Serum FGF23 and VEGF-A Levels as Potential Biomarkers of Disease Severity in Retinopathy of Prematurity

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Рівні сироваткових FGF23 та VEGF-A як потенційні біомаркери тяжкості захворювання при ретинопатії недоношених

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Abstract

Purpose. *To evaluate the diagnostic and prognostic significance of serum FGF23 and VEGF-A levels in newborns with retinopathy of prematurity and to analyze their association with clinical characteristics of the disease.*

Material and Methods. *A prospective comparative study was conducted including 120 newborns: 42 preterm infants with retinopathy of prematurity, 40 preterm infants without signs of the disease, and 38 full-term newborns. Serum concentrations of FGF23 and VEGF-A were determined using enzyme-linked immunosorbent assay (ELISA). The relationship between biomarker levels and clinical parameters of ROP was assessed using Spearman's rank correlation coefficient.*

Results. *Significantly higher serum levels of FGF23 (185±42 pg/mL) and VEGF-A (1,35±0,42 ng/mL) were detected in preterm infants with retinopathy of prematurity compared with both preterm infants without ROP and full-term newborns ($p<0.05$). FGF23 levels demonstrated a moderate positive correlation with disease stage ($r=0,611$; $p<0.05$), while VEGF-A levels also showed a statistically significant positive correlation ($r=0,505$; $p<0.05$). In addition, higher FGF23 concentrations were observed in patients who required treatment.*

Conclusion. *Serum FGF23 and VEGF-A levels were significantly elevated in preterm infants with ROP and showed positive correlations with disease severity. Higher FGF23 concentrations were also associated with the need for treatment, supporting its potential prognostic value. Combined assessment of FGF23 and VEGF-A may provide additional information for evaluating disease severity in preterm infants with ROP.*

Keywords: *retinopathy of prematurity; FGF23; VEGF-A; angiogenesis; biomarkers; preterm infant.*

Резюме

Мета. *Оцінити діагностичне та прогностичне значення рівнів FGF23 та VEGF-A у сироватці крові новонароджених з ретинопатією недоношених (РН) та проаналізувати їх зв'язок з клінічними характеристиками захворювання.* ***Матеріали та методи.*** *Було проведено проспективне порівняльне дослідження за участю 120 новонароджених: 42 недоношених дітей з ретинопатією недоношених, 40 недоношених дітей без ознак захворювання та 38 доношених новонароджених. Концентрації FGF23 та VEGF-A у сироватці крові визначали за допомогою імуноферментного аналізу (ІФА). Зв'язок між рівнями біомаркерів та клінічними параметрами РН оцінювали за допомогою коефіцієнта рангової кореляції Спірмена.* ***Результати.*** *У недоношених дітей з РН були виявлені значно вищі рівні FGF23 (185±42 пг/мл) та VEGF-A (1,35±0,42 нг/мл) у сироватці крові порівняно як з не-*

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доношеними дітьми без РН, так і з доношеними новонародженими (p<0,05). Рівні FGF23 продемонстрували помірну позитивну кореляцію зі стадією захворювання (r=0,611; p<0,05), тоді як рівні VEGF-A також показали статистично значущу позитивну кореляцію (r=0,505; p<0,05). Крім того, вищі концентрації FGF23 спостерігалися у пацієнтів, які потребували лікування. ***Висновок.*** *Рівні FGF23 та VEGF-A у сироватці крові були значно підвищені у недоношених дітей з ROP та демонстрували позитивну кореляцію з тяжкістю захворювання. Вищі концентрації FGF23 також були пов'язані з потребою в лікуванні, що підтверджує його потенційну прогностичну цінність. Комбінована оцінка FGF23 та VEGF-A може надати додаткову інформацію для оцінки тяжкості захворювання у недоношених дітей з РН.*

Ключові слова: *ретинопатія недоношених; FGF23; VEGF-A; ангіогенез; біомаркери; недоношена дитина.*

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder that develops in preterm infants as a result of disrupted normal retinal vascular development. The disease remains one of the leading causes of preventable childhood blindness worldwide. Improvements in neonatal care and the increasing survival of extremely preterm infants have contributed to a rising incidence of ROP, particularly in low- and middle-income countries [1].

The pathogenesis of ROP is associated with disruption of the physiological process of retinal vasculogenesis. Under normal conditions, retinal vascularization begins at approximately the 14th week of gestation and is completed near term. Premature birth interrupts this process, leading to incomplete vascular development of the retina and subsequent retinal ischemia followed by pathological neovascularization [2]. The development of ROP is traditionally described as a two-phase process. In the first phase, hyperoxic conditions suppress normal retinal vascular growth, whereas in the second phase hypoxia of the avascular retina stimulates pathological neovascularization. Angiogenic factors and inflammatory mediators play a central role in these processes [3].

One of the key regulators of angiogenesis is vascular endothelial growth factor A (VEGF-A). This factor stimulates endothelial cell proliferation and the formation of new blood vessels and plays a crucial role in hypoxia-induced retinal neovascularization [4].

Changes in VEGF-A levels are closely associated with the phases of ROP development. Under hyperoxic conditions, VEGF-A expression decreases, leading to suppression of physiological retinal vascular growth, whereas subsequent hypoxia results in increased VEGF-A production and stimulation of pathological neovascularization. Clinical studies have shown that serum VEGF-A concentrations may increase in preterm infants at the time of diagnosis of severe ROP [2]. Similar findings were reported by Goswami et al., who demonstrated that changes in serum VEGF levels were associated with disease progression [5].

However, available data remain inconsistent. According to a systematic review and meta-analysis investigating circulating VEGF levels, systemic concentrations of this factor demonstrate considerable variability across studies and do not always reliably reflect the risk or severity of ROP [4]. In recent years, increasing attention has been directed toward other biomarkers of angiogenesis and inflammation, including various cytokines and growth factors detectable in peripheral blood of preterm infants. These mediators may participate in the regulation of angiogenesis and inflammatory processes involved in the development and progression of ROP [6].

Despite the substantial number of studies focusing on VEGF-A and other angiogenic factors in ROP, the diagnostic value of systemic biomarkers remains controversial. Differences in study design, timing of blood sampling, and laboratory methods contribute to significant heterogeneity of reported results [4]. Furthermore, most research has primarily focused on VEGF-A, whereas other potentially important regulators of angiogenesis remain insufficiently investigated. In particular, data regarding the role of fibroblast growth factor-23 (FGF23) in the development of ROP are virtually absent.

Recently, our group reported the first clinical evidence of an association between circulating FGF23 levels and the severity of retinopathy of prematurity in preterm infants using an immunochemiluminescence assay (ICLA). That study [7] demonstrated that elevated serum FGF23 concentrations were associated with more severe stages of ROP, suggesting that FGF23 may serve as a potential biomarker of disease progression. However, the previous investigation was limited to the evaluation of FGF23 alone. The present study extends these findings by simultaneously assessing both FGF23 and VEGF-A using enzyme-linked immunosorbent assay (ELISA), allowing evaluation of their combined association with disease severity and providing additional evidence regarding the potential clinical utility of systemic angiogenic biomarkers in ROP.

Therefore, the aim of the present study was to evaluate the diagnostic and prognostic significance of serum levels of FGF23 and VEGF-A in newborns with retinopathy of prematurity and to analyze their association with disease stage and clinical characteristics.

Materials and Methods.

Study design

This study was conducted as a prospective comparative clinical and laboratory investigation aimed at evaluating the diagnostic and prognostic significance of serum levels of fibroblast growth factor-23 (FGF23) and vascular endothelial growth factor A (VEGF-A) in newborns with retinopathy of prematurity. The study was carried out at the Republican Perinatal Center in Tashkent (Republic of Uzbekistan) between 2023 and 2026. Newborns who were hospitalized in

the neonatal and ophthalmology departments of the center and underwent routine screening for retinopathy of prematurity were eligible for inclusion. A total of 120 newborns were included in the study and divided into three groups according to gestational age and the presence of ROP.

Ethical approval

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Local Bioethics Committee of the Republican Specialized Scientific and Practical Medical Center of Eye Microsurgery (Approval №1(23) from 23rd of January 2023). Written informed consent was obtained from the parents or legal guardians of all enrolled infants before inclusion in the study.

Study population

The main group consisted of 42 preterm infants diagnosed with retinopathy of prematurity during ophthalmologic examination. The control group included 40 preterm infants with no signs of ROP detected during screening examinations. The comparison group consisted of 38 full-term newborns born at term without ophthalmologic pathology. The overall distribution of patients and the number of examined eyes are presented in Table 1.

The severity of retinopathy of prematurity was assessed according to the International Classification of Retinopathy of Prematurity (ICROP) [1, 3]. In cases of asymmetry between the eyes, the stage of the disease was determined according to the more severely affected eye, which is a commonly accepted approach in clinical studies assessing ROP severity .

The distribution of patients in the main group according to ROP stage is presented in Table 2.

Inclusion and exclusion criteria

The main group included preterm newborns with a gestational age of less than 32 weeks and a birth weight of less than 1500 g in whom ROP of any stage was diagnosed during ophthalmologic examination in accordance with the ICROP classification. Ophthalmologic screening was performed at a postmenstrual age of 31–36 weeks after obtaining written informed consent from parents or legal guardians.

The control group consisted of preterm newborns with a gestational age of less than 32 weeks and a birth weight of less than 1500 g in whom no signs of ROP were detected during ophthalmologic examination. Examinations in this group were performed at the same postmenstrual age.

The full-term newborn group included infants born at a gestational age of 37–41 weeks with an uncomplicated early neonatal period and no ophthalmologic pathology.

Newborns with congenital anomalies of the eye, genetic syndromes and chromosomal abnormalities, congenital TORCH infections, severe systemic diseases that could affect angiogenesis, as well as infants who had received blood component transfusions less than 14 days before blood sampling were excluded from the study. Patients who had undergone treatment for ROP before blood sampling or those with incomplete clinical or laboratory data were also excluded from the analysis.

Ophthalmological examination

Ophthalmological examination was performed as part of the ROP screening program. The examination was conducted by a pediatric ophthalmologist using indirect binocular ophthalmoscopy after pharmacological pupil dilation. Combined mydriatic agents were used to achieve adequate mydriasis. Retinal examination was performed using condensing lenses allowing evaluation of both central and peripheral retinal areas.

Diagnosis and staging of ROP were carried out according to the International Classification of Retinopathy of Prematurity (ICROP) with mandatory assessment of the disease stage, retinal zone involvement, and the presence of plus disease [1, 3].

Laboratory determination of FGF23 and VEGF-A levels

Peripheral venous blood samples were obtained from all newborns under aseptic conditions during routine clinical examination. Blood was collected into vacuum tubes with a clot activator to obtain serum. Samples were allowed to clot at room temperature for 30 minutes and were then centrifuged at 3000 rpm for 10 minutes. The obtained serum was aliquoted and stored at −80 °C until analysis. Repeated freeze–thaw cycles were avoided.

Table 1. Characteristics of the study groups.

Study group	Number of patients (n)	Number of eyes (n)
Preterm infants with ROP	42	80
Preterm infants without ROP	40	80
Full-term newborns	38	76
Total	120	236

Note. ROP – retinopathy of prematurity. n – number of patients/eyes.

Table 2. Distribution of patients with ROP according to disease stage (ICROP).

ROP stage	Number of patients (n)	Percentage (%)
Stage 1	13	31,0
Stage 2	15	35,7
Stage 3	10	23,8
Stage 4	3	7,1
Stage 5	1	2,4
Total	42	100

Note. ROP – retinopathy of prematurity; ICROP – International Classification of Retinopathy of Prematurity. Patient distribution was based on the more severely affected eye in cases of asymmetric disease.

Serum concentrations of fibroblast growth factor-23 (FGF23) and vascular endothelial growth factor A (VEGF-A) were determined using enzyme-linked immunosorbent assay (ELISA) with commercially available diagnostic kits according to the manufacturer's instructions. The method was based on the sandwich ELISA principle using monoclonal antibodies specific for human FGF23 and VEGF-A.

Following sample incubation and washing steps, detection antibodies and streptavidin conjugated with horseradish peroxidase were added. The reaction was visualized using tetramethylbenzidine substrate, after which optical density was measured at a wavelength of 450 nm using a microplate spectrophotometer. Concentrations of the studied proteins were calculated from calibration curves constructed using standard solutions of recombinant proteins and expressed in pg/mL for FGF23 and ng/mL for VEGF-A.

The analytical sensitivity of the method was less than 5 pg/mL for FGF23 and less than 10 pg/mL for VEGF-A. The intra-assay and inter-assay coefficients of variation did not exceed 10 % and 12 %, respectively. All laboratory analyses were performed in a blinded manner without information regarding the clinical group of the samples.

Statistical analysis

Statistical analysis was performed using SPSS Statistics (IBM Corp., USA) and R Statistical Software. Quantitative variables were initially tested for normal distribution using the Shapiro–Wilk test. Normally distributed data were presented as mean±standard deviation (M±SD), whereas non-normally distributed data were presented as median and range.

Comparisons of quantitative variables between independent groups were performed using parametric or non-parametric methods depending on the distribution of the data. When normal distribution was observed, one-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used. For non-normally distributed data, the Kruskal–Wallis test followed by pairwise comparisons using the Mann–Whitney U test with Bonferroni correction was applied.

The relationship between biomarker levels and clinical characteristics of ROP was evaluated using Spearman's rank correlation coefficient. Correlation analysis was performed between biomarker concentrations and the stage of retinopathy of prematurity. Additional analysis of the clinical significance of FGF23 levels was performed by comparing its concentrations in patients with ROP depending on the need for treatment using the Mann–Whitney U test. Differences were considered statistically significant at $p<0.05$.

Results

The obtained results demonstrate a significant increase in the concentrations of FGF23 and VEGF-A in preterm infants with ROP compared with both preterm infants without the disease and full-term newborns. Comparative analysis of the studied biomarkers revealed statistically significant differences between the groups of newborns. The highest FGF23 levels were recorded in preterm infants with ROP, which were significantly higher than those observed both in preterm infants without the disease ($p<0.05$) and in full-term newborns ($p<0.05$). A similar trend was observed for VEGF-A. In preterm infants with ROP, the level of this factor was 1.35±0.42 ng/mL, which was significantly higher than the levels detected in preterm infants without signs of the disease ($p<0.05$) and in full-term newborns ($p<0.05$).

The analysis of the relationship between the levels of the studied biomarkers and the severity of ROP revealed a statistically significant correlation between serum FGF23 concentration and the stage of the disease. As shown in Figure 1, FGF23 levels demonstrated a moderate positive correlation with the stage of ROP. With increasing disease stage, a gradual rise in the concentration of this biomarker was observed. The Spearman correlation coefficient was $r = 0.611$ ($p<0.05$), indicating a significant association between FGF23 levels and the severity of the pathological process.

A similar analysis was performed for vascular endothelial growth factor A. As presented in Figure 2, VEGF-A levels also showed a statistically significant positive correlation with the stage of ROP. Disease progression was accompanied by an increase in serum VEGF-A concentration. The Spearman correlation coefficient was r=0,505

Table 3. Serum levels of FGF23 and VEGF-A in newborns of the study groups

Parameter	Preterm infants with ROP (n=42)	Preterm infants without ROP (n=40)	Full-term newborns (n=38)
FGF23, pg/mL (M±SD)	185±42 *#	120±35 #	55±20
FGF23, median (min–max)	182 (110–265)	118 (55–210)	52 (30–100)
VEGF-A, ng/mL (M±SD)	1.35±0.42 *#	0.85±0.28 #	0.40±0.15
VEGF-A, median (min–max)	1.32 (0.70–2.20)	0.83 (0.45–1.25)	0.38 (0.20–0.60)

Note. FGF23 – fibroblast growth factor 23; ROP – retinopathy of prematurity; * – differences are statistically significant compared with the group of preterm infants without ROP ($p<0.05$). # – differences are statistically significant compared with the group of full-term newborns ($p<0.05$).

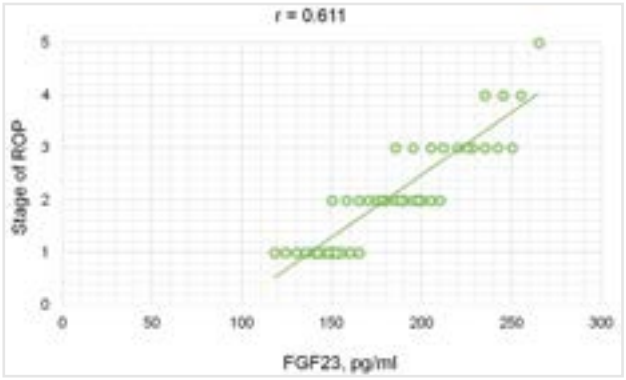

Fig. 1. Correlation between serum FGF23 levels and the stage of retinopathy of prematurity.

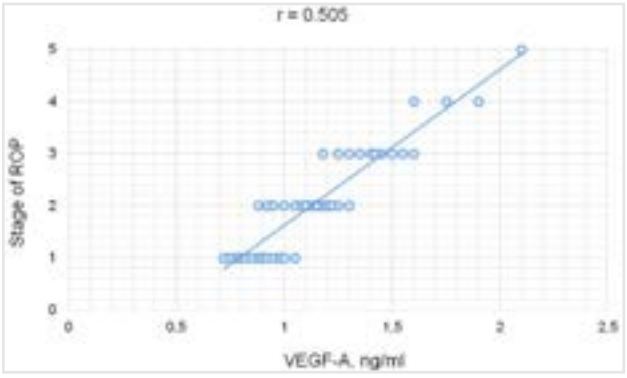

Fig. 2. Correlation between serum VEGF-A levels and the stage of retinopathy of prematurity.

($p<0.05$), corresponding to a moderate positive relationship between the level of this angiogenic factor and the severity of retinopathy of prematurity.

An additional analysis of the clinical significance of FGF23 was performed by comparing its levels in patients with ROP depending on the need for laser treatment. As shown in Figure 3, patients who required treatment had significantly higher FGF23 levels compared with those who did not require therapy. The differences between the groups were statistically significant ($p<0.05$, Mann–Whitney U test). This finding suggests a potential prognostic value of elevated FGF23 levels in assessing disease severity and the risk of ROP progression.

Clinical examples of the ophthalmoscopic appearance at different stages of retinopathy of prematurity are presented in Figure 4 (see cover page 3). The images illustrate the progression of retinal pathological changes from early stages of the disease to advanced proliferative forms.

The observed ophthalmoscopic findings are consistent with the results of the laboratory and correlation analyses: patients with more severe stages of ROP demonstrated higher levels of the studied biomarkers. In particular, increasing concentrations of FGF23 and VEGF-A were associated with greater disease severity, which corresponds to the identified positive correlation between the levels of these factors and the stage of ROP.

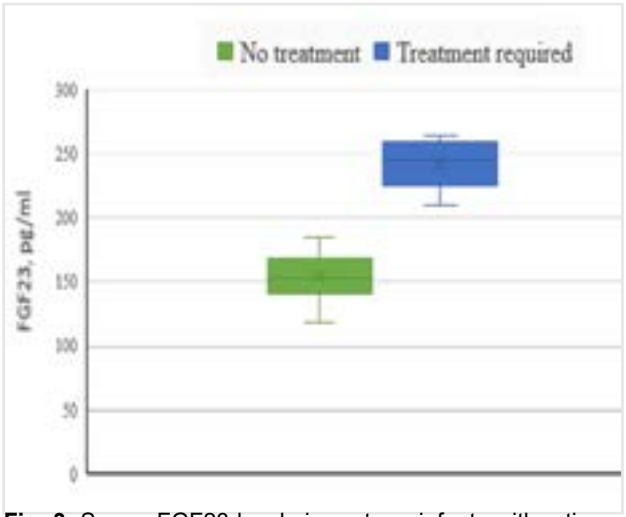

Fig. 3. Serum FGF23 levels in preterm infants with retinopathy of prematurity depending on the need for treatment. Note. A box-and-whisker plot with overlaid individual FGF23 concentration values is presented. Differences between the groups were statistically significant ($p<0.05$, Mann–Whitney U test).

Discussion

In the present study, a statistically significant increase in serum levels of FGF23 and VEGF-A was observed in preterm infants with ROP compared with both preterm infants without the disease and full-term newborns. In addition, a positive correlation was identified between the concentrations of these biomarkers and the clinical severity of the disease, including the stage of ROP, the presence of plus disease, the zone of retinal involvement, and the need for treatment. These findings suggest a potential diagnostic and prognostic value of these angiogenic factors in assessing the severity of ROP.

The findings of our study regarding VEGF-A are consistent with current understanding of its key role in the pathogenesis of ROP. VEGF is a major regulator of angiogenesis and plays a central role in the development of pathological retinal neovascularization. According to the two-phase model of ROP pathogenesis, hyperoxic conditions following premature birth suppress VEGF expression and inhibit normal retinal vascular growth, whereas subsequent hypoxia of avascular retinal regions induces increased VEGF expression and stimulates pathological neovascularization.

Our data are comparable with the results of several clinical studies. For example, Hellgren et al. [2] demonstrated that preterm infants who subsequently developed severe ROP had significantly higher serum VEGF concentrations at the time of the first diagnosis compared with infants without ROP. Similar results were reported by Goswami et al. [5], who showed significant changes in serum VEGF levels in preterm infants with ROP, confirming the

involvement of this factor in disease development and progression.

However, the literature on systemic VEGF levels remains inconsistent. According to a systematic review and meta-analysis by Sjöbom et al. [4], which included more than 50 studies, circulating VEGF-A concentrations demonstrate substantial inter-study variability and do not always show a consistent association with the development or severity of ROP. Such heterogeneity may be related to differences in the timing of blood sampling, laboratory methods used, and clinical characteristics of the study populations.

Another factor influencing systemic VEGF levels is the treatment administered. Cheng et al. [6] demonstrated that after intravitreal administration of the anti-VEGF agent conbercept in patients with ROP, circulating VEGF-A levels significantly decreased during the first week following treatment and gradually returned to baseline levels after several weeks. These findings further support the close relationship between systemic VEGF concentrations and angiogenic activity.

The present findings [7-11] are consistent with our previously published study, in which elevated circulating FGF23 concentrations were shown to be associated with increasing severity of retinopathy of prematurity. In that earlier investigation, serum FGF23 was measured using ICLA, whereas the current study employed ELISA and additionally evaluated VEGF-A. Despite methodological differences, both studies demonstrated a significant association between elevated FGF23 levels and disease severity, supporting the reproducibility of this observation. Furthermore, the simultaneous assessment of VEGF-A together with FGF23 provides additional evidence that these angiogenic factors may complement each other in reflecting the biological activity of ROP.

Several limitations of this study should be acknowledged. First, the study was conducted at a single medical center, which may limit the generalizability of the findings. Second, biomarker levels were assessed at a single time point, whereas longitudinal monitoring could provide more comprehensive information on temporal changes in angiogenic factors during disease progression. In addition, the relatively small sample size may limit the statistical power of the analysis. Nevertheless, despite these limitations, the results expand current knowledge regarding the role of systemic angiogenic factors in the pathogenesis of ROP and highlight the potential diagnostic and prognostic significance of FGF23. Further studies involving larger patient cohorts and longitudinal biomarker assessments are required to confirm these findings and clarify the role of FGF23 in the development and progression of the disease.

Overall, the obtained results support the concept that systemic levels of angiogenic factors may reflect the activity of pathological processes underlying ROP. The identified positive correlation between VEGF-A concentrations and disease severity is consistent with existing evidence regarding the crucial role of this factor in the regulation of pathological retinal neovascularization. At the same time, the observed association between elevated FGF23 levels and clinical characteristics of ROP suggests a potential involvement of this factor in molecular mechanisms of vascular remodeling and angiogenesis in this condition.

The findings are of particular interest in the context of identifying systemic biomarkers that could help objectively assess the risk of disease progression in preterm infants. Currently, diagnosis and monitoring of ROP are primarily based on ophthalmoscopic examinations that require specialized equipment and experienced ophthalmologists. In this regard, the identification of accessible laboratory markers may contribute to improving screening strategies and facilitating earlier identification of infants at high risk of severe disease.

Conclusion

The present study demonstrated that serum levels of fibroblast growth factor-23 (FGF23) and vascular endothelial growth factor A (VEGF-A) are significantly elevated in preterm infants with retinopathy of prematurity compared with both preterm infants without the disease and full-term newborns. Moreover, increased concentrations of these biomarkers were associated with clinical indicators of disease severity, including ROP stage, retinal zone involvement, the presence of plus disease, and the need for treatment. These findings support the important role of angiogenic factors in the pathogenesis of ROP and are consistent with current understanding of the central role of VEGF-A in pathological retinal neovascularization. At the same time, the observed association between elevated FGF23 levels and disease severity suggests a potential involvement of this factor in molecular mechanisms of vascular remodeling and pathological angiogenesis. Thus, the assessment of serum FGF23 and VEGF-A levels may represent a promising additional laboratory approach for evaluating disease severity and prognosis in retinopathy of prematurity.

Author Contributions

Karimova M. Kh. – reviewing and editing; Yusupov A. F. – design, conceptualisation, review and revision; Djamalova Sh. A. – writing formal analysis; software; review and revision; Usmanova Y. A. – methodology, drafting. All authors read the and approved the final version of the manuscript.

Disclaimers

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Informed consent

The research was conducted with the participation of people. This study was approved by the local bioethics committee (Protocol №5, 02.04.2023).

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to improve the English language, grammar, readability, and overall clarity of the manuscript. The AI-assisted tool was used exclusively for language editing and text refinement. The authors reviewed and edited all AI-generated suggestions, take full responsibility for the content of the manuscript, and confirm that all scientific interpretations, study design, data analysis, results, and conclusions are entirely their own.

Conflict of Interest

The authors declare that they have no conflicts of interest that that could influence their opinion on the subject matter or materials described and discussed in this manuscript.

Data Availability Statement

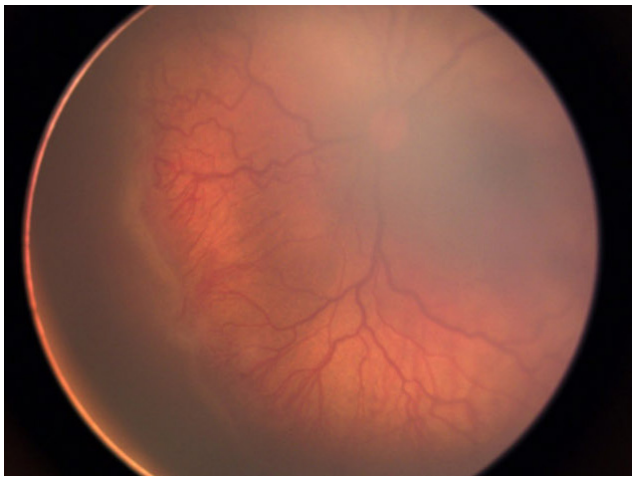
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations

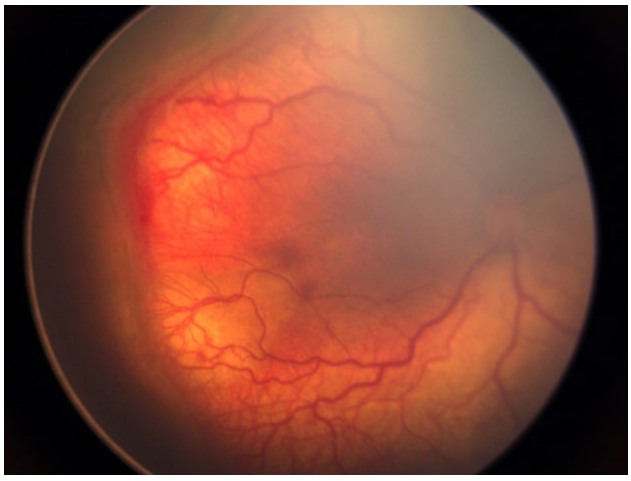
ELISA – Enzyme-Linked Immunosorbent Assay; FGF23 – Fibroblast Growth Factor 23; ICLA – Immunochemiluminescence Assay; ICROP – International Classification of Retinopathy of Prematurity; ROP – Retinopathy of Prematurity; VEGF-A – Vascular Endothelial Growth Factor A.

References

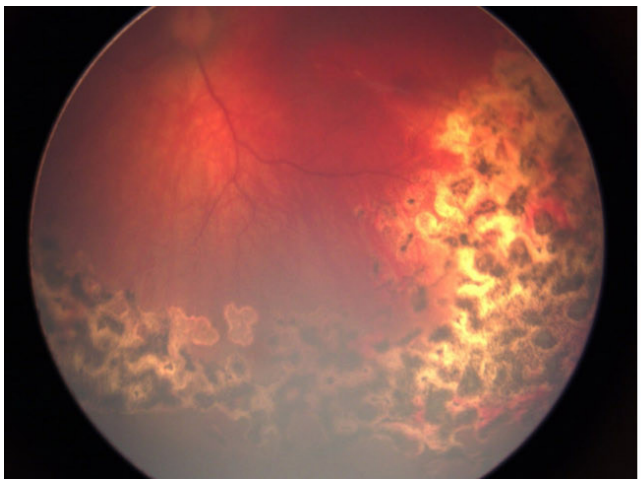
1. Marra KV, Chen JS, Nudleman E, Robbins SL. Review of Retinopathy of Prematurity Management in the Anti-VEGF Era: Evolving Global Paradigms, Persistent Challenges and Our AI-Assisted Future. Clin Exp Ophthalmol. 2025 Dec;53(9):1202-1217. doi: 10.1111/ceo.14598.
2. Hellgren G, Löfqvist C, Hård AL, Hansen-Pupp I, Gram M, Ley D, Smith LE, Hellström A. Serum concentrations of vascular endothelial growth factor in relation to retinopathy of prematurity. Pediatr Res. 2016 Jan;79(1-1):70-5. doi: 10.1038/pr.2015.181.
3. Huang D, Liu Z, Deng Y. Retinopathy of Prematurity (ROP): An Overview of Biomarkers in Various Samples for Prediction, Diagnosis, and Prognosis. Clin Ophthalmol. 2025 May 7;19:1515-1530. doi: 10.2147/OPTH.S519292.
4. Sjöbom U, Hellqvist T, Humayun J, Nilsson AK, Gyllensten H, Hellström A, Löfqvist C. Circulating VEGF-A Levels in Relation to Retinopathy of Prematurity and Treatment Effects: A Systematic Review and Meta-Analysis. Ophthalmol Sci. 2024 May 7;4(6):100548. doi: 10.1016/j.xops.2024.100548.
5. Goswami B, Goyal M, Beri S, Garg R, Saili A, Jain A. Role of Serum Levels of Vascular Endothelial Growth Factor and Its Receptor in Retinopathy of Prematurity. Iran J Pediatr. 2015 Aug;25(4):e2373. doi: 10.5812/ijp.2373.
6. Cheng Y, Zhu X, Linghu D, et al. Serum levels of cytokines in infants treated with conbercept for retinopathy of prematurity. Sci Rep. 2020 Aug;10:12695. doi: 10.1038/s41598-020-69684-7.
7. Yusupov AF, Karimova MKh, Usmanova YA. Relationship of Fibroblast Growth Factor 23 With Retinopathy of Prematurity Severity in Preterm Infants. Int J Med Sci Clin Res. 2025 Aug;5(8):12-15. doi: 10.37547/ijmscr/Volume05Issue08-03
8. Kaur K, Mikes BA. Retinopathy of Prematurity. 2025 Jun 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.
9. Kumawat D, Kandasamy S, Chandra P. Reactivation of retinopathy of prematurity after anti-VEGF treatment: a review. Br J Ophthalmol. 2026 Jan 22;110(2):117-124. doi: 10.1136/bjo-2025-327597.
10. Shah PK, Abiramalatha T, Quinn GE, Darlow BA, Marlow N, Fielder AR. Retinopathy of prematurity: Still more to do. Indian J Ophthalmol. 2025 Nov 1;73(11):1693-1694. doi: 10.4103/IJO.IJO_669_25.
11. Pieh C, Agostini H, Buschbeck C, Krüger M, Schulte-Mönting J, Zirrgiebel U, Drevs J, Lagrèze WA. VEGF-A, VEGFR-1, VEGFR-2 and Tie2 levels in plasma of premature infants: relationship to retinopathy of prematurity. Br J Ophthalmol. 2008 May;92(5):689-93. doi: 10.1136/bjo.2007.128371.



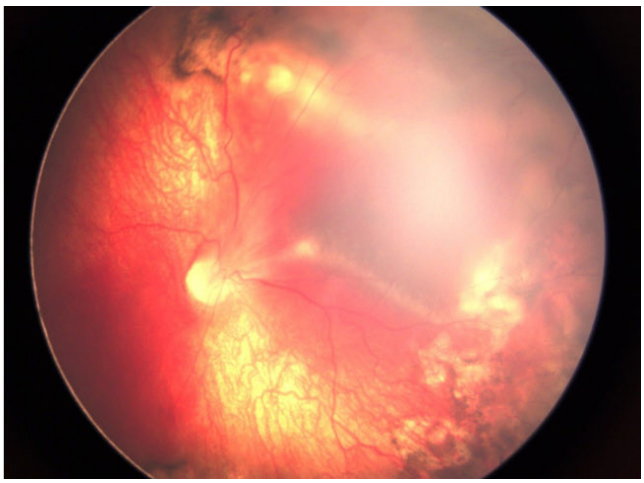
Stage 1 ROP. A thin demarcation line is observed between the vascularized and avascular portions of the retina without the formation of a pronounced ridge. The vascular pattern remains relatively organized, and no signs of pathological neovascularization are detected. FGF23 level — 138 pg/mL; VEGF-A level — 0.82 ng/mL.



Stage 2 ROP. A demarcation line with the formation of an elevated ridge is visualized at the border between the vascularized and avascular retina. Retinal vessels are directed toward the demarcation zone, with no signs of pronounced extraretinal neovascularization. FGF23 level — 182 pg/mL; VEGF-A level — 1.28 ng/mL.



Stage 4 ROP, status after laser photocoagulation of the retina. Multiple laser photocoagulation marks are observed in the peripheral retina within previously avascular areas, performed to suppress pathological neovascularization. FGF23 level — 248 pg/mL; VEGF-A level — 1.85 ng/mL (before treatment).



Stage 5 ROP, status after laser photocoagulation of the retina. ronounced fibrovascular proliferation, tractional retinal deformation, and multiple laser photocoagulation marks in the peripheral retina are visualized. FGF23 level — 262 pg/mL; VEGF-A level — 2.05 ng/mL (before treatment).

Figure 4. Clinical examples of ophthalmoscopic findings and levels of the biomarkers FGF23 and VEGF-A in different stages of retinopathy of prematurity.