p> 0.05$).

Post-hoc power analysis

Post-hoc power analysis for the Kruskal–Wallis test was performed using the non-parametric eta-squared (η^2) effect size. Among the non-significant parameters, the achieved power ranged from 5.0% to 37.5%, suggesting that the non-significant findings should be interpreted with caution because of the limited statistical power.

Table 1: *Demographic Data*				
	Group 1(n=16)	Group 2 (n=14)	Group 3 (n=17)	P value
Age (years)	12 (7-14)	11.60 (6-14.50)	14 (5.5-16)	0.323
Height (cm)	135.65 (104-147.60)	132 (104.80-151.90)	146.60 (110-163.50)	0.190
Weight (kg)	32.55 (15-56.60)	29.60 (15.60-46)	37.50 (16-64.80)	0.384
Treatment duration (months)	0	4	24 (12-36)	**<0.001***

Table 2. *Distribution of Tanner stages according to the study groups.*					
Tanner stage	Group 1	Group 2	Group 3	Total	p value
Stage 1	1 (6.2%)	6 (42.9%)	7 (41.2%)	14 (29.8%)	<0,001
Stage 2	7 (43.8%)	0 (0.0%)	2 (11.8%)	9 (19.1%)	
Stage 3	8 (50.0%)	6 (42.9%)	1 (5.9%)	15 (31.9%)	
Stage 4	0 (0.0%)	2 (14.2%)	3 (17.6%)	5 (10.6%)	
Stage 5	0 (0.0%)	0 (0.0%)	4 (23.5%)	4 (8.6%)	
Total	16	14	17	47	

Table 3: *OCTAVA measurements among 3 groups*				
Parameter	Group 1 (n=16)	Group 2 (n=14)	Group 3 (n=17)	p value
VAD	24.65 (2.74–38.20)	33.23 (7.20–38.30)	31.85 (20.17–37.99)	0.202
VLD (mm)	14.72 (1.69–25.28)	19.76 (4.12–24.66)	19.59 (11.32–25.18)	0.183
Total VL	123.82 (14.29–212.59)	166.23 (34.73–207.37)	164.83 (95.17–211.75)	0.183
Mean VL	69 (58–151)	67 (55–74)	65 (50–74)	0.193
Median VL	48 (38–53)	47 (41–51)	47 (35–55)	0.819
Mean VD	17 (15–18)	17 (15–19)	17 (15–18)	0.976
Median VD	16 (14–17)	17 (13–17)	16 (14–17)	0.507
BD	1.46 (0-8.22)	1.44 (0-7.41)	1.32 (0-5.23)	0.445
Tortuosity	1.04 (1-1.15)	1.07 (1-1.23)	1.02 (1-1.17)	0.277
FAZ Area	0.43 (0.10–0.94)	0.40 (0.03–0.71)	0.45 (0.03–0.97)	0.616
Circularity	0.59 (0.21–0.83)	0.74 (0.60–0.96)	0.68 (0.24–0.96)	0.108
Acircularity Index	1.31 (1.09–2.20)	1.17 (1.01–1.29)	1.17 (1.00–2.05)	0.145
Axis Ratio	1.12 (1.02–5.90)	1.14 (1.03–1.91)	1.14 (1.03–1.98)	0.973
FAZ VD	7 (2-28)	9 (3-26)	7 (1-30)	0.709

DISCUSSION

Evidence from experimental animal models indicates a potential contribution of GH to retinal neural formation and eye development. Harvey et al [16] supported this information by showing GH is present in both retina and vitreous fluids in humans. Previous researches have largely concentrated on retinal neural tissue. When patients with GH deficiency were compared with healthy controls, no differences were observed in retinal nerve fiber layer (RNFL) thickness, macular thickness, or overall retinal thickness. Yuce and colleagues [9] suggested that the development of retinal neural tissue occurs independently of GH levels during the early intrauterine period, or it may be influenced by non-pituitary or locally produced GH.

The effect of GH on retinal vasculature has not been fully clarified. Retinal angiogenesis is mainly completed during the intrauterine period. Hellström and friends [7] found that retinal vascularity decreases in children with IGHD whether or not they receive rhGH therapy. Vascular branching points were significantly reduced when compared with age-matched healthy subjects. According to these findings they suggested that GH may be important for angiogenesis. It has not yet been clearly established whether GH exerts a direct effect on retinal angiogenesis or acts indirectly through other mediators. Recently, research interest has increasingly shifted toward locally synthesized angiogenic mediators, including vascular endothelial growth factor, fibroblast growth factor, and insulin-like growth factors I and II (IGF-I and IGF-II) [17-19]. Sonntag at al [20] researched in rodent models and got new evidence indicating that the GH/IGF-I axis may play a role in regulating angiogenesis within the brain. Smith et al [21] found that IGF-1 has a critical role on retinal angiogenesis. They inhibited the GH-receptors in mice. As a result, IGF-1 levels decreased and neovascularization was inhibited. However, they administered exogenous IGF-1 in the presence of GH -receptor inhibition and they showed that neovascularization was started.

In the study of Yuce at al, they searched for the differences in the neural and vascular parameters between 28 children with isolated GHD and controls. Macular thickness and RNFL thickness were not different between groups while retinal vascularization decreased in GHD group. Similar to our result, they also suggested that one year of GH treatment did not cause any retinal neuro-vascular changes [9].

Menezes et al found decreased branching points with OCT-A in adults with lifelong congenital IGHD when compared with healthy controls. On the other hand, other results such as normality of the foveal thickness, foveal avascular zone, superficial and deep retinal vascular densities were thought about presence of local compensatory mechanisms in the retinal microvascular architecture [22].

Omar et al investigated the differences of vessel densities with OCT-A in terms of superficial capillary plexus, deep capillary plexus and choriocapillaris between the children with congenital IGHD under rhGH therapy and healthy controls. Results were statistically nonsignificant [23].

As a summary, some OCTA-based studies of idiopathic GH deficiency demonstrate reduced microvascular density, whereas others show largely preserved retinal and choroidal structure and perfusion. In the literature, we were unable to find any study evaluating OCT-A data of patients who had used rhGH for more than two years. In this regard, our study is the first to investigate this issue.

Within the constraints of this retrospective, non–control-comparator study and a modest sample size, we did not observe statistically significant differences in OCT-A–derived retinal microvascular parameters across groups stratified by rhGH therapy duration. These findings are compatible with the interpretation that, GH therapy does not produce large, readily detectable alterations in retinal microcirculation; nonetheless, inference is tempered by several limitations. First, this study's retrospective design introduces potential selection and information biases, and the absence of a healthy control group limits contextual interpretation of the findings. Second, the sample size was small, which reduces statistical power and may limit the generalizability of our findings. Third, we did not conduct longitudinal follow-up, preventing assessment of temporal trajectories and limiting conclusions about progression or durability of effects. Fourth, patients in Group 3 had significantly higher Tanner stages than those in the other groups. Because pubertal maturation may influence retinal microvascular parameters, this baseline imbalance represents a potential confounding factor and should be considered when interpreting the study findings. Future

studies should include groups matched for pubertal stage or adjust for Tanner stage in the statistical analysis. Larger, prospectively designed investigations with standardized longitudinal follow-up and appropriately matched controls are warranted to refine these estimates.

ACKNOWLEDGEMENTS

We would like to thank Orhan Beger for the statistical analysis.

REFERENCES

1. Aguiar-Oliveira MH, Bartke A. 2019 Growth hormone deficiency: health and longevity. Endocr Rev. 40(2):575–601. doi: 10.1210/er.2018-00216.
2. Ghigo E, Bellone J, Aimaretti G, et al. 1996 Reliability of provocative tests to assess growth hor- mone secretory status. Study in 472 normally growing children. J Clin Endo- crinol Metab. 81(9):3323-7. doi: 10.1210/jcem.81.9.8784091.
3. Grimberg A, DiVall SA, Polychronakos C, et al. 2016 Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm. Res. Paediatr. 86(6):361–397. doi: 10.1159/000452150.
4. Stewart C, Garcia-Filion P, Fink C, et al. 2016 Efficacy of growth hormone replacement on anthropometric outcomes, obesity, and lipids in children with optic nerve hypoplasia and growth hormone deficiency. Int J Pediatr Endocrinol 2016: 5. doi: 10.1186/s13633-016-0023-9.
5. Cemeroglu AP, Coulas T, Kleis L. 2015 Spectrum of clinical presentations and endocrinological findings of patients with septo-optic dysplasia: a retrospective study. J Pediatr Endocrinol Metab 28: 1057-1063. doi: 10.1515/jpem-2015-0008.
6. Nalcacioglu-Yuksekkaya P, Sen E, Elgin U, et al. 2014 Corneal properties in children with congenital isolated growth hormone deficiency. Int J Ophthalmol 7: 317-320. doi: 10.3980/j.issn.2222-3959
7. Hellström A, Svensson E, Carlsson B, et al. 1999 Reduced retinal vascularization in children with growth hormone deficiency. J Clin Endocrinol Metabol 84: 795- 798. doi: 10.1210/jcem.84.2.5484.
8. Parentin F, Tonini G, Perissutti P. 2004 Refractive evaluation in children with growth defect. Curr Eye Res. 28: 11-15. doi: 10.1076/ceyr.28.1.11.23491.
9. Yuce O, Yalcın NG, Bideci A, et al. 2018 Retinal Neural and Vascular Structure in Isolated Growth Hormone Deficiency Children and Evaluation of Growth Hormone Treatment Effect. J Clin Res Pediatr Endocrinol. 10(2):113–118. doi: 10.4274/jcrpe.4758.
10. N G Yalcin, Z Aktas, O Yuce, et al. Choroidal thickness measurements in children with isolated growth hormone deficiency. Eye 2018,32:364–369
11. Spaide RF, Klancnik JM Jr, Cooney MJ. 2015 Retinal vascular layers imaged by fluo- rescein angiography and optical coherence tomographyangiography. JAMA Ophthalmol. 133(1):45–50. doi: 10.1001/jamaophthalmol.2014.3616.
12. Matsunaga D, Yi J, Puliafito CA, et al. 2014 OCT angiography in healthy human subjects. Ophthalmic Surg Lasers Imaging Retina. 45(6):510-5. doi: 10.3928/23258160-20141118-04
13. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44:291–303. doi: 10.1136/adc.44.235.291
14. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab. 2000;85:3990–3993. doi: 10.1210/jcem.85.11.6984
15. Untracht GR, Matos RS, Dikaios N, Bapir M, Durrani AK, Butsabong T, Campagnolo P, Sampson DD, Heiss C, Sampson DM. OCTAVA: An open-source toolbox for quantitative analysis of optical coherence tomography angiography images. PLoS One. 2021 Dec 9;16(12):e0261052. doi: 10.1371/journal.pone.0261052.
16. Steve Harvey, Eve Parker, Ian Macdonald, et al. 2009 Growth hormone is present in the human retina and vitreous fluid. Neuroscience Letters. 455:199–202. doi: 10.1016/j.neulet.2009.03.073.
17. Battegay EJ. 1995 Angiogenesis: mechanistic insights, neovascular diseases, and therapeutic prospects. J Mol Med. 73:333–346. doi: 10.1007/BF00192885.
18. Delafontaine P. 1995 Insulin-like growth factor I and its binding proteins in the cardiovascular system. Cardiovasc Res. 30:825–834. PMID: 8746194
19. Folkman J. 1995 Clinical applications of research on angiogenesis. N Engl J Med. 333: 1757–1763. doi: 10.1056/NEJM199512283332608.
20. Sonntag WE, Lynch CD, Cooney PT, et al. 1997 Decreases in cerebral microvasculature with age are associated with the decline in growth hormone and insulin-like growth factor 1. Endocrinology. 138: 3515–3520. doi: 10.1210/endo.138.8.5330.
21. Smith LEH, Kopchick JJ, Chen W. 1997 Essential role of growth hormone in ischemia-induced retinal

neovascularisation. Science. 276:1706–1709. doi:10.1126/science.276.5319.1706.

22. Menezes NV, Barros-Oliveira CS, Salvatori R, et al. 2022 Quantitative measures of the vascular and neural components of the retina in adult individuals with congenital and untreated growth hormone deficiency. International Journal of Retina and Vitreous. 8:72. doi: 10.1186/s40942-022-00408-x.

23. Omar I, Fadle YS, El Bakry NMI. 2024 Retinal and choroidal microvascular assessment of children receiving recombinant growth hormone therapy. International Journal of Retina and Vitreous. 10:90. doi: 10.1186/s40942-024-00610-z.