BIOMEDICINSKA ISTRAŽIVANJA

Časopis Medicinskog fakulteta Foča, Univerzitet u Istočnom Sarajevu
Godište 17, broj 1, suplement 1, jun 2026.

Journal of the Faculty of Medicine Foča, University of East Sarajevo
Volume 17, No 1, Suppl 1, June 2026

BIOMEDICINSKA ISTRAŽIVANJA

Časopis
Medicinskog fakulteta Foča,
Univerzitet u Istočnom Sarajevu

ISSN 1986-8529 (Print)
ISSN 1986-8537 (Online)
UDK 57+61

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Članci su u cjelosti dostupni na internet stranici:
http://biomedicinskaistrazivanja.mef.ues.rs.ba

Štamparija
„Kopikomerc", Istočno Novo Sarajevo

Tiraž
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BIOMEDICINSKA ISTRAŽIVANJA

Journal of the Faculty of Medicine Foča, University of East Sarajevo

ISSN 1986-8529 (Print)
ISSN 1986-8537 (Online)
UDC 57+61

Published by
Faculty of Medicine Foča University of East Sarajevo Studentska 5, 73 300 Foča

On behalf of the publisher
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All articles are available on the following website:
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Text capture and processing
Vedrana Krsmanović

Print
„Kopikomerc", Istočno Novo Sarajevo

Printing
100 copies

The journal "Biomedicinska istraživanja" is indexed in Directory of Open Access Journals, Google Scholar, Directory of Research Journal Indexing, CrossRef, DOI Srpska.

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Iz uredništva

Poštovane koleginice i kolege,

Sa velikim zadovoljstvom predstavljamo suplement posvećen stručnom skupu „Sistemske bolesti i oko“, održanom u Foči 4. i 5. juna 2026. godine, u organizaciji oftalmologa, kliničara i akademskih institucija regiona. Ovaj skup okupio je eminentne stručnjake iz Srbije, Bosne i Hercegovine, Crne Gore, Hrvatske, Švedske, Katara i Ujedinjenog Kraljevstva, sa zajedničkim ciljem – produbljivanja razumijevanja kompleksnih veza između sistemskih bolesti i očnih manifestacija.

Savremena oftalmologija sve više prevazilazi granice izolovane specijalnosti. Oko danas predstavlja ne samo organ vida, već i „prozor“ u vaskularne, imunološke, metaboličke, neurološke i onkološke procese organizma. Brojne sistemske bolesti prve znake mogu ispoljiti upravo na oku, dok retinalna i horioretinalna mikrocirkulacija postaju važni biomarkeri opšteg zdravstvenog stanja. Upravo zato multidisciplinarni pristup predstavlja osnov savremene dijagnostike i terapije.

Program ovog suplementa obuhvata širok spektar tema – od retinalnih vaskulitisa, paraneoplastičnih sindroma i hipertenzivne retinopatije, do dijabetičke retinopatije, OCTA analiza, oculomics pristupa i savremenih radioloških metoda u evaluaciji orbite. Posebnu vrijednost daju predavanja posvećena glaukomu kao mogućoj sistemskoj bolesti, hlorokinskoj makulopatiji prema novim protokolima, Graves orbitopatiji, kao i izazovima diferencijalne dijagnostike u oftalmologiji.

Značajan segment suplementa čine i prikazi slučajeva i sesija mladih oftalmologa. Upravo kroz rijetke i kompleksne kliničke

Editorial

Dear Colleagues,

It is our great pleasure to present this supplement dedicated to the scientific meeting “Systemic Diseases and the Eye”, held in Foča on June 4–5, 2026, bringing together ophthalmologists, clinicians, and academic institutions from across the region. The meeting assembled distinguished experts from Serbia, Bosnia and Herzegovina, Montenegro, Croatia, Sweden, Qatar, and the United Kingdom, united by a common goal—to advance the understanding of the complex interactions between systemic diseases and ocular manifestations.

Modern ophthalmology increasingly transcends the boundaries of an isolated specialty. The eye is no longer viewed solely as an organ of vision, but also as a “window” into vascular, immunological, metabolic, neurological, and oncological processes within the human body. Numerous systemic diseases may first manifest through ocular findings, while retinal and chorioretinal microcirculation are becoming increasingly important biomarkers of overall systemic health. For this reason, a multidisciplinary approach represents a cornerstone of contemporary diagnosis and treatment.

The program presented in this supplement encompasses a broad spectrum of topics, ranging from retinal vasculitis, paraneoplastic syndromes, and hypertensive retinopathy, to diabetic retinopathy, OCTA-based analyses, oculomics, and advanced radiological imaging of the orbit. Particular value is added by lectures addressing glaucoma as a potentially systemic disease, chloroquine maculopathy in the context of updated screening protocols, Grawes’ orbitopathy, as well as the diagnostic challenges encountered in complex ophthalmic disorders.

slučajeve medicina pokazuje svoju punu interdisciplinarnu dimenziju. Prikazi Takayasu sindroma, Waldenströmove makroglobulinemije, pioderma gangrenozuma, tumora optičkog nerva, Tersonovog sindroma, Susac sindroma i drugih stanja potvrđuju koliko oko može biti prvi signal ozbiljne sistemske bolesti.

Posebno nas raduje prisustvo mladih ljekara i istraživača, čiji radovi potvrđuju da regionalna oftalmologija posjeduje značajan naučni i klinički potencijal. Njihovo uključivanje u stručne i naučne aktivnosti predstavlja važan korak ka budućem razvoju interdisciplinarne medicine i translacionih istraživanja.

Ovaj suplement nije samo zbir sažetaka i predavanja. On predstavlja dokument savremenog trenutka oftalmologije regiona – discipline koja se intenzivno razvija kroz integraciju kliničkog iskustva, naprednih imaging tehnologija, molekularne medicine i personalizovanog pristupa pacijentu.

Zahvaljujemo svim predavačima, autorima, učesnicima i organizatorima koji su svojim znanjem, iskustvom i entuzijazmom doprinijeli realizaciji ovog stručnog skupa. Posebnu zahvalnost upućujemo institucijama koje kontinuirano podržavaju razvoj oftalmologije i interdisciplinarne saradnje u regionu.

Vjerujemo da će sadržaj ovog suplementa biti koristan izvor znanja oftalmolozima, internistima, reumatolozima, endokrinolozima, radiolozima, neurolozima i svim ljekarima koji se u svakodnevnoj praksi susreću sa kompleksnim odnosom sistemskih bolesti i oka.

Gost urednik
Prof. dr Nada Avram
Foča, jun 2026.

An important component of this supplement is dedicated to case reports and the session of young ophthalmologists. It is precisely through rare and challenging clinical cases that medicine demonstrates its full interdisciplinary dimension. Presentations involving Takayasu syndrome, Waldenström macroglobulinemia, pyoderma gangrenosum, optic nerve tumors, Terson syndrome, Susac syndrome and other entities emphasize how ocular manifestations may represent the first sign of severe systemic disease.

We are especially encouraged by the participation of young physicians and researchers, whose contributions demonstrate the considerable scientific and clinical potential of regional ophthalmology. Their active involvement in scientific and professional activities represents an important step toward the future development of interdisciplinary medicine and translational research.

This supplement is not merely a collection of abstracts and lectures. It represents a reflection of the current state of regional ophthalmology — a discipline rapidly evolving through the integration of clinical expertise, advanced imaging technologies, molecular medicine, and personalized patient care.

We would like to express our sincere gratitude to all invited speakers, authors, participants, and organizers whose knowledge, experience, and enthusiasm contributed to the success of this scientific meeting. Special appreciation is extended to the institutions that continuously support the advancement of ophthalmology and interdisciplinary collaboration throughout the region.

We believe that the contents of this supplement will serve as a valuable source of knowledge for ophthalmologists, internists, rheumatologists, endocrinologists, radiologists, neurologists, and all physicians engaged in the management of complex interactions between systemic diseases and ocular pathology.

Guest editor
Nada Avram, MD, PhD
Foča, June 2026

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):3–8

UDK: 617.735-002-053.31+615.277
DOI: 10.59137/BII202601640M

Original article

Neonatal risk factors for the development of aggressive retinopathy of prematurity (A-ROP) and anti-VEGF treatment outcomes

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Summary

Introduction. Retinopathy of prematurity (ROP) is a neurovascular disease that, if left untreated, leads to severe visual impairment and blindness. Early diagnosis and timely therapy reduce the risk of a severe outcome. The most significant risk factors for the development of the disease are low gestational age, low birth weight, development of respiratory distress and prolonged need for oxygen therapy, neonatal sepsis, anaemia, and others. This paper analyses the most significant risk factors and the outcome of treatment with anti-VEGF therapy, as well as the additional need for laser photocoagulation.

Methods. A retrospective study was conducted involving 30 children (60 eyes) with the A-ROP form of retinopathy, divided into two groups according to the anti-VEGF agent administered (bevacizumab or ranibizumab).

Results. Regarding gestational age, a statistically significant difference was found between the two groups. Birth weight was higher in the group that received intravitreal bevacizumab (IVB). Readministration of the drug was required in three patients (five eyes) treated with bevacizumab, and in four patients (nine eyes) who received ranibizumab (IVR). The need for laser photocoagulation was 40% in the IVB group versus 100% in the IVR group, a statistically highly significant difference.

Conclusion. Timely diagnosis and adequate therapy significantly improve outcomes and reduce the risk of severe visual impairment. In this study, bevacizumab showed superiority over ranibizumab with respect to the effect on ROP reactivation and the need for additional laser intervention.

Key words: ROP, retinopathy of prematurity, anti-VEGF, bevacizumab, ranibizumab

Primljen – Received: 26/05/2026
Prihvaćen – Accepted: 29/05/2026

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Introduction

Retinopathy of prematurity (ROP) is a neurovascular disease that, if left untreated, leads to severe visual impairment and blindness. Early diagnosis and timely therapy reduce the risk of a severe outcome. The main risk factor for the development of the disease is premature birth. As neonatal survival continues to improve due to advances in perinatal and neonatal care, especially in underdeveloped and developing countries, the incidence and recognition of ROP have significantly increased. ROP represents a unique interaction of systemic immaturity, disrupted development of retinal blood vessels, and exposure to environmental risk factors, primarily oxygen therapy. This condition highlights the importance of timely screening, diagnosis, and intervention to prevent lifelong visual impairment [1].

Preterm birth is common worldwide. In addition to increased mortality, short and longterm complications resulting from arrested normal development after preterm birth include retinopathy of prematurity (ROP), as well as delayed physical growth, vascular abnormalities (including intraventricular haemorrhage), pulmonary disease, sepsis, poor neurocognitive development, and metabolic dysregulation with an increased risk of diabetes in young adulthood. In humans, the development of the retinal vascular system begins in the second trimester of pregnancy and is completed around term. In infants born extremely preterm, before 28 weeks of gestation, the retina is incompletely vascularized at birth. The lower the gestational age (GA) at birth, the less developed the neural retina and the larger the area of peripheral avascularity [2].

Stages of the disease

1. **Acute disease stages** (Stages 1–3): defined by the appearance of a structure at the vascular-avascular junction as Stage 1 (demarcation line), Stage 2 (ridge), and Stage 3 (extraretinal neovascular proliferation or flat neovascularization). If more than one stage of ROP is present in the same eye, the eye is classified according to the most severe stage.

   Aggressive ROP (A-ROP): the term aggressiveposterior ROP (APROP) was previously used to describe a severe, rapidly progressive form of ROP found in the posterior Zone I or Zone II. Because of the growing recognition that this can occur outside the posterior retina and in larger preterm infants, especially in resourcelimited regions of the world, the Committee recommends the new term A-ROP.

2. **Retinal detachment (Stages 4–5)**

   a. Stages of retinal detachment are defined as Stage 4 (partial: 4A with fovea attached, 4B with foveal detachment) and Stage 5 (total).

   b. Definition of Stage 5 subcategories: Stage 5A, in which the optic disc is visible by ophthalmoscopy (indicating openfunnel detachment); Stage 5B, in which the optic disc is not visible because of retrolental fibrovascular tissue or closedfunnel detachment; and Stage 5C, in which Stage 5B is accompanied by anterior segment changes (e.g., marked shallowing of the anterior chamber, iridocorneolenticular adhesions, corneal opacification), indicating a closedfunnel configuration [3].

Treatment

In the United States, the BEATROP study investigators demonstrated benefit in infants with zone I disease, but less so for zone II. The BEATROP study indicated a benefit of bevacizumab over laser in some ROP cases, particularly in infants with zone I disease. The multicenter, randomized, openlabel RAINBOW study found that ranibizumab may be superior to laser with fewer adverse structural ophthalmic outcomes. A third anti-VEGF antibody, aflibercept, showed an 85% success rate in a multicenter, randomized trial, with laser

treatment having similarly high success rates of 82% [4].

This study aimed to determine the most significant risk factors for the development of ROP and the treatment outcomes of bevacizumab versus ranibizumab, as reflected by the need for additional laser treatment.

Methods

A retrospective comparative study was conducted involving 30 children (60 eyes) with A-ROP who were treated at the Centre for Neonatology of the Institute for Child Diseases, Clinical Centre of Montenegro, between January 2022 and March 2024. The main inclusion criterion was the presence of aggressive ROP (A-ROP). Examination was performed after adequate patient preparation with instillation of tropicamide 0.5% and phenylephrine 2.5% three times at 15minute intervals, after achieving adequate mydriasis. The examination was performed using an indirect ophthalmoscope and a 20 D lens with a blepharostat and indentor. Fundus findings were documented using a RetCam3 (Natus) device. After the diagnosis was established, informed parental consent and approval for intravitreal injection in both eyes were obtained. Patients were divided into two groups according to the anti-VEGF agent administered (bevacizumab 0.625 mg [0.025 ml] and ranibizumab 0.2 mg [0.02 ml]). After the intervention, patients were examined on days 1, 7, 14, and 21, and then every two weeks for the following three months. Thereafter, repeat intravitreal drug administration or laser intervention was performed according to the clinical findings.

Results

Regarding gestational age, a statistically significant difference (*p* = 0.039) was found between the two groups. Birth weight was higher in the group that received intravitreal bevacizumab (IVB).

Analysis of birth weight and its influence on the development of A-ROP revealed a statistically significant difference in birth weight (*p* < 0.05), with the mean birth weight being lower in the group that received ranibizumab compared to the group that received bevacizumab.

The one-minute Apgar score was analyzed and showed no statistically significant difference (*p* = 0.66) between the two groups.

Table 1. Gestational age (weeks)

Drug	N	Mean	SD	Median	Min	Max
Bevacizumab	15	30.3	2.5	32	26	33
Ranibizumab	15	28.5	2.1	28	26	32

Table 2. Birth weight (grams)

Drug	N	Mean	SD	Median	Min	Max
Bevacizumab	15	1510.7	364.8	1530	860	2000
Ranibizumab	15	1205.3	392.6	1060	550	1880

Table 3. Need for laser photocoagulation

Drug	Laser	No laser	Total
Bevacizumab	6 (40%)	9 (60%)	15
Ranibizumab	15 (100%)	0 (0%)	15

Readministration of the drug was required in 3/15 patients (five eyes) treated with bevacizumab (20%), and in 4/15 patients (nine eyes) who received ranibizumab (26.7%). The need for laser photocoagulation was 40% in the IVB group versus 100% in the IVR group, a statistically highly significant difference (Fisher's exact test, *p* = 0.0007).

Discussion

This study analyzed the treatment outcomes of aggressive retinopathy of prematurity (A-ROP) with intravitreal bevacizumab and ranibizumab, with particular emphasis on neonatal factors and the need for additional therapeutic procedures. The results indicate certain differences between the groups that may have clinical significance.

Analysis of gestational age revealed a statistically significant difference (*p* = 0.039) between the groups, with infants treated with bevacizumab having a higher mean gestational age compared to the group treated with ranibizumab. It is well known that lower gestational age and lower birth weight are among the most important risk factors for the development of severe forms of retinopathy of prematurity, including A-ROP. Therefore, it can be assumed that the ranibizumabtreated group represented a more vulnerable population with a more severe initial clinical presentation and a higher risk of disease progression.

The oneminute Apgar score did not show a statistically significant difference between the groups, indicating that the immediate postnatal condition of the newborns probably did not significantly influence treatment outcomes.

Regarding treatment efficacy, the results showed that readministration of the drug was required in both groups, but somewhat more frequently in patients treated with ranibizumab (4/15, 26.7%) compared to those treated with bevacizumab (3/15, 20%). The higher number of eyes requiring repeat injection in the IVR group may be explained by the shorter intravitreal and systemic halflife of ranibizumab, potentially leading to earlier disease reactivation. These findings are consistent with literature data indicating that after ranibizumab administration, additional treatment or more careful longterm followup is more often required because of the possibility of disease relapse.

The most significant result of this study concerns the need for laser photocoagulation. In the bevacizumabtreated group, additional laser therapy was required in 40% of subjects, while all patients treated with ranibizumab required laser photocoagulation. This difference was statistically highly significant (Fisher's exact test, *p* = 0.0007), indicating greater longterm efficacy of bevacizumab in controlling A-ROP. A possible explanation for this finding is the longer duration of action of bevacizumab and stronger VEGF suppression, achieving more stable regression of neovascularization. On the other hand, although ranibizumab has the advantage of lower systemic exposure and potentially less impact on the development of other organs in premature infants, its shorter activity may account for the more frequent need for additional interventions.

Nevertheless, the results should be interpreted with certain study limitations. First, the number of subjects was relatively small, which may affect the statistical power of the study. Moreover, differences in gestational age and birth weight between the groups may represent confounding factors affecting therapeutic response. Additionally, masked patient allocation was not used. Future studies with larger sample sizes and randomized designs could provide more precise data on the comparative efficacy and safety of anti-VEGF therapy in the treatment of A-ROP.

Based on the results of this study, it can be concluded that both anti-VEGF agents demonstrated efficacy in treating A-ROP, but bevacizumab was associated with a lower need for additional laser photocoagulation and a smaller number of readministrations,

which may indicate a more stable therapeutic effect compared to ranibizumab.

Timely diagnosis and adequate therapy improve outcomes and reduce the risk of severe visual impairment.

Conclusion

Based on the findings of this study, it can be concluded that both anti-VEGF agents demonstrated clinical efficacy in the management of A-ROP. However, bevacizumab was associated with a significantly lower requirement for supplemental laser photocoagulation and a reduced rate of re-treatment, suggesting a more stable and sustained therapeutic effect compared to ranibizumab. Ultimately, timely screening, accurate diagnosis, and adequate therapeutic intervention facilitate a complete structural and functional resolution of the disease.

Funding source. The authors received no specific funding for this work.

Ethical approval. The Ethics Committee of the Clinical Center of Montenegro, Institute for Children's Diseases, Podgorica, Montenegro, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Neonatalni faktori rizika za razvoj teške forme prematurne retinopatije (A-ROP) i ishod liječenja anti-VEGF terapijom

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Uvod. Retinopatija prematuriteta (ROP) je neurovaskularna bolest koja ukoliko se ne liječi dovodi do teškog oštećenja vida i sljepila. Rana dijagnoza i pravoremena terapija smanjuju rizik za teški ishod. Najznačajniji faktori rizika za razvoj bolesti su niska gestaciona starost, niska porođajna tjelesna masa, razvoj respiratornog distresa i dugotrajna potreba za oksigenoterapijom, neonatalna sepsa, anemija i dr. U ovom radu analizirani su najznačajniji faktori rizika i ishod liječenja anti-VEGF terapijom, te dodatna potreba sa laserfotokoagulacijom.

Metode. Sprovedena je retrospektivna studija u kojoj je učestvovalo 30 djece (60 očiju) sa A-ROP formom retinopatije koja su podijeljena u dvije grupe u odnosu na anti-VEGF preparat koji je primijenjen (bevacizumab ili ranibizumab).

Rezultati. Kada je u pitanju gestaciona starost postoji statistički značajna razlika između dvije grupe. Porođajna tjelesna masa je veća u grupi koja je dobila intravitrealno bevacizumab (IVB). Reaplikacija lijeka je bila potrebna kod 3 pacijenata (5 očiju) liječenih bevacizumabom, te kod 4 pacijenata (9 očiju) koji su dobili ranibizumab (IVR). Potreba za laserfotokoagulacijom je bila 40% u grupi IVB, odnosno 100% u IVR što je statistički veoma značajna razlika.

Zaključak. Pravovremena dijagnoza i adekvatna terapija značajno poboljšavaju ishod i smanjuju rizik od teškog oštećenja vida. U ovom istraživanju je bevacizumab pokazao superiornost u odnosu na ranibizumab kada je u pitanju uticaj na reaktivaciju ROP i potrebu za dodatnom laserskom intervencijom.

Ključne riječi: ROP, retinopatija prematuriteta, anti-VEGF, bevacizumab, ranibizumab

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):9–19

UDK: 611.84:616-073
DOI: 10.59137/BII202601635B

Original article

Anthropometric characteristics of the orbit assessed by multislice computed tomography in individuals without orbital pathology

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Primljen – Received: 22/05/2026
Prihvaćen – Accepted: 29/05/2026

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Summary

Introduction. Knowledge of orbital anthropometry is essential for reconstructive surgery, ophthalmology and forensic identification, yet normative multislice computed tomography (MSCT) data for this region are scarce. The study aimed to determine the principal orbital parameters in adults without orbital pathology and to examine sex, age and side differences.

Method. In this retrospective study, 154 orbits in 77 adults (51 men, 26 women; aged 24–86 years) were measured on three-dimensional reconstructions from a 64-slice MSCT scanner. Orbital height, width, volume, orbital index and the interorbital and biorbital distances were recorded and compared by sex, age group and side.

Results. Men had significantly greater orbital width, volume and biorbital and interorbital distances than women bilaterally ($p \leq 0.009$), whereas orbital height did not differ by sex. The right orbital index was higher in women (90.02 ± 6.45 versus 86.36 ± 7.26; $p = 0.034$). In the older group the right orbit showed greater height, volume and orbital index ($p \leq 0.031$), with no significant age effect on the left. The right orbit was significantly wider and had a higher orbital index than the left ($p \leq 0.011$), while orbital volume was symmetrical ($p = 0.099$).

Conclusion. Orbital morphometry is sex-, age- and side-dependent, and the MSCT-derived values reported here provide population-specific reference data for clinical and forensic use.

Key words: orbit, anthropometry, multidetector computed tomography, sex characteristics, imaging, three-dimensional

Introduction

The orbit is a structurally demanding cavity of the human skull, shaped as a four-sided pyramid with its base opening anteriorly and its apex directed posteromedially towards the optic canal. It houses the globe, extraocular muscles, neurovascular structures and orbital fat [1]. Because the orbit lies at the intersection of the cranium, the paranasal sinuses and the midface, its dimensions are relevant to ophthalmology, maxillofacial and plastic surgery, neurosurgery, radiology and forensic anthropology.

The orbit is described quantitatively through a handful of standard measurements — orbital height, orbital width, orbital volume, and the interorbital and biorbital distances. Broca defined the orbital index as the ratio of orbital height to orbital width multiplied by one hundred, so that the shape of the orbital aperture could be expressed independently of its size. By convention, the index sorts orbits into three groups: microseme (below 83), mesoseme (83 to 89) and megaseme (above 89). These categories were tied originally to broad population groupings, and they are still used in anthropological and forensic practice [2]. What makes such data valuable is also what makes them difficult: the orbital index and the linear dimensions vary not only from one population to another, but within a single population they differ between the sexes and shift with age — which is exactly why normative values cannot simply be borrowed from elsewhere [3].

How these measurements are obtained has changed considerably. For most of the last century they came from dry skulls or from plain radiographs — the former restricted to skeletal collections, the latter distorted by superimposition and magnification. Multislice computed tomography (MSCT), coupled with three-dimensional reconstruction, has transformed the field. The bony orbit can now be measured in the living patient, non-invasively and to within a fraction of a millimeter, and volume rendering allows the cavity to be quantified reliably and reproducibly [4]. This is not merely a technical convenience. Accurate orbital dimensions guide the repair of the orbit after trauma, the correction of congenital deformity, and the management of conditions in which the volume of the orbit is itself disturbed — blow-out fractures and dysthyroid orbitopathy among them [5, 6].

Yet for all their clinical relevance, MSCT-based normative values are spread unevenly across populations, and for the Western Balkan region — specifically Serbia and neighboring countries — they are largely missing. We set out, therefore, to determine the main anthropometric parameters of the orbit — height, width, volume, orbital index, and the interorbital and biorbital distances — in adults free of orbital pathology, using multislice computed tomography, and to ask how these parameters differ between the sexes, between age groups, and between the two orbits of the same person.

Methods

This was a retrospective study of facial computed-tomography scans from 77 adults, amounting to 154 orbits. Both sexes were represented; ages ranged from 24 to 86 years, with a mean of 56, and no participant had pathological changes within the orbit. The material was gathered at the Clinical Centre in Kragujevac and comprised examinations performed between January 2010 and November 2015 in patients referred to facial-region scanning for various clinical reasons unrelated to this analysis. We excluded anyone who had undergone previous facial surgery, anyone with severe facial trauma, and those younger than 20 years. The institutional Ethics Committee approved the study.

Imaging used a 64-slice MSCT scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan). Participants lay supine, arms resting along the body, the head supported by a headrest. Acquisitions were made in the axial plane and then reformatted by multiplanar recon-

struction, with the scan range set on the lateral topogram according to the region of interest. The parameters were as follows: tube voltage 120 kVp, tube current 500 mAs, section thickness 0.5 mm, tube rotation time 0.75 s, and reconstruction thickness 0.4–0.6 mm. All datasets were analyzed on a Vitrea 2 workstation (version 4.1.14.0; Vital Images, Minnetonka, MN, USA). The orbital index, orbital volumetry and the biorbital and interorbital distances were measured on the same workstation and software, on three-dimensional reconstructions of the bony structures, and a single radiologist performed every measurement.

Measurements followed standard anatomical landmarks. Orbital width was the distance from the dacryon — where the frontal, lacrimal and maxillary bones meet to form the medial orbital margin — to a point on the lateral orbital margin. Orbital height was the maximum distance between the superior and inferior orbital margins, taken perpendicular to the width. The orbital index was orbital height divided by orbital width, multiplied by one hundred. The biorbital distance was measured between the right and left ectoconchion (the lateral orbital margin points), and the interorbital distance between the right and left dacryon. Linear measurements were given in millimeters and volumes in cubic centimeters. For every participant we compared the right and left orbit, and we tested for differences between the sexes and between age groups; for the latter, the sample was split into a younger group (24–55 years) and an older group (56–86 years).

Orbital volume was measured by delineating the bony orbital cavity on sequential axial slices. The anterior boundary was defined as a plane connecting the orbital rim, and the posterior boundary at the orbital apex, excluding the optic canal and the superior and inferior orbital fissures. The software then calculated the volume of the segmented region of interest in cubic centimeters.

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics included measures of central tendency and dispersion — arithmetic mean, standard deviation, and minimum and maximum values — for all continuous variables, and absolute and relative frequencies for categorical variables. Differences between groups for continuous variables were assessed with the Student t-test: the independent-samples t-test was used for comparisons by sex and by age group, and the paired-samples t-test for comparisons between the right and left orbit of the same participant. For each significant comparison, the effect size was reported as Cohen's d (for independent-samples tests) or Cohen's dz (for paired-samples tests), together with the 95% confidence interval for the mean difference. A p-value below 0.05 was considered statistically significant. The a priori power analysis indicated that 88 participants would be required to achieve a power of 0.90 at $\alpha = 0.05$ for detecting a medium effect size (Cohen's d = 0.5); with the 77 participants included, the achieved statistical power was approximately 0.83. Results are presented in tables and graphs.

Results

Table 1 summarizes the sample. Of the 77 participants, 51 (66.2%) were men and 26 (33.8%) women, with a mean age of 56.11 ± 17.13 years. Split by age, 32 (41.6%) fell into the younger group (24–55 years) and 45 (58.4%) into the older group (56–86 years).

Table 1. Sociodemographic characteristics of the participants (n = 77)

Characteristic	n (%) or mean ± SD
Sex - male	51 (66.2)
Sex - female	26 (33.8)
Age (years)	56.11 ± 17.13
Age group - 24–55 years	32 (41.6)
Age group - 56–86 years	45 (58.4)

SD - standard deviation

Sex differences were pronounced for the size-dependent parameters, and they are set out for both orbits in Table 2 and Figure 1. On the right side, orbital width was greater in men than in women (44.40 ± 2.21 mm versus 42.39 ± 2.34 mm; t(75) = 3.790, p = 0.001, Cohen's d = 0.89, 95% CI for the difference: 0.95 to 3.07 mm), and so was orbital volume (23.43 ± 3.71 cm³ versus 20.71 ± 2.37 cm³; t(75) = 3.387, p = 0.001, Cohen's d = 0.84, 95% CI for the difference: 1.12 to 4.32 cm³). Orbital height, by contrast, was essentially identical in the two sexes (38.31 ± 3.30 mm versus 38.16 ± 3.43 mm; p = 0.851). The orbital index ran the other way: it was higher in women than in men (90.02 ± 6.45 versus 86.36 ± 7.26; t(75) = −2.162, p = 0.034, Cohen's d = 0.53, 95% CI for the difference: 0.29 to 7.03), a reflection of the comparatively narrower female orbit (Table 2, Figure 1).

Table 2. Orbital height, width, volume and orbital index by sex for the right and left orbit

Parameter	Side	Male (mean ± SD)	Female (mean ± SD)	t(df)	p	Cohen's d	95% CI for difference
Height (mm)	Right	38.31 ± 3.30	38.16 ± 3.43	0.189 (75)	0.851	0.04	−1.43 to 1.73
Height (mm)	Left	38.43 ± 2.91	37.25 ± 2.88	1.689 (75)	0.095	0.41	−0.21 to 2.57
Width (mm)	Right	44.40 ± 2.21	42.39 ± 2.34	3.790 (75)	0.001	0.89	0.95 to 3.07
Width (mm)	Left	42.69 ± 2.04	40.39 ± 2.26	3.447 (75)	0.002	1.08	1.30 to 3.30
Volume (cm³)	Right	23.43 ± 3.71	20.71 ± 2.37	3.387 (75)	0.001	0.84	1.12 to 4.32
Volume (cm³)	Left	22.50 ± 3.29	19.88 ± 1.74	3.783 (75)	0.001	0.94	1.24 to 4.00
Orbital index	Right	86.36 ± 7.26	90.02 ± 6.45	−2.162 (75)	0.034	0.53	0.29 to 7.03
Orbital index	Left	90.19 ± 7.10	91.08 ± 6.11	−0.545 (75)	0.587	0.13	−4.12 to 2.34

SD - standard deviation; t(df) - independent-samples Student t-test statistic with degrees of freedom; p - probability value; Cohen's d - standardized effect size; CI - confidence interval. Statistically significant differences (p < 0.05) are observed for width and volume bilaterally and for the right orbital index.

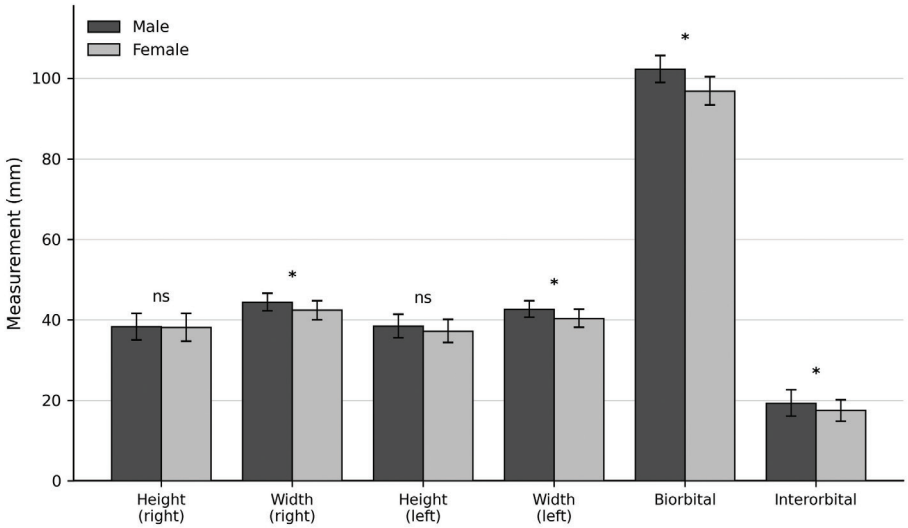


Figure 1. Orbital linear dimensions and the interorbital and biorbital distances in men and women (mean ± SD). Group comparisons by independent-samples Student t-test. Asterisks denote a statistically significant sex difference (p < 0.05); ns = not significant

The left orbit told much the same story. Width was again greater in men (42.69 ± 2.04 mm versus 40.39 ± 2.26 mm; t(75) = 3.447, p = 0.002, Cohen's d = 1.08, 95% CI for the difference: 1.30 to 3.30 mm), as was volume (22.50 ± 3.29 cm^3 versus 19.88 ± 1.74 cm^3; t(75) = 3.783, p = 0.001, Cohen's d = 0.94, 95% CI for the difference: 1.24 to 4.00 cm^3). On this side, however, neither orbital height (38.43 ± 2.91 mm versus 37.25 ± 2.88 mm; p = 0.095) nor the orbital index (90.19 ± 7.10 versus 91.08 ± 6.11; p = 0.587) differed significantly between men and women.

The interorbital and biorbital distances showed unambiguous sexual dimorphism. The biorbital distance was much greater in men (102.30 ± 3.36 mm versus 96.91 ± 3.51 mm; t(75) = 6.549, p = 0.001, Cohen's d = 1.58, 95% CI for the difference: 3.75 to 7.03 mm), and the interorbital distance followed suit (19.35 ± 3.33 mm versus 17.48 ± 2.66 mm; t(75) = 2.685, p = 0.009, Cohen's d = 0.60, 95% CI for the difference: 0.48 to 3.26 mm) (Table 3).

Age-related differences were almost entirely a right-sided phenomenon. The older participants had a greater right orbital height than the younger ones (39.27 ± 3.46 mm versus 36.85 ± 2.55 mm; t(75) = −3.357, p = 0.001, Cohen's d = 0.78, 95% CI for the difference: 0.98 to 3.86 mm), a greater right orbital volume (23.24 ± 4.08 cm^3 versus 21.48 ± 2.33 cm^3; t(75) = −2.194, p = 0.031, Cohen's d = 0.51, 95%

Table 3. Biorbital and interorbital distances by sex

Parameter	Male (mean ± SD)	Female (mean ± SD)	t(df)	p	Cohen's d	95% CI for difference
Biorbital distance (mm)	102.30 ± 3.36	96.91 ± 3.51	6.549 (75)	0.001	1.58	3.75 to 7.03
Interorbital distance (mm)	19.35 ± 3.33	17.48 ± 2.66	2.685 (75)	0.009	0.60	0.48 to 3.26

SD - standard deviation; t(df) - independent-samples Student t-test statistic with degrees of freedom; p - probability value; Cohen's d - standardized effect size; CI - confidence interval

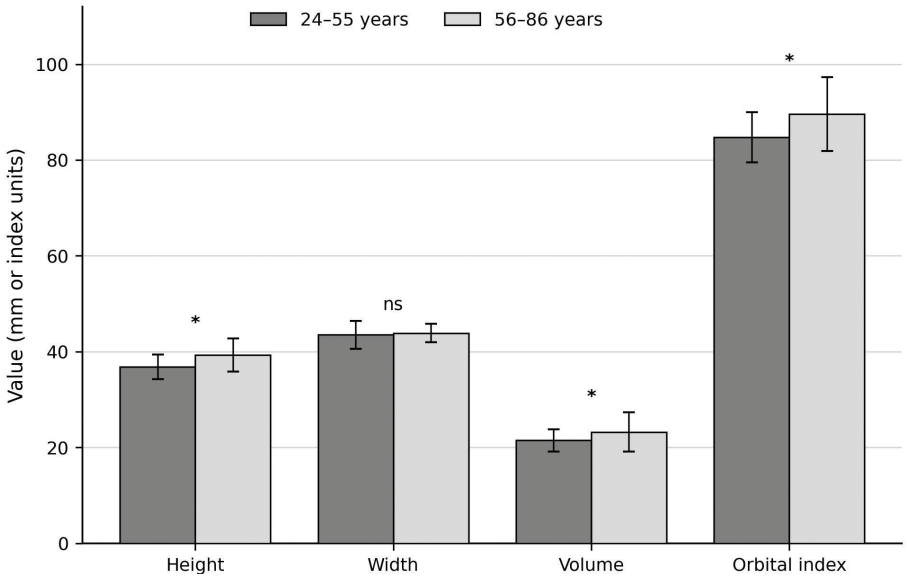


Figure 2. Right-orbit parameters in the younger (24–55 years) and older (56–86 years) age groups (mean ± SD). Group comparisons by independent-samples Student t-test. Asterisks denote a statistically significant difference (p < 0.05); ns = not significant

CI for the difference: 0.16 to 3.36 cm³), and a higher right orbital index (89.61 ± 7.72 versus 84.77 ± 5.22; t(75) = −3.072, p = 0.003, Cohen's d = 0.71, 95% CI for the difference: 1.70 to 7.98). Right orbital width was unaffected by age (p = 0.536). On the left, not one of the four parameters — height, width, volume or index — differed between the age groups (all p > 0.05) (Table 4 and Figure 2).

Age told on the biorbital distance as well: it was greater in the older group (101.56 ± 3.91 mm versus 98.96 ± 4.31 mm; t(75) = −2.750, p = 0.007, Cohen's d = 0.64, 95% CI for the difference: 0.72 to 4.48 mm). The interorbital distance, on the other hand, was unchanged across age groups (p = 0.162).

A final comparison set the two sides against each other, irrespective of sex or age, and a consistent right-sided predominance emerged in two parameters. The right orbit was wider than the left (43.72 ± 2.38 mm versus 42.09 ± 2.26 mm; t(76) = 4.338, p = 0.002, paired, Cohen's dz = 0.49, 95% CI for the mean difference: 0.88 to 2.38 mm), and its orbital index was lower (87.60 ± 7.17 versus 90.49 ± 6.76; t(76) = −2.575, p = 0.011, paired, Cohen's dz = 0.29, 95% CI for the mean difference: −5.11 to −0.67). Height (p = 0.652) and volume (p = 0.099) were statistically the same on both sides (Table 5 and Figure 3).

Table 4. Right-orbit parameters by age group

Parameter	24–55 years (n=32)	56–86 years (n=45)	t(df)	p	Cohen's d	95% CI for difference
Height (mm)	36.85 ± 2.55	39.27 ± 3.46	−3.357 (75)	0.001	0.78	0.98 to 3.86
Width (mm)	43.52 ± 2.92	43.86 ± 1.93	−0.621 (75)	0.536	0.14	−1.43 to 0.75
Volume (cm³)	21.48 ± 2.33	23.24 ± 4.08	−2.194 (75)	0.031	0.51	0.16 to 3.36
Orbital index	84.77 ± 5.22	89.61 ± 7.72	−3.072 (75)	0.003	0.71	1.70 to 7.98

Right orbit by age group. SD - standard deviation; t(df) - independent-samples Student t-test statistic with degrees of freedom; p - probability value; Cohen's d - standardized effect size; CI - confidence interval

Table 5. Side-to-side comparison of orbital parameters (all participants)

Parameter	Right orbit	Left orbit	t(df)	p	Cohen's dz	95% CI for mean difference
Height (mm)	38.26 ± 3.32	38.04 ± 2.94	0.452 (76)	0.652	0.05	−0.74 to 1.18
Width (mm)	43.72 ± 2.38	42.09 ± 2.26	4.338 (76)	0.002	0.49	0.88 to 2.38
Volume (cm³)	22.51 ± 3.55	21.61 ± 3.11	1.660 (76)	0.099	0.19	−0.17 to 1.97
Orbital index	87.60 ± 7.17	90.49 ± 6.76	−2.575 (76)	0.011	0.29	−5.11 to −0.67

SD - standard deviation; t(df) - paired-samples Student t-test statistic with degrees of freedom; p - probability value; Cohen's dz - standardized effect size for paired comparisons; CI - confidence interval. The right orbit is significantly wider than the left and has a significantly lower orbital index.

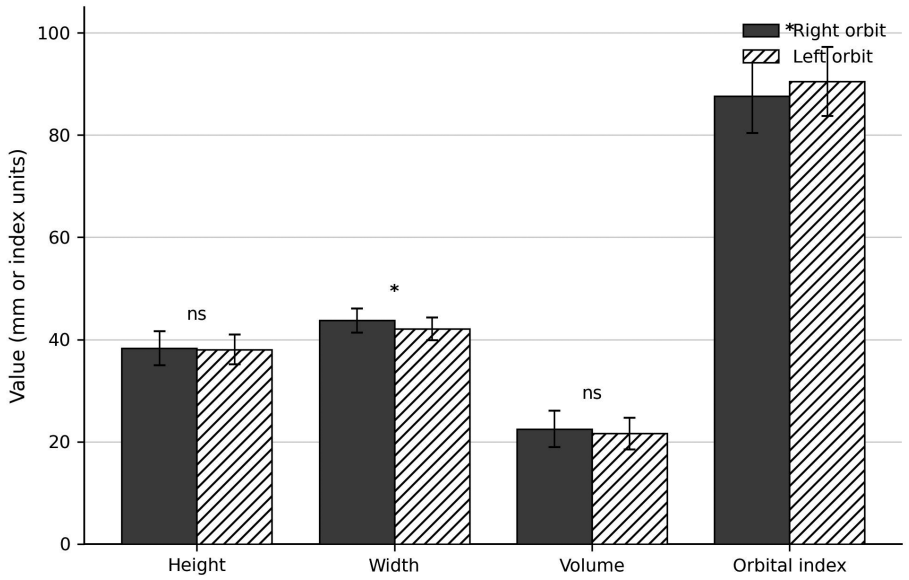


Figure 3. Comparison of the right and left orbit for height, width, volume and orbital index (mean ± SD). Side comparisons by paired-samples Student t-test. Asterisks denote a statistically significant side difference ($p < 0.05$); ns = not significant

Discussion

This study offers MSCT-based reference values for the bony orbit in adults without orbital disease, and three patterns stand out from it: a clear sexual dimorphism in the size-dependent dimensions, an age-related enlargement that is largely confined to the right orbit, and a right-sided predominance in width and orbital index. All three patterns are consistent with the international literature — and where they diverge from it, the divergence itself merits closer examination.

The most straightforward finding is that men have larger orbits than women. Width, volume, and both the biorbital and interorbital distances were greater in men on both sides; height alone showed no sex difference. This combination — strong dimorphism in most linear and volumetric measurements, but little or none in height — turns up repeatedly in CT-based work. A Saudi study using three-dimensional CT found every orbital measurement larger in men, yet the orbital index showed no dimorphism at all [3]. Orbital volume, in particular, tends to be greater in men: among healthy Koreans, orbital tissue volume was larger in men throughout adult life [7], and a recent three-dimensional Turkish study likewise reported a larger bony orbital volume in men in every age band [8]. The size of the volume difference we observed — somewhere around 2.5 cm^3 — is in line with these series, and it carries an obvious practical lesson: orbital implants and reconstruction targets ought to be chosen with the patient's sex in mind [9].

The orbital index calls for a more careful word. In our material it was higher in women than in men on the right side — the female orbit being relatively narrower while the heights were much the same — but on the left the difference vanished. Whether the index is sexually dimorphic at all is a question on which literature simply does not agree. In Ghanaians it was significantly higher in women, though both sexes still fell within the microseme range [2]; in the Saudi series and several others it did not separate the sexes despite obvious dimorphism in the underlying measurements [3].

This apparent discrepancy arises from the nature of a ratio: when height and width scales differ in the two sexes, the ratio can either preserve or cancel the underlying size difference. The index, then, is best read as a descriptor of orbital shape and population affinity — not as a reliable indicator of sex [10].

Our age analysis showed the orbit growing larger with age, but in a curiously one-sided way: on the right, height, volume and orbital index were all greater in the older group, whereas the left orbit showed no age effect whatsoever. That orbital volume increases with age, it is well established, and it is usually attributed to bony remodeling and resorption around the rim over time. Ugradar and Lambros, working from CT volumetry, found that the female orbit expanded with age while the male orbit barely changed [11]; the Turkish three-dimensional study came to a similar conclusion, the age effect on bony orbital volume reached significance only in women [8]. A larger Jordanian craniofacial series, too, picked out orbital height and orbital index among the parameters that shifted with age [12]. The fact that our age effect appeared on one side only was unusual, and we were inclined to read it cautiously — it may owe more to the uneven age distribution and the modest sample than to any genuine biological lateralization, and it would need a larger, age-balanced cohort to confirm.

It should be noted that sex and age effects were analyzed separately in this study using univariate tests. The possibility of a sex–age interaction — for instance, a more pronounced age-related orbital expansion in women than in men, as suggested by Ugradar and Lambros [11] — was not formally tested across all parameters owing to limited subgroup sizes. This remains an open question for future research with larger, sex-balanced samples.

Setting the two sides against each other, the right orbit proved wider but carried a lower orbital index than the left, while height and volume were no different. A degree of orbital asymmetry is normal in the human skull and has been reported many times over. One recent three-dimensional CT study found bony orbital volume symmetrical between the sides while height and width differed significantly — a pattern that mirrors our own, in which the volumes were statistically indistinguishable ($p = 0.099$) but the width was not [8]. Orbital and periorbital asymmetry has also been tied to wider craniofacial asymmetry in patients being assessed for orthognathic surgery [13]. The clinical point is a simple one: the opposite orbit, useful as it is as a template for reconstruction, is not a flawless mirror of the injured side, and small native asymmetries should be expected whenever the intact orbit is used to plan a repair.

These measurements are more than descriptive. Orbital volume is the parameter that matters most in managing orbital fractures: an increase in bony orbital volume after a blow-out fracture invites enophthalmos, and the aim of reconstruction is to bring the volume back as close to its original value as possible [5]. Intraoperative CT and three-dimensional volumetry are increasingly relied upon to confirm that this has been done [6], and the methods for measuring herniated orbital volume continue to be refined [5]. Population-specific normative values like ours, together with mean-shape orbital models built from CT data, supply the yardstick against which an individual orbit can be judged and against which implants can be designed [9]. The interorbital and biorbital distances, for their part, bear on the assessment of hypertelorism and hypotelorism and on craniofacial surgical planning [14].

The study has several limitations. First, it was retrospective and single-center, and with 77 participants the achieved statistical power was approximately 0.83, meaning that small effects may have gone undetected — which could partly explain some of the side-specific and age-specific findings. Second, the sexes were unevenly represented (66.2% male), which may have affected sex-specific esti-

mates and reduced the precision of subgroup analyses. Third, because participants were drawn from patients referred for clinical CT scanning, they did not constitute a strictly random sample of the general population, even though orbital pathology was excluded. Fourth, all measurements were performed by a single radiologist; while that ensured internal consistency, both intraobserver and interobserver reliability remained untested. Fifth, correction for multiple comparisons was not applied, and borderline significant results (e.g., right orbital index by sex, $p = 0.034$; right orbital volume by age, $p = 0.031$) should therefore be interpreted with caution. Finally, although a sex × age interaction was explored, the limited subgroup sizes did not permit a robust analysis of such interaction effects across all parameters. Future studies should recruit a larger, prospective sample balanced for age and sex, employ multiple independent observers with formal reliability testing, and assess potential sex-age interaction effects using multivariable models.

Conclusion

Multislice computed tomography with three-dimensional reconstruction measures the bony orbit reliably in the living patient, and here it has produced normative anthropometric data for a population that had none. In adults without orbital pathology, the male orbit was larger than the female orbit in width, in volume, and in the biorbital and interorbital distances, while height was much the same in both sexes; the orbital index, a descriptor of shape, was higher in women on the right side. Orbital dimensions tended to grow with age — in this sample, mostly on the right — and the right orbit was, on average, wider but had a lower orbital index than the left. Together these findings confirm that orbital morphometry depends on sex, age and side, and that population-specific reference values are worth having. The values reported here can serve as a baseline for diagnosing orbital disease and for planning reconstructive and decompressive surgery in this region. The documented physiological asymmetry between the right and left orbit (significant for width and orbital index) indicates that the contralateral orbit, while useful as a surgical template, is not a perfect mirror, and a degree of native asymmetry should be anticipated during preoperative planning. These findings also lay the groundwork for larger studies aimed at refining the classification of the orbit by sex and age and for the development of population-specific orbital models for implant design.

Funding source. The authors received no specific funding for this work.

Ethical approval. The Ethics Committee of the Clinical Centre in Kragujevac, Serbia, where the imaging data were collected, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Antropometrijske karakteristike orbite procijenjene multislajsnom kompjuterizovanom tomografijom kod ispitanika bez patoloških promjena u orbiti

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Uvod. Poznavanje antropometrije orbite je značajno za rekonstruktivnu hirurgiju, oftalmologiju i forenzičku identifikaciju, ali su normativni podaci dobijeni multislajsnom kompjuterizovanom tomografijom (MSCT) oskudni. Cilj rada je bio da se odrede osnovni parametri orbite kod odraslih ispitanika bez patoloških promjena u orbiti i ispitati razlike u odnosu na pol, starost i stranu.

Metod. U ovoj retrospektivnoj studiji izmjereno je 154 orbita kod 77 odraslih ispitanika (51 muškarac, 26 žena; starosti 24–86 godina) na trodimenzionalnim rekonstrukcijama dobijenim 64-slajsnim MSCT aparatom. Mjereni su visina, širina, volumen i orbitalni indeks orbite, kao i interorbitalni i biorbitalni razmak, te upoređivani prema polu, starosnoj grupi i strani.

Rezultati. Muškarci su imali statistički značajno veće vrijednosti širine, volumena te biorbitalnog i interorbitalnog razmaka u odnosu na žene, obostrano ($p \leq 0,009$), dok se visina orbite nije razlikovala prema polu. Orbitalni indeks desne orbite bio je veći kod žena ($90,02 \pm 6,45$ naspram $86,36 \pm 7,26$; $p = 0,034$). Kod starije grupe desna orbita je imala veću visinu, volumen i orbitalni indeks ($p \leq 0,031$), bez značajnog uticaja starosti na lijevoj strani. Desna orbita bila je značajno šira i imala viši orbitalni indeks od lijeve ($p \leq 0,011$), dok je volumen bio simetričan ($p = 0,099$).

Zaključak. Morfometrija orbite zavisi od pola, starosti i strane, a prikazane MSCT vrijednosti predstavljaju referentne podatke specifične za populaciju.

Ključne riječi: orbita, antropometrija, multidetektorska kompjuterizovana tomografija, polne karakteristike, trodimenzionalni prikaz

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):20–26

UDK: 617.735:616.379-008.64
DOI: 10.59137/BII202601642T

Original article

Chorioretinal microvascular changes in patients with type 1 diabetes mellitus in the absence of diabetic retinopathy - an OCTA study

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Summary

Introduction. Diabetic retinopathy (DR) is the leading cause of visual impairment in the working-age population. Microvascular changes in the retina occur before clinical signs of DR appear. Optical coherence tomography angiography (OCTA) enables non-invasive visualisation of retinal microvasculature. The aim is to investigate retinal microvascular changes using OCTA in patients with type 1 diabetes mellitus (T1DM) without clinical DR.

Methods. Cross-sectional study of 98 eyes from 49 subjects (29 T1DM patients, 20 healthy controls). All underwent comprehensive ophthalmic examination and OCTA (Cirrus 6000, 3×3 mm angiogram). Superficial capillary density (SCD, mm/mm^2), perfusion density (PD, %), foveal avascular zone area (FAZ, mm^2), central macular thickness (CMT) and macular volume were analysed. Demographic and clinical data were collected.

Results. T1DM patients had significantly higher perfusion density (PD full right: median 38.20% vs. 37.40%, p=0.029). No significant differences were found for other OCTA parameters. FAZ showed a borderline increase in patients with comorbidities (p=0.055). No correlation was observed between OCTA parameters and diabetes duration or HbA1c levels. A positive correlation was found between total daily insulin dose and central macular vascular density. OCTA successfully demonstrated changes in the foveal microvascular zone that are not visible on clinical examination, while all other OCT and OCTA parameters showed no statistically significant difference between groups.

Conclusion. OCTA can detect early microvascular changes in T1DM patients before clinical DR. Comorbidities and glycaemic control may influence OCTA parameters. Longitudinal studies are needed to assess predictive value for DR progression.

Key words: type 1 diabetes, macular microvascular changes, risk factors, OCTA

Primljen – Received: 27/05/2026
Prihvaćen – Accepted: 29/05/2026

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Introduction

Diabetic retinopathy is a leading cause of vision loss in working-age individuals. The development of microvascular lesions in diabetes begins with biochemical changes, leading to functional and then anatomical vascular alterations. Retinal microvascular changes occur before the appearance of clinical signs of DR. New technologies have provided better insight into the pathophysiology of DR. OCTA allows non-invasive visualisation of retinal microvasculature without the use of contrast agents [1, 2]. This study aims to investigate retinal microvascular changes using OCTA in patients with type 1 diabetes mellitus without clinical DR, taking into account disease duration, glycaemic control (HbA1c), comorbidities and treatment modality.

Methods

Study design and participants

This observational cross-sectional study included 98 eyes of 49 subjects, divided into two groups: T1DM patients (n=29) and healthy controls (n=20). T1DM patients were further subdivided according to disease duration, comorbidities, HbA1c levels, total daily insulin dose (TDD) and type of insulin therapy (insulin pump vs. basal insulin). The study was conducted at the Clinic for Eye Diseases and the Department of Endocrinology, University Clinical Center of the Republic of Srpska, from October 2024 to March 2025.

All participants underwent a comprehensive ophthalmic examination including fundus photography. OCTA imaging was performed using the Cirrus 6000 (Carl Zeiss Meditec) with a 3×3 mm angiogram. Superficial capillary density (SCD, mm/mm²), perfusion density (PD, %), foveal avascular zone area (FAZ, mm²), central macular thickness (CMT) and macular volume were calculated using automated software. Images with significant artefacts (motion, poor signal, projection artefacts) were excluded from further analysis.

Statistical analysis

Numerical variables showed significant deviation from normal distribution; data are presented as median (interquartile range) and minimum-maximum. Differences between groups were tested using the Mann-Whitney U test, and associations between categorical variables were analysed using the Chi-square test. A p-value ≤0.05 was considered statistically significant.

General participant characteristics

Table 1 summarises the demographic and clinical characteristics of the study population. There were no significant differences in sex distribution between T1DM patients and healthy controls (p=0.343). However, T1DM patients were significantly younger (median 26.0 years vs. 37.5 years, p<0.001) and age category distribution also differed significantly (p=0.013). Median diabetes duration was 15.0 years, with 58.6% of patients having diabetes for >10 years. The majority of T1DM patients used insulin pumps (51.7%) and had HbA1c >7% (58.6%). Comorbidities were present in 75.9% of T1DM patients, with hypertension, hyperlipoproteinemia, PCOS and pulmonary hypertension being the most frequent (37.9%).

OCTA parameters: DM patients vs. healthy controls

When comparing macular vascular parameters between T1DM patients and healthy controls, a statistically significant difference

Table 1. General participant characteristics

Parameter	DM patients (N=29)	Healthy controls (N=20)	Total (N=49)	p-value
Sex				0.343a
Male	11 (37.9%)	5 (25.0%)	16 (32.7%)	
Female	18 (62.1%)	15 (75.0%)	33 (67.3%)	
Age (years), median (IQR), min-max	26.00 (15.00), 19-56	37.50 (12.75), 28-53	31.00 (16.50), 19-56	<0.001b
Age categories				0.013a
19-29	18 (62.1%)	4 (20%)	22 (44.9%)	
30-39	7 (24.1%)	9 (45%)	16 (32.7%)	
40+	4 (13.8%)	7 (35%)	11 (22.4%)	
Diabetes duration (years), median (IQR), min-max	15.00 (9.00), 2-29	NA	NA	NA
Diabetes duration categories		NA	NA	NA
<10 years	12 (41.4%)	NA	NA	
>10 years	17 (58.6%)	NA	NA	
Type of insulin therapy		NA	NA	NA
Insulin pump	15 (51.7%)	NA	NA	
Basal insulin	14 (48.3%)	NA	NA	
Insulin pump duration (years), median (IQR), min-max	4.00 (6.00), 1-16	NA	NA	NA
HbA1c (%), median (IQR), min-max	7.30 (2.90), 6.40-13.10	NA	NA	NA
HbA1c categories		NA	NA	NA
<7%	12 (41.4%)	NA	NA	
>7%	17 (58.6%)	NA	NA	
Complications		NA	NA	NA
Yes	12 (41.4%)	NA	NA	
No	17 (58.6%)	NA	NA	
Type of complication		NA	NA	NA
Polyneuropathy	6 (50%)	NA	NA	
Nephropathy	5 (41.7%)	NA	NA	
Retinopathy	1 (8.3%)	NA	NA	
Comorbidities		NA	NA	NA
Yes	22 (75.9%)	NA	NA	
No	7 (24.1%)	NA	NA	
Comorbidities of interest (HT, HLP, PCOS, PH)	11 (37.9%)	NA	NA	NA
Other comorbidities	18 (62.1%)	NA	NA	
Additional therapy		NA	NA	NA
Yes	18 (62.1%)	NA	NA	
No	11 (37.9%)	NA	NA	

Numerical values are presented as median (interquartile range), minimum-maximum. NA - not applicable; a Chi-square test; b Mann-Whitney U test. HT - hypertension; HLP - hyperlipoproteinemia; PCOS - polycystic ovary syndrome; PH - pulmonary hypertension

was found for perfusion density (PD) full right (p=0.029). T1DM patients had higher values (median 38.20%) compared to controls (median 37.40%). This finding may indicate early adaptive or compensatory microvascular changes. No significant differences were observed for other OCTA parameters (SCD, FAZ, CMT, macular volume).

Correlation with diabetes duration

No statistically significant differences were observed in any retinal microvascular network parameter with respect to diabetes duration. The risk of diabetes-related microvascular and macrovascular complications increases with age and is particularly low before the age of 20 years [11].

Correlation with HbA1c levels

No correlation was found between retinal microvascular network parameters and HbA1c values. This lack of association may be explained by the fact that HbA1c reflects short- to medium-term glucose balance (days to months), whereas OCTA vascular changes represent years of anatomical remodelling.

Impact of comorbidities

Patients with comorbidities of interest (hypertension, coronary artery disease, obesity, hyperlipoproteinemia, etc.) showed a **borderline trend towards larger FAZ** compared to those without comorbidities (p=0.055). FAZ changes and capillary non-perfusion are more common in diabetic patients. Poorer glycaemic regulation tends to reduce parafoveal superficial vessel density [9].

Correlation with insulin dose

A positive correlation was found between total daily insulin dose (TDD) and central macular vascular density. This suggests that OCTA may be a more sensitive biomarker than conventional clinical examinations. High TDD serves as a surrogate for intensive treatment, which has long-term beneficial effects on vascular damage (average TDD: 66.3 units in patients with HbA1c >9% vs. 54.9 units in patients with HbA1c <9%) [6].

OCTA detection of subclinical foveal changes

OCTA successfully demonstrated changes in the foveal microvascular zone that are not visible on clinical examination, while all other OCT and OCTA parameters showed no statistically significant difference between groups [1,9].

Discussion

This study demonstrates that OCTA can detect early microvascular changes in type 1 diabetes patients without clinical signs of diabetic retinopathy. The significantly higher perfusion density in DM patients compared to controls is an intriguing finding. While most previous studies report decreased vessel density in early diabetes, our result may reflect a compensatory phase of microvascular adaptation, possibly due to autoregulatory dysfunction or early inflammation. Mechanistic explanations require longitudinal investigation.

The lack of correlation with diabetes duration and HbA1c levels is consistent with the concept that OCTA captures long-term structural remodelling rather than short-term metabolic fluctuations. Our observation of larger FAZ in patients with comorbidities (borderline significance) aligns with previous reports

that systemic vascular risk factors exacerbate retinal ischaemia.

The positive correlation between total daily insulin dose and central macular vessel density is noteworthy. Intensive insulin therapy is known to reduce long-term complications [6, 8] and may preserve microvascular integrity. However, residual confounding (e.g., better overall diabetes management in pump users) cannot be excluded.

A major limitation of this cross-sectional study is the lack of standardisation among OCTA devices, imaging protocols, analysis techniques and nomenclature, making comparisons with other studies difficult [5]. Future multicentre research should adopt standardised OCTA protocols to confirm the clinical utility of OCTA in detecting early diabetic microvascular changes.

Conclusion

OCTA can detect early retinal microvascular changes in patients with type 1 diabetes before the onset of clinical signs of diabetic retinopathy. Associated comorbidities and poorer glycaemic control may be linked to specific changes in OCTA parameters. Longitudinal studies are needed to determine whether these findings have predictive value for the development and progression of diabetic retinopathy. OCTA parameters cannot be used alone for diagnosis but may aid in risk stratification.

Funding source. The authors received no specific funding for this work

Ethical approval. The Ethics Committee of the Clinical Centre of Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Mikrovaskularne promjene horioretine kod pacijenata oboljelih od dijabetesa tipa 1 u odsustvu dijabetičke retinopatije - OCTA studija

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Uvod. Dijabetička retinopatija (DR) predstavlja vodeći uzrok oštećenja vida u populaciji radno sposobnog uzrasta. Mikrovaskularne promene na retini nastaju prije pojave kliničkih znakova DR. Optička koherentna tomografska angiografija (OCTA) omogućava neinvazivnu vizualizaciju retinalne mikrovaskulature. Cilj rada bio je ispitivanje mikrovaskularnih promjena retine primjenom OCTA kod pacijenata sa dijabetes melitusom tip 1 (T1DM) bez klinički manifestne DR.

Metode. Studija presjeka obuhvatila je 98 očiju kod 49 ispitanika (29 pacijenata sa T1DM i 20 zdravih kontrola). Kod svih ispitanika urađen je kompletan oftalmološki pregled i OCTA analiza (Cirrus 6000, angiogram 3×3 mm). Analizirani su površinska gustina kapilara (SCD, mm/mm^2), perfuziona gustina (PD, %), površina fovealne avaskularne zone (FAZ, mm^2), centralna debljina makule (CMT) i volumen makule. Prikupljeni su demografski i klinički podaci.

Rezultati. Pacijenti sa T1DM imali su statistički značajno veću perfuzionu gustinu (PD full right: medijana 38,20% naspram 37,40%, p = 0,029). Za ostale OCTA parametre nisu utvrđene statistički značajne razlike. Uočeno je granično povećanje FAZ kod pacijenata sa komorbiditetima (p = 0,055). Nije utvrđena korelacija između OCTA parametara i trajanja dijabetesa niti nivoa HbA1c. Utvrđena je pozitivna korelacija između ukupne dnevne doze insulina i centralne vaskularne gustine makule. OCTA je uspješno prikazala promjene u fovealnoj mikrovaskularnoj zoni koje nisu bile vidljive kliničkim pregledom, dok za ostale OCT i OCTA parametre nije nađena statistički značajna razlika između grupa.

Zaključak. OCTA može detektovati rane mikrovaskularne promjene kod pacijenata sa T1DM prije pojave klinički manifestne DR. Komorbiditeti i glikoregulacija mogu uticati na OCTA parametre. Potrebne su longitudinalne studije radi procjene prediktivne vrijednosti OCTA nalaza za progresiju DR.

Ključne riječi: dijabetes melitus tip 1, mikrovaskularne promjene makule, faktori rizika, OCTA

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):27–32

UDK: 617.72:616-006.8
DOI: 10.59137/BII202601638B

Case series

Clinical characteristics of uveal melanoma: a case series from a secondary level hospital

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Summary

Introduction. Uveal melanoma is the most common primary malignant intraocular tumor in adults, characterized by a high risk of haematogenous metastasis, particularly to the liver. The clinical presentation varies considerably, from asymptomatic lesions discovered incidentally to severe visual impairment. Early diagnosis and multidisciplinary management are essential to optimize functional and oncological outcomes. This study presents the clinical characteristics and diagnostictherapeutic management of patients with uveal melanoma treated at a secondarycare hospital.

Case series. Three patients with different clinical presentations of uveal melanoma were evaluated. A 53-year-old man presented for routine presbyopic correction without any visual complaints. Fundus examination revealed serous retinal detachment associated with a pigmented choroidal lesion. B-scan ultrasound confirmed an intraocular tumor, and enucleation was performed after multidisciplinary assessment. Histopathology confirmed choroidal melanoma. A 63-year-old woman presented with floaters in the left eye. Ophthalmic examination identified a pigmented superotemporal choroidal lesion; subsequent diagnostic workup confirmed melanoma. She underwent brachytherapy and maintained good visual acuity without metastases during followup. A 58-year-old man with progressive visual decline had been previously treated for chronic uveitis and cataract. Initial B-scan findings were inconclusive; however, intraoperative suspicion of a ciliary body melanoma during cataract surgery prompted ultrasound biomicroscopy, which confirmed the tumor. Iridocyclectomy was subsequently performed, with a postoperative uncorrected visual acuity of 0.6.

Conclusion. Uveal melanoma can present with diverse and subtle clinical manifestations, underscoring the importance of a detailed fundus examination even in asymptomatic patients. Diagnostic challenges are particularly evident in ciliary body melanoma, where standard ultrasonography may be inconclusive.

Key words: uveal melanoma, choroidal neoplasms, ciliary body, ultrasonography, optical coherence tomography

Primljen – Received: 26/05/2026
Prihvaćen – Accepted: 29/05/2026

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Introduction

Uveal melanoma is the most common primary malignant intraocular tumor in adults, arising from melanocytes located in the uveal tract of the eye, which comprises the iris, ciliary body and choroid [1, 3]. It is most often localized in the choroid, while melanomas of the ciliary body and iris are rarer [2]. Although the incidence of uveal melanoma is significantly lower than that of cutaneous melanoma, its clinical importance derives from its high potential for haematogenous metastasis, particularly to the liver [5, 12, 14].

The clinical presentation of uveal melanoma depends on tumor size and location. Smaller tumors often remain asymptomatic and are discovered incidentally during routine fundus examination, whereas advanced lesions may cause decreased visual acuity, photopsia, metamorphopsia, floaters or visual field defects [2, 4]. Ciliary body melanomas present a particular diagnostic challenge because of their hidden anatomical location and often late detection [10, 18].

Diagnosis is based on a detailed ophthalmic examination together with additional diagnostic methods such as ocular ultrasonography (B-scan), optical coherence tomography (OCT), fluorescein angiography and ultrasound biomicroscopy (UBM) [4, 10]. The therapeutic approach depends on tumor size and location, as well as on the patient's general condition, and includes brachytherapy, local tumor resection and enucleation [6, 7, 11].

Given the limited number of case reports from secondarylevel healthcare institutions, this paper aims to present the different clinical presentations of uveal melanoma, diagnostic challenges and therapeutic options through a series of cases from everyday clinical practice.

Case Reports

Case 1

A 53-year-old patient presented for a routine ophthalmological examination for reading vision correction. He denied any subjective symptoms, including visual decline, photopsia or floaters. Fundus examination of the right eye revealed serous retinal detachment in the superior nasal quadrant, associated with a protruding pigmented lesion highly suspicious for choroidal melanoma.

Ocular ultrasonography (B-scan) confirmed the presence of an intraocular tumor measuring 8 mm × 5 mm, characteristic of uveal melanoma. After multidisciplinary board assessment, the decision was made to perform enucleation of the affected eye. Histopathological analysis confirmed the diagnosis of choroidal melanoma. The patient is followed up every six months, with no signs of disease progression to the liver.

Case 2

A 63-year-old female patient presented because of floaters in the left eye. Fundus examination revealed a pigmented protruding lesion localized in the superior temporal quadrant, approximately two optic disc diameters in size.

Further diagnostic workup, including ocular ultrasonography, confirmed the diagnosis of a protruding choroidal melanoma measuring 4 mm × 3 mm. After multidisciplinary board assessment, the patient was referred to brachytherapy. During subsequent follow-up, good visual acuity was preserved, with no signs of local disease progression and no distant metastases verified by abdominal ultrasonography.

Case 3

A 58-year-old patient presented because of a gradual decline in visual acuity in the right eye over a prolonged period. During previous treatment, he had been managed under the diagnoses of chronic uveitis and cataract. Ocular ultrasonography (B-scan) showed no pathological changes.

During cataract surgery, while placing the retractor, an intraoperative lesion highly suspicious of ciliary body melanoma was observed. The surgical procedure was completed, and postoperatively an uncorrected visual acuity of 1.0 was achieved. After surgery, ultrasound biomicroscopy (UBM) clearly demonstrated a ciliary body tumor measuring 4.10 mm × 5.5 mm, following which iridocyclectomy was performed. In the postoperative course, the patient achieved an uncorrected visual acuity of 0.6. He was regularly followed up every six months, with no signs of disease progression in other organs and normal laboratory values.

Discussion

Uveal melanoma is a rare but clinically significant malignancy because of its aggressiveness and pronounced potential for haematogenous metastasis, particularly to the liver [3, 5]. Despite advances in diagnostic and therapeutic methods, overall survival of patients with metastatic disease remains limited, making early tumor detection of crucial importance [5, 8, 12, 14]. The presented cases illustrate the considerable heterogeneity of clinical presentation of uveal melanoma and confirm that the disease may be detected in both completely asymptomatic patients and those with nonspecific ophthalmic complaints.

In the first patient, choroidal melanoma was discovered incidentally during a routine examination. Such findings are not uncommon, given that smaller or peripherally located tumors may remain clinically silent for a long time [2, 4]. The presence of serous retinal detachment represented an important clinical sign that further increased suspicion of malignancy. In this case, enucleation was the optimal therapeutic choice because of tumor size and characteristics. Although current trends favor eyepreserving treatment whenever possible, enucleation still has an important place in the management of advanced intraocular melanomas [6, 11].

The second case presents a patient with relatively mild symptoms (floaters), in whom timely diagnosis allowed more conservative treatment with brachytherapy. Brachytherapy today is a standard treatment option for mediumsized choroidal melanomas, offering good local disease control and the possibility of preserving functional vision [7, 11]. The absence of metastases during followup in this patient underscores the importance of early detection and an adequate therapeutic approach.

The third case is particularly significant because of the diagnostic challenges posed by ciliary body melanomas. These tumors often remain unrecognized because of their anatomical location and can mimic other chronic ophthalmic conditions, including uveitis or complicated cataract [10, 18]. In the presented patient, standard B-scan examination did not indicate the presence of a tumor, whereas a definitive suspicion was raised only intraoperatively. Subsequent ultrasound biomicroscopy (UBM) enabled precise visualization of the ciliary body lesion. This case confirms the importance of UBM diagnostics when anterior segment tumors are suspected, especially when standard methods do not provide sufficient information [10].

B-scan ultrasonography is the basic diagnostic modality for assessing intraocular tumors because of its availability and high sensitivity for detecting protruding lesions [4]. However, for tumors located in the ciliary body or peripheral parts of the uvea, UBM can provide significant additional diagnostic value

[10]. The combination of clinical examination and modern imaging methods enables timely diagnosis and adequate treatment planning [4, 10, 16].

The therapeutic approach to uveal melanoma depends on tumor size and location, as well as on preservation of visual function and the patient's general condition [6]. In recent decades, treatment options that allow eye preservation, including brachytherapy and local surgical procedures, have developed considerably. Nevertheless, enucleation remains an indispensable treatment modality for large tumors, secondary glaucoma, pronounced pain or when eye preservation is not possible [4, 6, 11].

This case series highlights the importance of a detailed ophthalmological examination in everyday clinical practice, even in secondarylevel healthcare institutions. Timely recognition of suspicious lesions and a multidisciplinary approach enable appropriate treatment selection and better functional and oncological outcomes for patients.

Conclusion

Uveal melanoma can have a very diverse clinical presentation and is often asymptomatic. A detailed ophthalmological examination and a high degree of clinical suspicion are crucial for timely diagnosis. Ciliary body melanomas represent a particular diagnostic challenge, for which standard diagnostic methods may be insufficient. Timely diagnostics, appropriate use of additional imaging methods and a multidisciplinary approach enable optimal treatment selection and better functional and oncological outcomes for patients [6, 18–20].

Funding source. The authors received no specific funding for this work.

Ethical approval. This article does not contain any studies with human participants performed by any of the authors.

Conflicts of interest. The authors declare no conflict of interest.

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Kliničke karakteristike melanoma uvee: serija slučajeva iz bolnice sekundarnog nivoa

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Uvod. Uvealni melanom je najčešći primarni maligni intraokularni tumor kod odraslih, karakterisan visokim rizikom od hematogenih metastaza, posebno u jetru. Klinička slika se značajno razlikuje, od asimptomatskih lezija otkrivenih slučajno do teškog oštećenja vida. Rana dijagnoza i multidisciplinarno liječenje su neophodni za optimizaciju funkcionalnih i onkoloških ishoda. Ova studija predstavlja kliničke karakteristike i dijagnostičko-terapeutsko liječenje pacijenata sa uvealnim melanomom liječenih u bolnici sekundarne zdravstvene zaštite.

Prikaz bolesnika. Procijenjena su tri pacijenta sa različitim kliničkim slikama uvealnog melanoma. Muškarac star 53 godine javio se na rutinsku korekciju presbiopije bez vizuelnih tegoba. Pregled fundusa otkrio je serozno odvajanje mrežnjače povezano sa pigmentiranom horoidalnom lezijom. B-sken ultrazvuk potvrdio je intraokularni tumor, a enukleacija je izvršena nakon multidisciplinarne procjene. Histopatologija je potvrdila horoidalni melanom. Žena stara 63 godine javila se zbog „mušica" u lijevom oku. Oftalmološkim pregledom identifikovana je pigmentirana superotemporalna horoidalna lezija, a naknadna dijagnostička obrada potvrdila je melanom. Podvrgnuta je brahiterapiji, održavajući dobru oštrinu vida bez metastaza tokom praćenja. Pedesetosmogodišnji muškarac sa progresivnim opadanjem vida prethodno je liječen od hroničnog uveitisa i katarakte. Početni nalazi B-skeniranja bili su neubjedljivi; međutim, intraoperativna sumnja na melanom cilijarnog tijela tokom operacije katarakte podstakla je ultrazvučnu biomikroskopiju, koja je potvrdila tumor. Naknadno je izvršena iridociklektomija, sa postoperativnom oštrinom vida od 0,6 bez korekcije.

Zaključak. Uvealni melanom može se javiti sa različitim i suptilnim kliničkim manifestacijama, što naglašava važnost detaljnog pregleda fundusa čak i kod asimptomatskih pacijenata. Dijagnostički izazovi su posebno očigledni kod melanoma cilijarnog tijela, gdje standardna ultrasonografija može biti neubjedljiva.

Ključne riječi: melanom uvee, neoplazme horioidee, cilijarno tijelo, ultrasonografija, optička koherentna tomografija

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):33–41

UDK: 617.7:616-073
DOI: 10.59137/BII202601639R

Review

Modern concept of orbital radiological imaging

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Primljen – Received: 25/05/2026
Prihvaćen – Accepted: 28/05/2026

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Summary

Radiological imaging modalities, particularly computed tomography (CT) and magnetic resonance imaging (MRI), play a pivotal role in the diagnosis of orbital diseases. CT remains the gold standard for the evaluation of orbital trauma, including fractures, calcifications, and metallic foreign bodies, whereas MRI is superior for assessing soft tissues and the optic nerve. Characteristic radiological signs include the "I'M SLOW" pattern in Graves' ophthalmopathy, the "tram-track" sign in optic nerve sheath meningioma, the "teardrop" sign in blowout fractures, and the "empty delta" sign in cavernous sinus thrombosis. An apparent diffusion coefficient (ADC) threshold value of 0.84×10^{-3} mm^2/s has been shown to differentiate malignant from benign orbital lesions. The presence of a metallic intraocular foreign body represents an absolute contraindication to MRI examination. Artificial intelligence is increasingly contributing to orbital imaging through automated muscle segmentation, fracture detection, and prediction of tumor histology. Appropriate selection of imaging modality and recognition of these characteristic findings significantly improve diagnostic accuracy.

Key words: orbit, CT, MRI, diffusion-weighted MRI, ADC, Graves' ophthalmopathy, fractures, artificial intelligence

Introduction

The orbit is an anatomically complex region where the eyeball, optic nerve, extraocular muscles, blood vessels, secretory glands and fat tissue are located within a small bony space [1, 2]. Because of the dense packing and overlapping of these structures, clinical examination alone is often not sufficient to establish an etiological diagnosis [3]. Two modern radiological methods, computed tomography (CT) and magnetic resonance imaging (MRI), enable non-invasive visualization of

orbital structures with high resolution [4]. CT is based on X-rays and is characterized by a short scan time and particularly good visualization of bones, calcifications and foreign bodies [5]. MRI uses a strong magnetic field and radiofrequency pulses, does not expose the patient to ionizing radiation, and provides superior contrast of soft tissues, especially the optic nerve and extraocular muscles [6, 7]. The choice between these two methods depends on the clinical question, the urgency of the condition, the availability of equipment and the individual characteristics of the patient [8, 9]. This review aims to outline the main indications, strengths and limitations of CT and MRI in orbital imaging and to suggest a practical approach to modality selection [1, 4].

Orbital anatomy from the radiological perspective

The bony orbit has a pyramidal configuration. The orbital floor is the thinnest and most often affected in trauma, resulting in the so-called blow-out fracture [10]. The medial wall, also known as the lamina papyracea, is also extremely thin and susceptible to injury. The orbital apex is a narrow bony channel through which the optic nerve and ophthalmic artery pass; any expansive lesion in that region can quickly lead to nerve compression and vision loss [11]. Among the soft tissue structures, the most important for radiological interpretation are the optic nerve, which is surrounded by a myelin sheath and meningeal layers [12], the four rectus muscles and two oblique muscles that enable eye movements [13], the retrobulbar fat tissue [4], the lacrimal gland located in the superolateral quadrant, and the ophthalmic artery with its branches [14]. The optic nerve is divided into four segments: intraocular, intraorbital, intracanalicular and intracranial. The intraorbital segment is surrounded by cerebrospinal fluid within the optic nerve sheath, which can be visualized on T2-weighted MRI. The extraocular muscles have variable thickness and signal intensity; the medial rectus is often the thickest. The ophthalmic artery arises from the internal carotid artery and enters the orbit with the optic nerve. These anatomical relationships are crucial for interpreting radiological findings correctly.

Computed tomography of the orbit

CT is based on measuring the attenuation of X-rays after passing through tissues [5]. Modern multidetector CT allows submillimeter slice thickness and isotropic resolution [9]. Imaging of the entire orbit takes less than one second [10]. The protocol involves axial acquisition with multiplanar reconstructions [8]. The native phase shows bone, calcifications, foreign bodies and acute hemorrhage. The contrast phase using iodinated contrast is indicated when inflammation, tumor, abscess or vascular malformation is suspected [5]. For specific vascular indications, such as carotid-cavernous fistula, CT angiography is used [14]. The effective radiation dose for orbital CT is 1-3 mSv, and the dose to the lens of the eye is 10–30 mGy per examination [8]. In children and in patients requiring multiple follow-ups, the ALARA principle (as low as reasonably achievable) is applied [9].

CT is the method of choice in orbital trauma because it accurately demonstrates blow-out fractures and retrobulbar hematoma [10]. It is particularly valuable for the detection of metallic and glass foreign bodies [5]. It is also indicated for the evaluation of calcifications such as those in meningioma and retinoblastoma, for bone lesions, for orbital cellulitis and subperiosteal abscess, and for preoperative planning [3, 5, 9]. In patients with contraindications to MRI, CT is the only available option [8]. CT offers clear advantages in speed, bone detail, detection of calcifications and metallic

foreign bodies, and is widely available at relatively low cost [5, 8, 10]. On the other hand, it carries the burden of ionizing radiation (particularly to the lens), offers limited soft tissue contrast on non-contrast scans, and is susceptible to metal and dental artifacts [5, 8].

Beam hardening from dense bone or metal implants causes dark stripes, and partial volume effects may create false lesions at the apex of the orbit. A normal variant consisting of intraorbital fat herniation through a dehiscence of the lamina papyracea can simulate a mass. Partial volume artifact, though rare on thin sections, can mimic erosion of the optic canal. Dental amalgam produces streak artifacts that may mask the orbital apex. CT can give a false impression of optic nerve thickening in optic neuritis because of poor soft tissue contrast.

Magnetic resonance imaging of the orbit

Given CT's limitations in soft tissue contrast and radiation exposure, MRI provides a complementary approach. MRI uses a strong magnetic field of 1.5 or 3 Tesla and radiofrequency pulses. The signal emitted by excited hydrogen protons depends on proton density and on the T1 and T2 relaxation times, which gives different tissues a different appearance and enables outstanding contrast of soft tissues [6, 15]. The following sequences are used to image the orbit: T1-weighted imaging for anatomy and adipose tissue, T2-weighted imaging for edema, inflammation and fluid, STIR for fat signal suppression with emphasis on edema, T1 with fat saturation after gadolinium for inflammation and tumor detection, DWI and ADC to differentiate abscesses from cysts and cellular tumors [16, 17], and time-of-flight MRA for angiography without contrast [14]. The examination time usually ranges from 25 to 40 minutes [3].

MRI is usually the method of choice for optic nerve lesions, including optic neuritis, glioma and meningioma [12]. In thyroid ophthalmopathy, MRI not only demonstrates muscle thickening but also assesses inflammatory activity using STIR sequences [6, 1]. Clear indications include soft tissue tumors such as cavernoma, lymphoma and metastases [19, 5], inflammatory diseases such as idiopathic orbital inflammatory syndrome, Tolosa-Hunt syndrome and IgG4-related orbital disease [20–22], vascular malformations [14], congenital anomalies [1], and orbital apex syndrome [11]. In the pediatric population, MRI is preferred over CT because it uses no ionizing radiation [1].

Topographic differential diagnosis on MRI: Lesions are described in relation to the muscle cone. Intraconal lesions (within the muscle cone) include optic nerve disorders (glioma, meningioma, neuritis, sarcoidosis), vascular lesions (cavernoma, varicose veins, arteriovenous malformation), and inflammatory conditions (idiopathic orbital inflammatory syndrome). Extraconal lesions involve the lacrimal gland (dermoid, adenoma, carcinoma, sarcoidosis, IgG4 disease) or the adipose tissue (lipoma, liposarcoma, orbital pseudotumor). Conal lesions affect the extraocular muscles and are seen in Graves' ophthalmopathy (thickening of muscle bellies with spared tendons), as well as in myositis, lymphoma and metastases. At the orbital apex, one may encounter Tolosa-Hunt syndrome (granulomatous inflammation of the cavernous sinus and apex), apex meningioma, or perineural tumor spread such as from adenoid cystic carcinoma. This topographic classification helps narrow the differential diagnosis [1, 2, 5].

Specific MRI findings in orbital conditions: Sarcoidosis shows characteristic T2 hypointensity due to granulomas and often affects the optic nerve and lacrimal gland. Vascular malformations are divided into capillary, cavernous and arteriovenous types; MRA is useful, and digital subtraction angiography is indicated for arteriovenous malformations [14]. Optic glioma in neurofibromatosis type 1 requires treatment when there is progression on volumetry, involvement of the chiasm, or vision

loss. Optic neuritis in neuromyelitis optica typically presents with long lesions extending over more than half the length of the nerve, frequent involvement of the chiasm, and positive AQP4 antibodies.

Extended MRI sequences: Susceptibility-weighted imaging (SWI) is useful for the detection of bleeding, melanin and calcium, which is helpful in melanoma metastases and cavernomas. Magnetization transfer improves contrast in demyelinating diseases of the optic nerve such as multiple sclerosis and neuromyelitis optica. Constructive interference in steady state (CISS) allows visualization of the intracanalicular optic nerve and the cerebrospinal fluid space with near myelographic resolution. Diffusion tensor imaging (DTI) and tractography allow visualization of the optic pathway and assessment of axonal damage, particularly in post-traumatic optic neuropathy when conventional MRI is normal. Perfusion techniques help to distinguish tumors from inflammatory changes and from radiation necrosis [16, 17].

Artifacts on MRI: Susceptibility artifacts from metal (titanium produces less artifact than steel) appear as dark holes on T2* or SWI sequences. Pulsation artifacts from the carotid artery or cerebrospinal fluid often appear in the direction of phase encoding. Normal contrast enhancement of the meibomian glands and iris can give false positive findings. The high signal of orbital fat on T1 and T2 may simulate a lipoma but is physiological. Pulsation artifact from the carotid artery can simulate a cavernous sinus lesion. MRI may miss small calcifications in retinoblastoma.

MRI is distinguished by the absence of ionizing radiation, superior soft tissue contrast, and the capacity to provide functional information using advanced sequences [6, 15–17]. The disadvantages are the long imaging duration, which makes the examination susceptible to motion artifacts, the presence of contraindications such as pacemakers, ICDs, cochlear implants, ferromagnetic clips and intraocular metallic foreign bodies, poor visualization of bones and calcifications, claustrophobia occurring in 2–5% of patients, higher cost and more limited availability [8, 9, 3].

Comparative analysis and economic perspective

When the two modalities are compared, CT uses X-rays and delivers 1–3 mSv of ionizing radiation, whereas MRI uses a magnetic field and no radiation. The scan duration for CT is less than one minute, while MRI takes 20–40 minutes. CT provides excellent spatial resolution (0.5 mm) and superior depiction of bone and calcifications, but only moderate soft tissue contrast. MRI has good spatial resolution (1–2 mm) and superior soft tissue contrast, but bone and calcifications are poorly seen. The optic nerve and extraocular muscles are moderately visible on CT but more clearly displayed on MRI. Metal foreign bodies are safely detected by CT but are contraindicated for MRI. CT is available 24 hours a day, 7 days a week, almost everywhere, while MRI availability is more limited. CT has lower cost, but repeat imaging is restricted by radiation; MRI is two to five times more expensive, but repeat imaging is possible.

From an economic and organizational perspective, orbital CT has lower cost, greater 24-hour availability, and a shorter imaging duration. Orbital MRI costs 2–5 times more than CT, has a longer imaging duration, but does not use ionizing radiation. Early CT in emergency situations such as trauma and cellulitis reduces unnecessary hospitalizations and speeds up the decision between conservative and surgical treatment.

Diagnostic algorithm

Building on the comparative strengths and weaknesses of CT and MRI, a clinically oriented algorithm can guide modality selection. The selection of the appropriate imaging modality

should follow a stepwise, clinically oriented approach. First, the urgency of the condition must be assessed. In an emergency such as blunt or penetrating trauma, native CT is indicated [10]. Sudden exophthalmos with pain requires CT angiography to rule out a carotid-cavernous fistula [14]. Orbital cellulitis with exophthalmos calls for native and contrast CT [3]. Sudden vision loss with ophthalmoplegia should start with CT, and if the CT scan is normal, MRI should be performed next [11, 12]. If the situation is not urgent, the next question is whether bone, calcification or a foreign body is suspected. If yes, native CT with contrast if needed is the appropriate choice [5]. If not, and soft tissue evaluation of the nerve, muscle, inflammation or tumor is required, then MRI with gadolinium, DWI, ADC and STIR is indicated [1, 12, 11, 16, 17]. For purely vascular questions, either CTA or MRA can be used depending on availability [14]. In the specific case of trauma with a normal CT but persistent symptoms, MRI should be performed.

In non-urgent clinical situations, the following guidance applies. Subacute vision loss is best investigated with contrast MRI [12]. Unilateral exophthalmos is initially studied by MRI, and CT can be added if a bone lesion is suspected [5]. Bilateral exophthalmos suggests thyroid ophthalmopathy, so MRI is the first choice [1, 12]. Diplopia without trauma should be evaluated first by MRI, and CT is reserved for suspected post-traumatic fracture [10]. Orbital tumors are assessed with MRI including DWI, and CT can be added if calcifications are sought [16, 19, 17, 5]. Orbital apex syndrome requires contrast MRI [11]. A child with leukocoria should first have ultrasound and CT to detect calcifications of retinoblastoma, followed by MRI [5]. Vascular malformations are well shown by MRA or CTA alone [14].

For orbital trauma with deformation, CT is the first choice because of its speed and bone visualization [10]. For acute vision loss with pain, CT angiography is used to exclude fistula or hematoma [14]. For subacute vision loss, MRI with gadolinium is preferred to evaluate the optic nerve, inflammation or tumor [12]. For exophthalmos in a child, MRI is chosen because there is no radiation and it provides excellent soft tissue detail; CT is used only if retinoblastoma is suspected [5]. For diplopia without trauma, MRI is the first choice to examine the muscles, nerves and apex, and CT is reserved for fractures only [10].

Special populations and postoperative evaluation

Beyond the general diagnostic algorithm, certain patient groups and postoperative situations require additional considerations. Children: MRI should be used whenever possible [1]. CT should be used only when clinically necessary, such as for suspected retinoblastoma to detect calcifications, for orbital trauma, or for suspected metallic foreign body. MRI is the first choice for exophthalmos, optic glioma in neurofibromatosis type 1, inflammatory diseases and congenital anomalies. Children often require short sedation with propofol or sevoflurane, or anesthesia, for MRI, whereas CT can often be performed without sedation using immobilization and a short imaging duration. CT protocols in children adhere to the ALARA principle with parameters adapted to age and weight. The differential diagnosis of leukocoria includes retinoblastoma (calcifications on CT), Coats disease (no calcifications, exudates), persistent hyperplastic primary vitreous (microphthalmos, hyaloid artery), and toxocariasis (granuloma with inflammatory changes).

Pregnancy: MRI may be performed in the second and third trimesters at 1.5 Tesla without gadolinium when clinically indicated, while CT should be avoided unless absolutely necessary (e.g., life-threatening retrobulbar hematoma with nerve compression) [8].

Renal insufficiency: In severe renal failure, native CT is an option but iodinated contrast

carries a risk of nephropathy. Native MRI can be used but there is a risk of nephrogenic systemic fibrosis in severe kidney disease; an alternative is DWI, ADC and T2 STIR for lesion characterization [17].

Claustrophobia: Affecting 2-5% of patients, options include CT if diagnostically sufficient, open MRI (lower signal-to-noise ratio but often adequate for the orbit), or sedation with an anxiolytic such as midazolam combined with a closed MRI using a mirror and ventilation [3].

Cardiac devices: For a patient with a heart pacemaker or ICD, MRI may be contraindicated depending on device compatibility, so CT is the alternative [8].

Absolute contraindications for MRI include implanted pacemakers or ICDs that are not MRI-compatible, older types of cochlear implants, ferromagnetic clips of cerebral aneurysms, and intraocular metallic foreign bodies (especially in patients with history of metal work or welding). Relative contraindications include older stents (depending on metal type), artificial heart valves (mostly safe except the older Starr-Edwards model), tattoos with ferromagnetic pigments (rare), and pregnancy before 12 weeks (MRI avoided unless clinically necessary).

Postoperative and posttraumatic evaluation: Imaging after orbital decompression for Graves' ophthalmopathy assesses the extent of the bone defect and the position of the muscles. After enucleation or evisceration, the normal appearance of implants (porous polyethylene, ceramic, spherical implants) must be distinguished from pathological findings such as infection, migration or extrusion. In post-traumatic optic neuropathy, DTI and fractional anisotropy play a role in assessing axonal damage when conventional MRI is normal.

Advanced and new techniques

In addition to the standard clinical protocols discussed above, several advanced techniques have expanded diagnostic capabilities. Dual-energy CT (DECT) allows distinguishing calcium from iodine and reducing metal artifacts from orbital plates after fracture [9]. At 3 Tesla, the signal-to-noise ratio is increased, enabling thinner slices (up to 1 mm) and better visualization of small structures [15]. Radiomic analysis of MRI sequences represents a promising new method for the characterization of orbital lesions [23]. PET/CT and PET/MRI combine metabolic information from fluorodeoxyglucose with anatomical information and are useful for the detection of lymphoma, metastases and sarcoidosis [19]. Orbital ultrasound remains useful as a first-line tool for rapid differentiation of solid from cystic lesions and for evaluation of papilledema [4].

Newer technologies continue to evolve. Photon-counting CT offers spatial resolution up to 0.2 mm with a dose less than 50% of conventional CT, but it is still primarily a research technology. Ultra-high-field MRI at 7 Tesla allows visualization of the laminar structure of the optic nerve and of orbital microvessels without contrast using time-of-flight MRA. Radiomics and artificial intelligence are being used for automatic segmentation of extraocular muscles in Graves' ophthalmopathy, for prediction of response to corticosteroids based on muscle T2 signal, and for prediction of orbital tumor malignancy from T2 and post-contrast sequences [23].

Conclusion

CT and MRI should be regarded not as competing modalities, but as complementary imaging tools. Each modality has specific advantages and limitations, and their correct application requires good knowledge of the clinical context. CT continues to serve as the first-line modality in emergencies, for trauma, for visualization of bone structures and calcifications, for detection of metal and glass

foreign bodies, and for patients in whom MRI is contraindicated. Its main limitations are ionizing radiation (especially risky for the lens and in children) and poor soft tissue contrast. MRI is the preferred modality for evaluating the optic nerve, extraocular muscles, and inflammatory and neoplastic changes. It uses no radiation, which makes it safe for children and pregnant women in the second and third trimesters, as well as for long-term monitoring. Its limitations are the long imaging duration, sensitivity to motion artifacts, strict contraindications, poor visualization of bone and calcifications, and higher cost. Modern analytical techniques, such as radiomics and artificial intelligence, further increase the diagnostic value of MRI. In complex cases, including orbital tumor with suspected bone invasion, retinoblastoma, and orbital apex syndrome, combined use of CT and MRI is recommended. Advanced techniques such as dual-energy CT, DWI, ADC, SWI, magnetization transfer, CISS, radiomics, artificial intelligence, PET/CT and PET/MRI further expand diagnostic capabilities. When the appropriate modality is chosen, an accurate diagnosis is achieved, unnecessary biopsies and invasive procedures are avoided, and appropriate therapy is introduced in a timely manner, thereby contributing to vision preservation and improved patient outcomes.

Funding source. The authors received no specific funding for this work.

Ethical approval. This article does not contain any studies with human participants performed by any of the authors.

Conflicts of interest. The authors declare no conflict of interest.

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Moderni koncept orbitalnog radiološkog snimanja

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Radiološke metode (CT i MRI) često su ključne u dijagnostici orbitalnih bolesti. CT je zlatni standard za traumu (frakture, kalcifikacije, metalna strana tijela), dok je MRI superioran za meka tkiva i optički nerv. Patognomonični znaci uključuju *I'M SLOW* (Gravesova oftalmopatija), *tram track* (meningiom), *teardrop* (*blow out* fraktura) i *empty delta* (tromboza kavernoznog sinusa). Granična ADC vrijednost od 0,84 × 10^{-3} mm^2/s razlikuje maligne od benignih lezija. Metalno strano tijelo u oku je apsolutna kontraindikacija za MRI. Vještačka inteligencija sve više pomaže u segmentaciji mišića, detekciji fraktura i predviđanju histologije tumora. Pravilan odabir modaliteta i poznavanje ovih znakova poboljšavaju dijagnostiku.

Ključne riječi: orbita, CT, MRI, difuzijski MRI, ADC, Gravesova oftalmopatija, frakture, vještačka inteligencija

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):42–55

UDK: 617.735:616.379-008.64:575.113
DOI: 10.59137/BII202601634A

Review

The role of gene polymorphisms in diabetic retinopathy

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Primljen – Received: 22/05/2026
Prihvaćen – Accepted: 29/05/2026

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Summary

Diabetic retinopathy (DR) is the most frequent microvascular complication of diabetes mellitus (DM) and remains a leading cause of preventable blindness in the working-age population. Its course is notoriously variable: some patients with long-standing, poorly controlled diabetes never develop sight-threatening disease, whereas others progress rapidly despite reasonable metabolic control. This clinical heterogeneity, which the traditional risk factors cannot fully explain, has directed attention towards the inherited component of susceptibility. This review summarizes current understanding of the genetic architecture of DR, with particular emphasis on three extensively studied candidate genes: the vascular endothelial growth factor A gene (*VEGFA*), the angiotensin-converting enzyme gene (*ACE*) and the apolipoprotein E gene (*APOE*), specifically their most investigated polymorphisms: *VEGFA* rs699947, rs2010963 and rs3025039; *ACE* rs1799752 I/D; and *APOE* rs429358 and rs7412 (ε2/ε3/ε4). The evidence linking individual polymorphisms to disease is examined alongside the picture emerging from genome-wide association studies (GWAS), and the persistent inconsistency among studies is discussed in the context of ethnic differences, phenotype definition and limited statistical power. Finally, the review considers how genetic insight is beginning to inform therapy, from the established anti-VEGF paradigm to gene-based approaches now in clinical trials, and outlines the main obstacles that still separate genetic findings from routine clinical use.

Key words: genetic susceptibility, renin-angiotensin system, apolipoproteins E, VEGFA protein, microvascular complications

Introduction

Diabetes mellitus (DM) has become one of the defining public health problems of the present century, and its complications now account for a substantial share of the global burden of disability. Among these complications, diabetic retinopathy (DR) occupies a particular place, because

it threatens a faculty — sight —loss of whichis irreversible and profoundly disabling. DR is a chronic microvascular, neuroinflammatory and neurodegenerative disorder of the retina developing on the background of sustained hyperglycaemia, and it remains the principal cause of legal blindness in adults of working age throughout much of the world [1].

Recent estimates underline the scale of the problem. A systematic review and meta-analysis of 59 population-based studies placed the global prevalence of any retinopathy among people with diabetes at roughly 22%, with vision-threatening disease affecting about 6% [1]. Translated into absolute numbers, more than a hundred million adults were estimated to be living with retinopathy in 2020, and projections that track the rising tide of diabetes itself foresee that figure climbing towards 160 million by 2045 [1]. The burden is shifting, too — increasingly concentrated in low- and middle-income regions where access to screening and to modern intravitreal therapy is least secure [2].

For decades, clinical and epidemiological researches have sought to map the determinants of who develops retinopathy and who escapes it. The duration of diabetes, the quality of glycaemic control, blood pressure, dyslipidaemia, renal impairment and pregnancy allhave been firmly implicated [3]. Yet anyone who has followed a cohort of diabetic patients over time will recognize a stubborn residual: a proportion of individuals with long-standing, badly controlled disease never develops appreciable retinopathy, while others deteriorate quickly despite metabolic parameters that look almost reassuring. This discordance is not merely anecdotal. It points to a component of susceptibility that the conventional risk factors do not capture, and the most plausible candidate for that missing component is the patient's genetic constitution.

The heritable contribution to DR is supported by several lines of evidence. Familial aggregation studies have repeatedly shown that a person whose relative has retinopathy carries a higher risk than expected from shared environment alone, and concordance for retinopathy is markedly greater in monozygotic than in dizygotic twins, in both type 1 and T2D [4]. On the basis of such observations, the heritability of DR has been estimated at between a quarter and a half of the total phenotypic variance, depending on the population and the definition of disease used. These figures are high enough to justify the considerable effort that has been invested in identifying the specific genes and variants responsible.

This review aims to summarize the current state of knowledge on the genetic basis of DR, to examine in detail three of the most intensively studied candidate genes — VEGFA, ACE and APOE — together with the broader picture supplied by genome-wide approaches, and to consider how this genetic understanding is beginning to shape both therapy and the obstacles that still stand in the way of clinical application.

Gene selection for this review. As a narrative review, this work does not follow the systematic review methodology. The three genes discussed in detail — VEGFA, ACE and APOE — were selected based on the following criteria: (i) biological plausibility of the gene product in DR pathogenesis; (ii) volume of published literature (at least 10 case-control studies or multiple meta-analyses); (iii) evidence of functional relevance for the polymorphism; and (iv) availability of recent meta-analyses or large cohort studies. Other genes are mentioned briefly where they provide context, but detailed discussion is limited to these three.

DR: clinical and pathophysiological background

Clinically, DR is divided into a non-proliferative stage and a proliferative stage, with diabetic macular oedema able to arise at any point and constituting the commonest cause of central vision loss. Non-proliferative disease is

characterized by microaneurysms, intraretinal haemorrhages, cotton-wool spots and venous abnormalities, and is graded from mild to severe according to the extent of these changes. The transition to the proliferative stage is defined by retinal neovascularization — the growth of fragile new vessels that bleed readily and may lead to tractional retinal detachment and severe visual loss [2].

Underlying these visible changes is a complex and only partly understood pathophysiology. Chronic hyperglycaemia drives a cluster of interlinked biochemical disturbances: increased flux through the polyol pathway, accumulation of advanced glycation end-products, activation of protein kinase C and overactivity of the hexosamine pathway. These converge on a common downstream state of oxidative stress and low-grade inflammation that damages the cellular constituents of the retina — the endothelial cells and pericytes of the microvasculature, but also neurons and glia [5]. The result is a breakdown of the blood–retinal barrier, capillary non-perfusion and retinal ischaemia. Ischaemic retina, in turn, upregulates vascular endothelial growth factor (VEGF), the principal molecular driver of both the increased vascular permeability responsible for macular oedema and the neovascularization that defines proliferative disease [6–9].

It is precisely because so many of these pathways are governed by gene products — enzymes, growth factors, receptors, transporters — that inherited variation in the corresponding genes can plausibly modulate the speed and severity with which retinopathy develops. A polymorphism that alters the expression or activity of an enzyme in the polyol pathway, or that shifts the set-point of VEGF production, need not cause disease on its own; it can act as a tuning element, nudging an individual towards or away from the threshold at which retinal damage becomes manifest. This is the conceptual framework within which the genetics of DR is best understood, and it is summarized schematically in Figure 1.

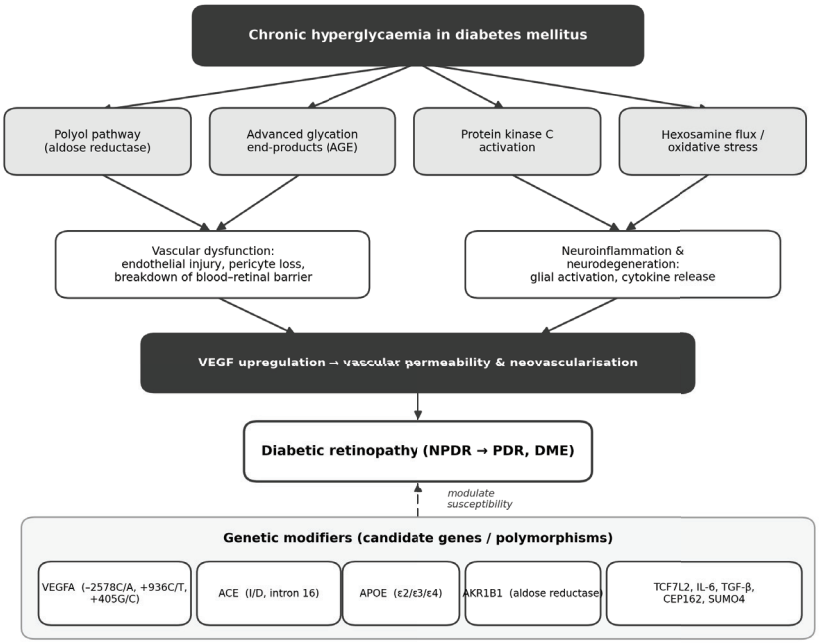


Figure 1. Schematic overview of the pathways through which chronic hyperglycaemia leads to diabetic retinopathy, and the candidate genes which polymorphisms are thought to modulate individual susceptibility. NPDR - non-proliferative diabetic retinopathy; PDR - proliferative diabetic retinopathy; DME - diabetic macular oedema; VEGF - vascular endothelial growth factor. Candidate genes discussed in this review are positioned according to the pathways they influence.

The genetic architecture of DR

Two broad strategies have been used to dissect the genetic basis of DR, and they rest on different assumptions. The candidate-gene approach starts from biological reasoning: a gene is selected because its product is known to participate in a pathway relevant to the disease, and variants within or around that gene are tested for association. The GWAS, by contrast, makes no prior assumption about which genes matter; it scans hundreds of thousands or millions of variants across the genome and lets the data identify the regions associated with disease [7].

The candidate-gene literature on DR is now very large, and a comprehensive narrative review has catalogued the chromosomes and individual genes implicated, organizing them around the metabolic pathways through which they are thought to act [5, 10–12]. Genes encoding components of the renin–angiotensin system, mediators of angiogenesis, enzymes of glucose metabolism, inflammatory cytokines and regulators of the extracellular matrix all appear in this catalogue. The difficulty is that, for almost every candidate, the published associations are inconsistent: a variant reported as a risk factor in one population fails to replicate in another or even shows an association in the opposite direction [13–15].

An umbrella review that pooled 32 meta-analyses covering 52 candidate SNP offers a useful corrective to over-interpretation of any single study [8]. When the evidence was graded by strength, only the transcription factor 7-like 2 (TCF7L2) C/T variant rs7903146 was supported by what the authors classed as convincing evidence, whereas the much-studied associations involving interleukin-6 and VEGF polymorphisms rested on weak evidence [8]. This sobering result illustrates a general truth about the field: many reported associations are real but small, and many others are artefacts of small samples, population stratification or selective reporting.

So far, genome-wide studies have been less transformative for DR than for many other complex traits. Nevertheless, cross-disease genome-wide meta-analysis in large biobank populations has begun to reveal that retinopathy shares genetic architecture with other ocular disorders, and that several implicated loci lie in genes governing neuronal differentiation and eye development — reinforcing the modern view of retinopathy as a neurovascular rather than a purely vascular disease, and signaling that the methodological groundwork for larger, better-powered studies is now being laid [7, 16–20].

Beyond classical candidate-gene studies, the field is gradually moving towards genome-wide and polygenic models. Genome-wide association studies offer the advantage of avoiding prior biological assumptions and can identify loci that would not have been selected through conventional pathway-based reasoning. However, compared with other complex diseases, GWAS of DR have been constrained by modest sample sizes, heterogeneous phenotyping and the difficulty of separating genetic susceptibility to diabetes itself from susceptibility to its retinal complications. Consequently, few loci have shown consistent replication across populations, and the effect sizes of individual variants remain small [21, 22].

An important implication is that DR is unlikely to be explained by single high-impact polymorphisms. Rather, susceptibility appears polygenic, with multiple common variants each contributing to a small increment of risk. Polygenic risk scores may therefore become more informative than isolated candidate variants, particularly if combined with established clinical predictors such as diabetes duration, HbA1c, blood pressure, renal function and lipid status [23, 24]. At present, such scores remain investigational and require validation in large, ethnically diverse cohorts before clinical application.

The next research frontier lies in integrating genomics with other omics layers. Transcriptomic studies may clarify which retinal or circulating genes are differentially expressed during early neurovascular injury, while proteomic and metabolomic profiling may identify molecular signatures preceding clinically visible retinopathy. Epigenomic data — including DNA methylation and microRNA expression — are particularly relevant because they may explain how long-term hyperglycaemia leaves a persistent molecular imprint, sometimes termed metabolic memory. Finally, integrating retinal imaging, OCT-derived biomarkers, artificial intelligence and molecular data may enable more precise classification of DR than clinical grading alone.

Key candidate genes

VEGFA - the angiogenic switch

If any single gene deserves to be considered first, it is VEGFA, the gene encoding vascular endothelial growth factor A. The reasoning is straightforward: VEGF is the central effector of the two processes that cause vision loss in DR — vascular hyperpermeability and neovascularization — and anti-VEGF therapy is now the mainstay of treatment for both diabetic macular oedema and proliferative disease [6]. The gene which product is so directly responsible for the disease phenotype is an obvious place to look for inherited variation influencing risk.

VEGFA lies on the short arm of chromosome 6, and it is markedly polymorphic, particularly in its promoter and untranslated regions where variants can plausibly affect the level of gene expression. The most extensively studied variants include the promoter polymorphism −2578C/A (rs699947), −634G/C (rs2010963, also designated +405G/C in some nomenclatures) and the 3′ untranslated region variant +936C/T (rs3025039). A systematic review and meta-analysis of 26 studies covering 10VEGFA polymorphisms found that the associations were both variant-specific and population-specific: rs2010963 was associated with retinopathy risk in Caucasian and overall populations, rs3025039 in Asians, and several other variants showed associations confined to particular ethnic groups or particular disease subtypes [10]. The authors concluded, reasonably, that VEGF polymorphisms contributed to susceptibility but that the effect of any individual variant was modest and context-dependent. Beyond individual SNP, specific VEGFA haplotypes combining these variants have been associated with altered promoter activity in functional studies, though their clinical utility remains unproven.

Subsequent meta-analyses focused on single variants have refined this picture. For the +936C/T polymorphism, pooled analysis of eight studies including over 1,500 patients with DR and type 2 DM found that the C allele and C-containing genotypes were associated with a reduced risk of retinopathy, an effect seen across allelic, dominant and recessive models [11]. For the −2578C/A promoter variant, a separate meta-analysis of 10 studies reported the opposite directionality, with the A allele associated with an increased risk of DR in type 2 DM under allelic and dominant models, though not under the recessive or homozygous models [12]. The contrast between these two variants is instructive: it shows that polymorphisms within the same gene can pull risk in opposite directions, presumably because they affect VEGF biology in different ways.

The umbrella review cited above, however, tempers enthusiasm by classing the VEGF associations as weak when judged against the most rigorous methodological standards [8]. The most honest summary is therefore that VEGFA variation genuinely modulates the risk of DR, but that the effect sizes are small, the directionality is variant-dependent, and replication across ethnic groups is imperfect. None of this diminishes the biological centrality of VEGF; it simply reflects the gap be-

tween a gene mattering mechanistically and a particular common variant being a reliable predictor of disease.

ACE - the renin–angiotensin system in the retina

The angiotensin-converting enzyme gene, ACE, situated on the long arm of chromosome 17, has attracted sustained interest because the renin–angiotensin system is active locally within the retina and contributes to the ischaemia and endothelial injury that characterize retinopathy [5]. The gene contains a well-known insertion/deletion (I/D) polymorphism, defined by the presence or absence of a 287-base-pair Alu repeat sequence within intron 16 (rs1799752). This variant is functionally relevant because the deletion allele is associated with higher circulating and tissue ACE activity, and thus, in principle, with greater generation of angiotensin II.

On biological grounds one might expect the D allele to predispose to retinopathy, and a number of individual studies have reported exactly that. The literature as a whole, however, has proved inconsistent, and the most recent and methodologically careful synthesis does not support a simple association. An updated meta-analysis of 16 studies found no significant relationship between the ACE I/D polymorphism and the risk of DR in T2D, whether the data were analyzed by genotype under a dominant model or by allele frequency [13]. The forest plots suggested that the discrepancies between earlier studies arose largely from differences in sample size, with smaller studies more prone to spuriously positive results [13]. Stratification by diabetes type in some studies has suggested a possible association between the D allele and retinopathy in type 1 but not T2D, indicating that the effect — if present — may be disease-subtype specific.

A subtler possibility is that polymorphism influences not the occurrence of retinopathy, but its severity once established. A cross-sectional case–control study in middle-aged Indian patients with T2D illustrates this nuance: the I/D genotype was not associated with the presence of retinopathy, yet the severity of retinopathy did vary with genotype under a recessive model and with allele contrast [14]. Such a dissociation between susceptibility and progression is biologically plausible and may partly explain why studies that lump all grades of retinopathy together reach divergent conclusions. The practical lesson is that phenotype definition matters: an effect on progression can be masked when cases are defined simply as the presence or absence of any retinopathy.

APOE - lipid transport and a protective allele

The apolipoprotein E gene, APOE, on chromosome 19, occupies an unusual position in this discussion because the most credible association points towards protection rather than harm. Apolipoprotein E is central to plasma lipid metabolism and to lipid homeostasis within the central nervous system, and it is synthesized locally in the retina by Müller cells, from where it is thought to participate in intraretinal lipid transport. The gene is polymorphic, with three common alleles — ε2, ε3 and ε4, defined by the variants rs429358 and rs7412 — that give rise to isoforms differing in their handling of lipids.

A case–control study in a Czech population that genotyped more than 1,200 patients with T2D found that carriers of at least one ε4 allele were protected against retinopathy, with the protective effect driven mainly by women and remaining significant after adjustment for diabetes duration and body mass index [15]. This finding is intriguing precisely because the ε4 allele is, in other contexts, a recognized risk factor — most famously for Alzheimer's disease and for cardiovascular events in diabetic

patients [16]. The apparent reversal of its effect in the retina is a reminder that the consequences of a genetic variant are tissue- and disease-specific, and that a single allele can be harmful in one organ and protective in another. The mechanism remains uncertain, but isoform-dependent differences in retinal lipid handling and in the local inflammatory response are plausible contributors. The ε2 allele has shown no consistent association with retinopathy risk in most studies, although isolated reports of modestly increased risk in ε2/ε2 homozygotes warrant further investigation.

Beyond these three genes, the candidate list extends considerably. Variants in the aldose reductase gene (AKR1B1), the rate-limiting enzyme of the polyol pathway, have been associated both with DR and with other microvascular complications, although the findings are not uniform across populations [17, 18]. More recent case–control work in Chinese populations has implicated variants in genes not previously prominent in the retinopathy literature — osteoprotegerin, and loci such as CEP162 and SUMO4 — broadening the catalogue of plausible contributors and underscoring how much of the genetic architecture remains to be charted [19, 20]. The principal genes discussed here, together with the directionality of their reported associations, are summarized in Figure 2 and Table 1.

Epigenetic modulation

Beyond fixed DNA sequence variation, epigenetic mechanisms — particularly DNA methylation and microRNAs — add another layer of regulation. In DR, hyperglycaemia-induced DNA methylation changes have been documented at the VEGFA promoter and at the SOD2 gene. Circulating microRNAs (e.g., miR-146a, miR-21, miR-155) are also dysregulated in patients with retinopathy. While a detailed discussion is beyond the scope of this review, these epigenetic factors likely interact with genetic polymorphisms to influence individual susceptibility.

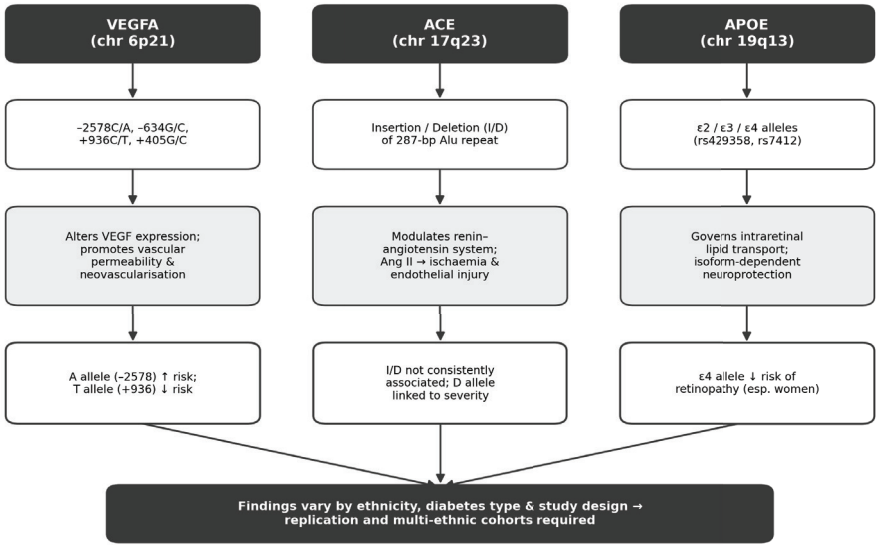


Figure 2. The three principal candidate genes discussed in this review, their key polymorphisms, putative mechanisms in the retina and the reported direction of association with diabetic retinopathy. The convergence at the foot of the figure indicates that, for all three genes, findings vary by ethnicity, diabetes type and study design.

Table 1. Summary of the main candidate genes implicated in diabetic retinopathy

Gene	Key polymorphism(s)	Putative role in the retina	Reported direction of association
VEGFA	−2578C/A (rs699947); +936C/T (rs3025039); −634G/C (rs2010963)	Central driver of vascular permeability and neovascularization	Variant-dependent: A allele (−2578) ↑ risk; C allele (+936) ↓ risk [10–12]
ACE	Insertion/deletion (I/D) of 287-bp Alu repeat (rs1799752)	Local renin–angiotensin system; angiotensin II promotes ischaemia and endothelial injury	No consistent association with occurrence; D allele may relate to severity [13, 14]
APOE	ε2 / ε3 / ε4 alleles (rs429358, rs7412)	Intraretinal lipid transport; isoform-dependent neuroprotection	ε4 allele associated with reduced retinopathy risk [15]
AKR1B1	Promoter and intronic variants (e.g. rs759853, rs752010122)	Rate-limiting enzyme of the polyol pathway	Inconsistent; some variants linked to altered risk [17, 18]

VEGFA - vascular endothelial growth factor A gene; ACE - angiotensin-converting enzyme gene; APOE - apolipoprotein E gene; AKR1B1 - aldo-keto reductase family 1 member B1 (aldose reductase) gene; ↑ - increased; ↓ - decreased

As shown in Table 2, several additional candidate genes have been investigated in DR, with varying levels of evidence supporting their association with disease susceptibility.

The level of evidence is approximate and reflects consistency of published associations, biological plausibility and availability of meta-analytic or replicated data. Most candidate-gene findings remain population-dependent and should not be interpreted as clinically validated markers.

From gene to therapy: gene-based treatment of diabetic retinopathy

Understanding the genetic and molecular basis of DR is not the end in itself; it points towards new ways of treating the disease. The current standard of care for sight-threatening retinopathy — repeated intravitreal injection of anti-VEGF agents such as ranibizumab, aflibercept and bevacizumab — is effective but burdensome. It demands frequent visits, imposes a cumulative risk of injection-related complications, and depends on a degree of adherence that many patients, particularly in resource-limited settings, cannot sustain [6]. The logic of gene therapy is to convert the retina itself into a durable biofactory producing a therapeutic protein continuously after a single administration, thereby removing the need for repeated injections.

Most gene-therapy programs in this field exploit adeno-associated virus (AAV) vectors to deliver a transgene encoding an anti-VEGF protein. Several such candidates have progressed into clinical trials. ABBV-RGX-314 uses an AAV vector to deliver a transgene encoding a ranibizumab-like antibody fragment and has reported encouraging results in early-phase studies, with later-phase trials under way; ixoberogenesoroparvovec employs an engineered capsid to express aflibercept after intravitreal delivery; and 4D-150 combines expression of aflibercept with an RNA-interference element directed against the second angiogenic factor [21]. A broader review of gene therapy for choroidal and retinal neovascularization sets these developments in the context of the wider effort to provide a one-time, long-lasting alternative to chronic anti-VEGF injection [22].

It is important to be clear about what these therapies are and are not. They are, for the most part, not corrections of an inherited defect; the patient's VEGFA, ACE or APOE

Table 2. Other candidate genes investigated in DR and approximate strength of evidence

Gene	Main biological pathway	Representative polymorphisms	Reported association with DR	Level of evidence
AKR1B1	Polyol pathway; sorbitol accumulation; osmotic and oxidative stress	rs759853, rs752010122 and promoter variants	Several studies report association; findings vary by population	Moderate but inconsistent
TCF7L2	Glucose metabolism; β-cell function; diabetes susceptibility	rs7903146	One of the more convincing associations among studied variants	Relatively stronger
IL6	Inflammation and endothelial activation	−174G/C and other promoter variants	Associations reported in some populations; meta-analytic support weak	Weak to moderate
TNF-α	Inflammation, endothelial dysfunction, blood–retinal barrier disruption	−308G/A	Biologically plausible; findings inconsistent	Weak
NOS3 / eNOS	Nitric oxide production; vascular tone; endothelial function	Glu298Asp, 4a/4b VNTR	Some association with vascular complications; limited replication	Weak to moderate
RAGE / AGER	Advanced glycation end-product signaling	Gly82Ser and promoter variants	Plausible link with hyperglycaemic injury; inconsistent genetic evidence	Weak
ICAM1	Leukostasis, endothelial adhesion and inflammation	K469E and other variants	Candidate pathway relevant; genetic associations not robust	Weak
HIF1A	Hypoxia signaling and VEGF regulation	Pro582Ser and related variants	May influence ischaemia-driven angiogenesis; limited direct evidence	Emerging / limited
MTHFR	Homocysteine metabolism and endothelial injury	C677T, A1298C	Some associations; not consistently replicated	Weak to moderate
OPG / TNFRSF11B	Vascular calcification, inflammation and endothelial protection	Several SNPs in Asian cohorts	Recent population-specific associations; requires replication	Emerging

genotype is not being altered. Rather, they use the tools of gene transfer to deliver a sustained pharmacological effect — a refinement of the anti-VEGF strategy rather than a treatment aimed at a specific susceptibility variant. Genuine genotype-directed therapy, in which a patient's polymorphism profile guides the choice of treatment, remains aspirational for DR. The path towards it runs through better identification of variants with reliable, clinically meaningful effects — exactly the work that the candidate-gene and genome-wide studies discussed above are intended to advance.

Challenges in clinical translation

Several obstacles continue to separate the genetics of DR from its bedside application. The first and most pervasive is the inconsistency

of association findings. As the umbrella review made plain, the great majority of reported gene–disease associations rest on weak evidence, and only a handful survive rigorous methodological scrutiny [8]. Small sample sizes, inadequate correction for multiple testing and selective publication of positive results have all contributed to literature that is larger than reliable.

The second obstacle is ethnic heterogeneity. The frequency of the given allele, and the strength of its association with disease, can differ substantially between populations, so that the variant that is informative in one ethnic group may be uninformative or even misleading in another [10]. This is not a statistical nuisance to be eliminated but a biological reality reflecting differences in genetic background and in the environmental exposures with which genes interact. It implies that genetic prediction tools will need to be developed and validated separately across populations, rather than transplanted wholesale from the cohorts in which they were derived.

The third challenge concerns phenotype. DR is not a single entity but a spectrum, and the genetic determinants of whether retinopathy develops at all may differ from those that govern its progression to a proliferative or oedematous stage. The ACE example, in which the effect on severity was detectable while the effect on occurrence was not, shows how a coarse phenotype definition can obscure a real genetic signal [14]. Future studies will need to phenotype retinopathy more finely, distinguishing carefully between the events of onset, progression and the development of macular oedema.

Finally, the inherited component of DR is polygenic and embedded in a dense web of gene–environment interaction. No single variant explains more than a small fraction of risk, and the clinically useful unit may turn out to be a polygenic score that aggregates the small effects of many variants, weighted appropriately for the patient's ancestry and combined with conventional risk factors. Building such scores, and demonstrating that they improve on existing clinical prediction, is a substantial undertaking that has only begun. Until it is accomplished, genetic testing for DR will remain a research tool rather than a part of routine care.

Future perspectives

Future research on the genetics of DR should move beyond isolated candidate-gene associations towards integrated, multi-layered models of disease risk. Large multicenter cohorts with standardized retinal phenotyping will be essential — particularly cohorts that distinguish between onset of any retinopathy, progression to proliferative disease and development of diabetic macular oedema. This distinction is important because the genetic determinants of susceptibility, severity and treatment response may not be identical.

The second priority is the development of ancestry-specific and externally validated polygenic risk scores. Such tools should not be evaluated in isolation but in combination with conventional clinical risk factors. Their clinical value will depend on whether they improve prediction sufficiently to alter screening intervals, identify patients requiring closer follow-up, or guide early preventive intervention.

Third, genetic data should be linked with high-resolution retinal imaging. OCT, OCT angiography and fundus photography analyzed by artificial intelligence may provide quantitative phenotypes that are more sensitive than traditional clinical categories. Combining these imaging biomarkers with genomic, transcriptomic, proteomic and epigenetic data could help define biologically distinct subtypes of DR.

Finally, pharmacogenetic studies are needed to determine whether inherited variation influences response to anti-VEGF therapy, corticosteroids or future gene-based

treatments. At present, gene therapy for DR mainly represents sustained intraocular delivery of anti-angiogenic molecules rather than correction of inherited susceptibility. In the longer term, however, genotype-informed screening, risk stratification and therapeutic selection may become realistic components of precision ophthalmology.

Limitations

As a narrative review, this work has several inherent limitations. The selection of genes for detailed discussion, while justified, inevitably omits other candidates with plausible biological roles (e.g., IL-6, TNF-α, AKR1B1). The literature cited reflects the authors' judgement and may not be exhaustive. Furthermore, the predominance of studies from European and East Asian populations limits the generalizability of conclusions to other ancestries. These caveats should be considered when interpreting the associations discussed.

Conclusion

DR is a heritable as well as a metabolic disease, and the search for genes governing its inherited susceptibility has now occupied investigators for several decades. The three genes examined most closely here — VEGFA, ACE and APOE — illustrate both the promise and the difficulty of this enterprise. Each is biologically compelling: VEGFA sits at the heart of the angiogenic process causing blindness, ACE links DR to the renin–angiotensin system, and APOE connects it to retinal lipid biology. Yet for each, the association between a specific common polymorphism and the disease is modest, variable across populations and, in the case of ACE, perhaps confined to severity rather than occurrence.

The most realistic assessment is that no single polymorphism will ever serve as a standalone marker of risk. The future of genetic prediction in DR lies in larger and more carefully phenotyped cohorts, in genome-wide and polygenic approaches validated across diverse ancestries, and in the integration of genetic information with the established clinical risk factors. In parallel, the molecular understanding that genetic research has helped to build is already bearing fruit in therapy, as gene-transfer strategies move the anti-VEGF paradigm towards durable, single-administration treatment. Recognizing the genetic determinants of DR therefore matters on two fronts at once: it promises better identification of the patients at the greatest risk, and it deepens the mechanistic understanding from which the next generation of treatments will emerge. Future progress will depend on larger, more diverse cohorts and on integrating genetic data with clinical risk factors to determine whether genotype-informed screening or treatment stratification improves outcomes.

Funding source. The authors received no specific funding for this work.

Ethical approval. This article does not contain any studies with human participants performed by any of the authors.

Conflicts of interest. The authors declare no conflict of interest.

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Uloga genskih polimorfizama u dijabetičkoj retinopatiji

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Dijabetička retinopatija (DR) je najčešća mikrovaskularna komplikacija dijabetes melitusa (DM) i ostaje jedan od vodećih uzroka sljepila koje se može spriječiti u radno sposobnoj populaciji. Tok bolesti je izrazito promjenljiv: neki bolesnici sa dugogodišnjim, loše regulisanim dijabetesom nikada ne razviju oblik bolesti koji ugrožava vid, dok kod drugih dolazi do brze progresije uprkos zadovoljavajućoj metaboličkoj kontroli. Ova klinička heterogenost, koju tradicionalni faktori rizika ne mogu u potpunosti objasniti, usmjerila je pažnju ka nasljednoj komponenti sklonosti ka bolesti. U ovom radu sažeto je prikazano savremeno razumijevanje genske arhitekture DR, sa posebnim osvrtom na tri detaljno proučavana kandidat-gena: gen za vaskularni endotelni faktor rasta (*VEGFA*), gen za angiotenzin-konvertujući enzim (*ACE*) i gen za apolipoprotein E (*APOE*), posebno njihovi najistraženiji polimorfizmi: *VEGFA* rs699947, rs2010963 i rs3025039; *ACE* rs1799752 I/D, i *APOE* rs429358 i rs7412 (ε2/ε3/ε4). Razmatraju se dokazi koji povezuju pojedine polimorfizme sa bolešću, nalazi studija asocijacije na nivou cijelog genoma, kao i razlozi za nedosljednost rezultata između studija u pogledu etničkih razlika, definicije fenotipa i ograničene statističke snage. Na kraju se razmatra kako genetski uvidi počinju da oblikuju terapiju, od ustaljenog anti-VEGF pristupa do genskih terapija koje se ispituju u kliničkim studijama.

Ključne riječi: genska sklonost, renin-angiotenzin sistem, apolipoprotein E, VEGFA, mikrovaskularne komplikacije

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):56–61

UDK: 617.735:616.379-008.64:615
DOI: 10.59137/BII202601643T

Review

Treatment of diabetic macular edema

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Primljen – Received: 27/05/2026
Prihvaćen – Accepted: 29/05/2026

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Summary

Diabetic macular edema (DME) is the most common cause of vision loss in individuals with diabetes mellitus, particularly in the working-age population, and its prevalence is increasing due to the global rise in diabetes incidence. The aim of this paper is to review current principles of DME diagnosis and treatment based on available scientific literature. This is a narrative review article, with a search of PubMed and Google Scholar databases. Optical coherence tomography (OCT) is the gold standard in diagnostics, enabling quantitative and qualitative assessment of edema. Anti-VEGF therapy is the first-line treatment for DME involving the center of the macula, demonstrating significant improvement in visual acuity. Corticosteroids represent a valuable alternative in patients who do not respond to anti-VEGF or have a prominent inflammatory component. Laser photocoagulation, although historically the gold standard, now plays a secondary role. Timely diagnosis and an individualized therapeutic approach are crucial for preserving visual function.

Key words: diabetic macular edema, diabetic retinopathy, anti-VEGF therapy, corticosteroids, laser photocoagulation

Introduction

Diabetic macular edema (DME) is defined as retinal thickening that involves or approaches the center of the macula and is the most common cause of vision decline in patients with diabetes mellitus [1]. Diabetic macular edema represents the accumulation of fluid within the central retina, resulting from breakdown of the blood-retinal barrier. DME is the leading cause of vision loss in the working-age population, and its frequency is increasing due to the significant rise in the incidence of diabetes mellitus worldwide [4]. The aim of this paper is to present, through a review of available professional and scientific literature, the current principles of

diagnosis and treatment of diabetic macular edema.

Methods

This paper is conceived as a narrative review. PubMed and Google Scholar databases were searched using the keywords: diabetic macular edema, anti-VEGF, laser photocoagulation, corticosteroids. Articles published between 2010 and 2024, as well as relevant clinical guidelines, were included.

Pathogenesis and classification

The pathogenesis of DME is complex and multifactorial, primarily involving breakdown of the blood-retinal barrier, which leads to accumulation of fluid and macromolecules from serum into intracellular spaces. Accelerated apoptosis of pericytes and endothelial cells, acellular capillaries, thickened basement membrane, and capillary occlusion result in endothelial damage and disruption of the inner blood-retinal barrier. DME can occur at any stage of diabetic retinopathy (DR), but is most commonly associated with longer duration and greater severity of DR [2].

The nature of DME is characterized by slow progression of retinal thickening until it involves the center of the macula, causing impairment of visual acuity. Spontaneous resolution of DME is rare and usually occurs secondary to improvement in systemic risk factors such as glycemic control, hypertension, and hypercholesterolemia [1].

DME can be classified as focal or diffuse. Focal macular edema manifests as a localized area of retinal thickening resulting from focal leakage from a microaneurysm or a cluster of microaneurysms. The area of focal leakage is usually clearly demarcated by a partial or complete ring of hard exudates in a circinate pattern.

Diffuse macular edema results from extensive damage to capillaries, microaneurysms, and arterioles, and manifests as more widespread macular thickening due to generalized abnormal leakage from the retinal capillary network. Diffuse macular edema tends to be symmetric and without significant exudation. Ocular and systemic risk factors for the development and progression of diffuse DME include increased number of microaneurysms, advanced retinopathy, vitreomacular traction, adult-onset diabetes, renal disease, and severe hypertension.

Cystoid macular edema, often associated with diffuse macular edema, results from generalized breakdown of the blood-retinal barrier with accumulation of fluid in a flower-petal pattern, primarily in the outer plexiform and inner nuclear layers. The presence or absence of cystic changes does not directly affect the prognosis or treatment of DME. In clinical practice, the distinction between focal and diffuse edema is not always clear, and mixed forms are frequently encountered [5].

Diagnosis

Diagnosis of DME is based on clinical examination, optical coherence tomography, fluorescein angiography, and OCT angiography. OCT can be used for screening, classification, monitoring, and assessment of DME treatment. It provides information on central macular thickness as well as various morphological characteristics of edema and can show morphological changes after DME treatment.

Fluorescein angiography (FA) can detect various signs of DR, such as microaneurysms, proliferative DR, and ischemic maculopathy. FA has been an important diagnostic tool in DR for decades and is formally recognized as a key component in assessing the severity of pathology and the precise location of retinal changes, enabling appropriate targeted laser therapy. FA is not required for diagnosing

DME, but it provides a qualitative assessment of vascular leakage, aiding in the detection of treatable changes, and is also important for assessing enlargement of the foveal avascular zone (FAZ), which may be associated with poor visual prognosis. The main advantage of OCT angiography over FA is the ability to focus on different retinal layers and to highlight changes at the level of the deep capillary plexus [6].

Treatment options

In addition to control of systemic disease, numerous ophthalmological treatment methods for DME exist: anti-VEGF agents, corticosteroids, laser photocoagulation, and pars plana vitrectomy.

Laser photocoagulation

Laser photocoagulation was the standard of care for DME before the advent of intravitreal injections [6]. Laser photocoagulation techniques for DME can be divided into focal or grid [8]. In clinical practice, mixed forms of DME are commonly encountered, where focal and diffuse leakage are combined, clearly visible on fluorescein angiography. In these cases, a modified grid laser technique is applied. This technique primarily consists of grid treatment of the area of diffuse leakage and focal treatment of localized leakages within or outside the area of diffuse edema [1].

A newer laser modality for DME is the micropulse laser, in which the laser beam is not continuous as in conventional laser, but is divided into multiple short, repetitive micro-pulses. A significant advantage of this laser is that there is currently no evidence of adverse effects or complications resulting from its use [4].

Clinical changes associated with worse visual acuity after DME laser photocoagulation include diffuse macular edema involving the center of the macula, macular ischemia, hard exudates in the fovea, diffuse fluorescein leakage, and pronounced cystoid macular edema [3].

Although historically the gold standard, laser photocoagulation today has a secondary role. Its use is recommended for focal DME without foveal center involvement or as adjunctive therapy to anti-VEGF.

Anti-VEGF therapy

Currently, drugs targeting excessive vascular endothelial growth factor (VEGF) in the eye are the most popular approach for treating DME. Their use requires numerous decisions, including choice of agent, treatment regimen, and combination with other options such as laser or corticosteroids [9]. Angiogenesis inhibitors block VEGF and other angiogenic factors influencing the development and progression of DME [4]. The most commonly used anti-VEGF agents are bevacizumab, ranibizumab, aflibercept, and faricimab.

Bevacizumab is a recombinant full-length monoclonal antibody that binds all VEGF isoforms [3, 6]. Ranibizumab is a recombinant humanized Fab fragment of a monoclonal antibody with high affinity for VEGF-A [5]. Aflibercept is a recombinant decoy receptor inhibitor for VEGF-A, VEGF-B, and placental growth factor, demonstrating efficacy and safety for DME treatment [7]. Faricimab is a monoclonal antibody that acts by inhibiting key mediators such as vascular endothelial growth factor-A (VEGF-A) and angiopoietin-2 (Ang-2) [10].

Table 1 compares the most commonly used anti-VEGF agents in the treatment of DME, showing their molecular structure and the standard intravitreal dose for each drug.

Anti-VEGF therapy is currently the most effective modality for treating DME involving the center of the macula, with level I evidence from randomized controlled trials.

Table 1. Comparison of anti-VEGF agents in the treatment of DME

Agent	Molecule type	Dose (intravitreal)
Bevacizumab	full-length monoclonal antibody	1.25 mg
Ranibizumab	Fab fragment	0.5 mg
Aflibercept	receptor-IgG fusion protein	2 mg
Faricimab	bispecific antibody (VEGF-A + Ang-2)	6 mg

Corticosteroids

Intravitreal corticosteroids have been used for a long time in the treatment of DME due to their anti-inflammatory and antiangiogenic effects. Corticosteroids reduce vascular permeability, fibrin accumulation, leukocyte migration, and help preserve the blood-retinal barrier. The use of corticosteroids in DME is indicated in cases where inflammation plays a key mechanism in the pathogenesis of the disease. The corticosteroids most commonly used in DME treatment can be administered intravitreally or parabulbarly [4]. Commercially available corticosteroids for intravitreal administration include triamcinolone acetonide, dexamethasone implant (Ozurdex), and fluocinolone (Iluvien) [9].

Corticosteroids (particularly the dexamethasone implant) represent a valuable alternative in patients who do not respond to anti-VEGF therapy, in those with pseudophakia (without risk of cataract), or in whom inflammation plays a key role. However, caution is needed due to possible elevation of intraocular pressure.

Individualized clinical choice

The clinical choice of therapy should be individualized, taking into account the morphological type of edema, OCT findings, the patient's systemic condition, and response to prior therapy.

Limitations

This paper represents a narrative literature review, not a systematic review or meta-analysis. No formal criteria for assessing the quality of included studies (e.g., PRISMA) were applied. The paper does not contain original clinical data, so the conclusions are based solely on the available literature. Therapeutic algorithms have not been validated in the local population of Bosnia and Herzegovina.

Conclusion

Diabetic macular edema (DME) is a major cause of vision loss in patients with diabetes. Diabetic macular edema progresses with the duration of diabetes and diabetic retinopathy. The development of various diagnostic methods and therapeutic options has increased the success rate of treatment and control of diabetic macular edema. Contemporary treatment of DME requires an individualized approach based on the morphological type of edema, OCT findings, and response to therapy, with anti-VEGF agents representing the current gold standard.

Funding source. The authors received no specific funding for this work.

Ethical approval. This article does not contain any studies with human participants performed by any of the authors.

Conflicts of interest. The authors declare no conflict of interest.

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Liječenje dijabetičkog makularnog edema

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Dijabetični makularni edem (DME) predstavlja najčešći uzrok gubitka vida kod osoba sa dijabetes melitusom, naročito u populaciji radno sposobnog uzrasta, a njegova prevalencija raste usljed globalnog porasta učestalosti dijabetesa. Cilj ovog rada jeste prikaz savremenih principa dijagnostike i liječenja DME na osnovu dostupne naučne literature. Rad predstavlja narativni pregled literature uz pretragu baza podataka PubMed i Google Scholar. Optička koherentna tomografija (OCT) predstavlja zlatni standard u dijagnostici, omogućavajući kvantitativnu i kvalitativnu procjenu edema. Anti-VEGF terapija predstavlja terapiju prvog izbora kod DME koji zahvata centar makule i pokazuje značajno poboljšanje vidne oštrine. Kortikosteroidi predstavljaju značajnu terapijsku alternativu kod pacijenata koji ne odgovaraju na anti-VEGF terapiju ili imaju izraženu inflamatornu komponentu. Laserska fotokoagulacija, iako istorijski zlatni standard, danas ima sekundarnu ulogu. Pravovremena dijagnoza i individualizovan terapijski pristup od ključnog su značaja za očuvanje vidne funkcije.

Ključne riječi: dijabetični makularni edem, dijabetična retinopatija, anti-VEGF terapija, kortikosteroidi, laserska fotokoagulacija

SAŽECI/ABSTRACTS

Periferni ulcerozni keratitis i nekrotizujući skleritis u autoimunim reumatskim bolestima

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Uvod. Periferni ulcerozni keratitis (PUK) i nekrotizujući skleritis predstavljaju najznačajnije i najteže promene na prednjem segmentu oka u reumatskim bolestima s obzirom da su udružene sa visokom stopom sniženja ili gubitka vida. Najčešće se ispoljavaju u kliničkom toku reumatoidnog artritisa ili kao inicijalna manifestacija i znak pogoršanja sistemskog vaskulitisa, najčešće granulomatoznog poliangitisa, ranije poznatog kao Wegenerova granulomatoza. Cilj rada je da prikažemo kliniče karakteristike i terapijski pristup kod nekrotizujućeg skleritisa i PUK u sklopu granulomatoznog poliangiitisa (GPA) i RA.

Prikazi bolesnika. Žena, stara 64 godine, sa desetogodišnjom dijagnozom seropozitivnog erozivnog reumatoidnog artritisa, razvila je obostrani PUK dva meseca nakon uvođenja indukcione terapije rituksimabom. Progresivno stanjivanje rožnjače zahvatilo je celu cirkumferenciju rožnjače uz limbus, sa tendencijom ka centralnom širenju keratolize na oba oka. Primenjena je pulsna doza ciklofosfamida kojom je zaustavljena inflamacija. Mada je keratitis u potpunosti izlečen, iregularni astigmatizam koji je nastao kao posledica perifernog istanjenja i ožiljavanja rožnjače doveo je do značajnog sniženja vidne oštrine na oba oka.

Muškarac, star 53 godine, sa GPA razvio je nekrotizujući skleritis i PUK na desnom, miopnom oku nakon klasične operacije protiv ablacije mrežnjače. Nekrotizujuća inflamacija zahvatila je u celini gornju polovinu sklere sa ekstruzijom serklaža i širenjem na susednu periferiju rožnjače u vidu PUK. Primena pulsnih doza ciklofosfamida nije dovela do očekivane regresije nekroze sklere i meltinga rožnjače, pa je lečenje ovog refrakternog oblika GPA nastavljeno rituksimabom. Nekrotizujući skleritis i PUK potpuno su sanirani primenom navedene biološke terapije u formiranje stafiloma sklere i perifernog istanjenja rožnjače.

Zaključak. Pravilno lečenje PUK i nekrotizujućeg skleritisa u sklopu autoimunih reumatskih bolesti podrazumeva primenu sistemske imunomodulatorne terapije uz adekvatno doziranje i praćenje neželjenih efekata. Promene na oku mogu da budu prvi znak autoimunih reumatskih bolesti, pa je bliska saradnja oftalmologa i reumatologa veoma značajna za ranu dijagnozu, sprovođenje sistemske terapije i bolju prognozu bolesti.

Ključne reči: periferni ulcerozni keratitis, nekrotizirajući skleritis, granulomatozni poliangitis, reumatoidni artritis, ciklofosfamid

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):65

Peripheral ulcerative keratitis and necrotizing scleritis in autoimmune rheumatic diseases

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Introduction. Peripheral ulcerative keratitis (PUK) and necrotizing scleritis represent the most significant and severe changes affecting the anterior segment of the eye in rheumatic diseases, as they are associated with a high rate of visual impairment or vision loss. They most commonly occur during the clinical course of rheumatoid arthritis or as an initial manifestation and sign of worsening systemic vasculitis, most frequently granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis. The aim of this paper is to present the clinical characteristics and therapeutic approach in necrotizing scleritis and PUK associated with granulomatosis with polyangiitis (GPA) and rheumatoid arthritis (RA).

Case reports. A 64-year-old woman with the 10-year history of seropositive erosive rheumatoid arthritis developed bilateral PUK two months after the introduction of induction therapy with rituximab. Progressive corneal melting involved the entire corneal circumference adjacent to the limbus, with a tendency toward central extension of keratolysis in both eyes. Pulse cyclophosphamide therapy was administered, resulting in cessation of inflammation. Although the keratitis healed completely, irregular astigmatism caused by peripheral corneal thinning and scarring led to significant reduction in visual acuity in both eyes.

A 53-year-old man with GPA developed necrotizing scleritis and PUK in the right myopic eye following conventional retinal detachment surgery. Necrotizing inflammation involved the entire upper half of the sclera, with extrusion of the scleral buckle and extension to the adjacent peripheral cornea in the form of PUK. Administration of pulse cyclophosphamide therapy did not result in the expected regression of scleral necrosis and corneal melting; therefore, treatment of this refractory form of GPA was continued with rituximab. Necrotizing scleritis and PUK were completely resolved with the use of this biologic therapy, resulting in the formation of scleral staphyloma and peripheral corneal thinning.

Conclusion. Proper treatment of PUK and necrotizing scleritis associated with autoimmune rheumatic diseases requires systemic immunomodulatory therapy with appropriate dosing and monitoring of adverse effects. Ocular manifestations may be the first sign of autoimmune rheumatic diseases; therefore, close collaboration between ophthalmologists and rheumatologists is essential for early diagnosis, implementation of systemic therapy, and improved disease prognosis.

Key words: peripheral ulcerative keratitis, necrotizing scleritis, granulomatosis with polyangiitis, rheumatoid arthritis, cyclophosphamide

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2026;17(Suppl 1):66

Hipertenzija i oko

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Sistematska hipertenzija pogađa krvne sudove oka i izaziva mikroangiopatiju mrežnjače, horoideje i optičkog živca. Rana detekcija vaskularnih promena na očnom dnu omogućava pravovremenu kontrolu pritiska i može sprečiti trajan gubitak vida. Hipertenzija pogađa oko 1,39 milijardi odraslih u svetu, a gotovo polovina obolelih nije adekvatno kontrolisana. Retinopatija se javlja kod značajnog broja tih pacijenata – studije navode prevalenciju ~30–70% među hipertoničarima, pri čemu 2–17% opšte populacije bez šećerne bolesti pokazuje retinopatijske znake verovatno zbog hipertenzije. Rizik raste sa trajanjem i jačinom hipertenzije, prisustvom bubrežne ili kardiovaskularne bolesti, pušenjem i genetikom. Kod mladih sa sekundarnom hipertenzijom moguće su teške manifestacije (npr. serozna eksudativna odvajanja mrežnjače) koje se često prvi put otkriju na očnom pregledu. Visok krvni pritisak izaziva tri faze vaskularne promene: vazokonstriktivnu, sklerotičnu i eksudativnu. Dugotrajna hipertenzija dovodi do vazospazma i zadebljanja zida arterija (hijalinske degeneracije, arterioskleroze). Na kraju se narušava barijera krv-retina, javljaju se hemoragije, eksudati i pamukaste mrlje usled ishemije retinalnog nervnog sloja. U fazi maligne hipertenzije dolazi do oštećenja i mreže arterija horoideje - formiraju se Elsničgove mrlje i Saudersove pruge, a nekad i serozna degeneracija RPE (pigmentnog epitela) sa eksudativnim odvojenjem mrežnjače. Hipertenzija takođe može izazvati optičku neuropatiju - akutni edem papile sa difuznim plamičastim hemoragijama, a kod hroničnih promena atrofične promene na disku. Dugoročno je zabeležena povezanost hipertenzije sa nastankom degeneracije žute mrlje i glaukoma oka. Klasična klasifikacija (Keith–Wagener–Barker, 1939) deli retinopatiju na 4 stepena; stadijum 4 (papiledem) ima izuzetno lošu prognozu. Hronična hipertenzivna retinopatija obično ne dovodi do izraženog pogoršanja vida - fundus se stabilizuje uz dobru kontrolu pritiska (premda arterijske promene ostaju). Nasuprot tome, maligna hipertenzija ima visoku smrtnost (~50% za 2 meseca) i često uzrokuje trajni gubitak vida usled papilne atrofije ili pigmentnih promena nakon eksudativnog odvajanja. Hipertenzija povećava rizik od arterijskih i venskih okluzija mrežnjače, arterijalnih makroaneurizmi, a u kombinaciji sa dijabetesom ubrzava prognozu retinopatije. Kod trudnica hipertenzija može izazvati eksudativne retinalne i rožnjačne promene (preeklampsija). Regulisanje pritiska smanjuje ove rizike. Mnogi podaci o oftalmološkim efektima hipertenzije dolaze iz starih studija i male kohorte. Potrebna su veća epidemiološka istraživanja o prevalenciji retinopatije u različitim populacijama, kao i longitudinalne studije o uticaju novih antihipertenziva na oko kao ciljni organ. Razvoj pouzdanih kvantitativnih metoda (OCT-A indeksi) za rano otkrivanje mikropromena obećava, ali je potrebno standardizovati ove tehnike i proveriti njihovu prognostičku vrednost u velikim kliničkim ispitivanjima.

Ključne reči: hipertenzija, retinopatija, hipertenzivna horoidopatija, krvni pritisak, oftalmologija

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):67

Hypertension and the eye

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Systemic hypertension affects the blood vessels of the eye and causes microangiopathy of the retina, choroid and optic nerve. Early detection of vascular changes in the ocular fundus enables timely blood pressure control and can prevent permanent vision loss. Hypertension affects approximately 1.39 billion adults worldwide, and nearly half of those affected are not adequately controlled. Retinopathy occurs in a significant number of these patients – studies report a prevalence of ~30–70% among hypertensives, with 2–17% of the general population without diabetes showing signs of retinopathy likely due to hypertension. Risk increases with duration and severity of hypertension, presence of renal or cardiovascular disease, smoking and genetics. In young people with secondary hypertension, severe manifestations are possible (e.g., serous exudative retinal detachments) that are often first detected on eye examination. High blood pressure causes three phases of vascular change: vasoconstrictive, sclerotic and exudative. Long-term hypertension leads to vasospasm and thickening of the arterial wall (hyaline degeneration, arteriosclerosis). Eventually, the blood-retinal barrier is disrupted, resulting in hemorrhages, exudates and cotton wool spots due to ischemia of the retinal nerve fiber layer. In the malignant hypertension phase, damage also occurs to the choroidal artery network – Elschnig spots and Siegrist streaks form, and sometimes serous RPE degeneration with exudative retinal detachment. Hypertension can also cause optic neuropathy – acute disc edema with diffuse flame-shaped hemorrhages, and in chronic changes atrophic disc changes. Long-term association of hypertension with the development of macular degeneration and glaucoma has been recorded. The classic classification (Keith–Wagener–Barker, 1939) divides retinopathy into four grades; grade 4 (papilledema) has an extremely poor prognosis. Chronic hypertensive retinopathy usually does not lead to significant visual deterioration – the fundus stabilizes with good blood pressure control (although arterial changes remain). In contrast, malignant hypertension has a high mortality (~50% at two months) and often causes permanent vision loss due to optic atrophy or pigmentary changes after exudative detachment. Hypertension increases the risk of arterial and venous occlusions of the retina, arterial macroaneurysms, and in combination with diabetes accelerates the progression of retinopathy. In pregnant women, hypertension can cause exudative retinal and corneal changes (preeclampsia). Blood pressure regulation reduces these risks. Much of the data on the ophthalmic effects of hypertension come from older studies and small cohorts. Larger epidemiological studies on the prevalence of retinopathy in different populations are needed, as well as longitudinal studies on the effect of new antihypertensives on the eye as a target organ. The development of reliable quantitative methods (OCT-A indices) for early detection of microchanges is promising, but these techniques need to be standardized and their prognostic value verified in large clinical trials.

Key words: hypertension, retinopathy, hypertensive choroidopathy, blood pressure, ophthalmology

Odjek sistemske bolesti u oku - neovaskularni glaukom

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Neovaskularni glaukom se definiše kao sekundarni glaukom koji je izazvan teškom ishemijom retine. Etiološki, neovaskularni glaukom je u čak tri četvrtine slučajeva posledica sledećih stanja: dijabetičke retinopatije (u 33% slučajeva), ishemičke okluzije stabla vene centralis retine (33% slučajeva) i okularnog ishemičnog sindroma (u 13% slučajeva). Ovo je jedan od najtežih tipova sekundarnog glaukoma i uvek je ozbiljna pretnja vidu oka na kome se razvija. U osnovi patofiziološkog mehanizma nastanka ovog glaukoma je nenormalni rast krvnih sudova u irisu i uglu prednje očne komore. Neovaskularni glaukom obično napreduje brzo, teško se leči i sem nepovratnog gubitka vida, dovodi i do jakih bolova, što drastično smanjuje kvalitet života obolelog. Otežavajuća okolnost kod neovaskularnog glaukoma, koji je posledica dijabetične retinopatije, je činjenica da je vrlo često bilateralan. Poznavanje ove teške komplikacije sistemskog oboljenja sa visokom prevalencijom u opštoj populaciji – dijabetesa – od krucijalne je važnosti zbog kompleksnosti oboljenja, potrebe da se leči multidisciplinarno i često operiše i po više puta. Opšti principi lečenja osoba sa neovaskularnim glaukomom uključuju identifikaciju osnovnog uzroka ovog oboljenja, smanjenje simptoma, kontrolu ili eliminisanje ishemije retine i snižavanje povišenog intraokularnog pritiska. U okviru lečenja tretira se ishemija retine, kako bi se smanjio stimulus za razvoj neovaskularizacije (intravitrealni anti-VEGF agensi), sprovodi se panretinalna fotokoagulacija, insistira se na pravilnom lečenju osnovne bolesti, kontroliše se intraokularni pritisak (medikamentno ili hirurški) i prateća inflamacija. I pored kompleksnosti i težine ove vrste glaukoma, radi se o preventabilnoj bolesti, pa se dijabetičarima uvek savetuju redovne i detaljne kontrole oftalmologa.

Ključne riječi: neovaskularni glaukom, dijabetička retinopatija, okluzija retinalne vene, okularni ishemijski sindrom, ishemija retine, inhibitori vaskularnog endotelnog faktora rasta

Echo of systemic disease in the eye - neovascular glaucoma

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Neovascular glaucoma is defined as secondary glaucoma caused by severe retinal ischemia. Etiologically, neovascular glaucoma is, in three quarters of cases, the result of the following conditions: diabetic retinopathy (33% of cases), ischemic central retinal vein occlusion (33% of cases), and ocular ischemic syndrome (13% of cases). This is one of the most severe types of secondary glaucoma and is always a serious threat to the vision of the affected eye. The pathophysiological mechanism underlying this glaucoma is abnormal blood vessel growth in the iris and the angle of the anterior chamber. Neovascular glaucoma usually progresses rapidly, it is difficult to treat, and in addition to irreversible vision loss, leads to severe pain, drastically reducing the patient's quality of life. An aggravating circumstance with neovascular glaucoma resulting from diabetic retinopathy is the fact that it is very often bilateral. Knowledge of this severe complication of a systemic disease with high prevalence in the general population – diabetes – is of crucial importance due to the complexity of the disease, the need for multidisciplinary treatment, and often repeated surgeries. General principles of treating patients with neovascular glaucoma include identifying the underlying cause of the disease, reducing symptoms, controlling or eliminating retinal ischemia, and lowering elevated intraocular pressure. Treatment addresses retinal ischemia to reduce the stimulus for neovascularization (intravitreal anti-VEGF agents), panretinal photocoagulation is performed, proper treatment of the underlying disease is emphasized, intraocular pressure is controlled (medically or surgically), and accompanying inflammation is managed. Despite the complexity and severity of this type of glaucoma, it is a preventable disease, so diabetics are always advised to have regular and thorough ophthalmological check-ups.

Key words: neovascular glaucoma, diabetic retinopathy, retinal vein occlusion, ocular ischemic syndrome, retinal ischemia, vascular endothelial growth factor inhibitors

Glaukom: bolest oka ili organizma?

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Glaukom je vodeći uzrok nepovratnog sljepila u svijetu. S obzirom na njegov potencijal da dovede do trajnog gubitka vida, važno je razumjeti na koji način sistemska oboljenja i njihove terapije mogu biti povezani s razvojem glaukoma ili povećati rizik za njegov nastanak. U ovom preglednom radu analizirana je dostupna literatura i pružen savremen uvid u glaukom, njegovu patofiziologiju i povezane faktore rizika, i to u kontekstu različitih sistemskih bolesti, njihovog uticaja, rizika i mehanizama koji doprinose razvoju glaukoma, uključujući inflamatorna i autoimuna oboljenja, dermatološka, kardiovaskularna, plućna, bubrežna, urološka, neurološka i psihijatrijska oboljenja. Cilj ovog preglednog predavanja je naglasiti značaj sistemskih oboljenja, njihove učestalosti, mehanizama djelovanja, terapijskih pristupa i povezanosti s razvojem glaukoma.

Ključne riječi: glaukom, sistemske bolesti, faktori rizika, sljepilo

Glaucoma: eye disease or disease of the organism?

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Glaucoma is the leading cause of irreversible blindness in the world. Given its potential to cause permanent vision loss, it is important to understand how systemic diseases and their therapies may be associated with the development of glaucoma or increase the risk of its occurrence. This review paper analyzes the available literature and provides a contemporary insight into glaucoma, its pathophysiology and associated risk factors, in the context of various systemic diseases, their impact, risks and mechanisms contributing to the development of glaucoma, including inflammatory and autoimmune diseases, dermatological, cardiovascular, pulmonary, renal, urological, neurological and psychiatric diseases. The aim of this review lecture is to emphasize the importance of systemic diseases, their frequency, mechanisms of action, therapeutic approaches and association with the development of glaucoma.

Key words: glaucoma, systemic diseases, risk factors, blindness

Susac sindrom - prikaz slučaja

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Uvod. Susakov sindrom (SS) je izuzetno retka autoimuna bolest koja se karakteriše kliničkom trijadom: encefalopatijom, okluzijom grana retinalnih arterija, kao i senzoneuralnim gubitkom sluha, uzrokovanim napadom imunološkog sistema ka sopstvenim ćelijama endotela sitnih krvnih sudova mozga, oka i uha (mikroangiopatija). Bolest je prvi put opisao John Susac 1979. godine. Računa se da za sada ima oko 700 obolelih osoba u celom svetu, mada se sama bolest vrlo često pogrešno dijagnostikuje.

Prikaz bolesnika. Prikazujemo slučaj 33-godišnje, prethodno zdrave žene koja se javlja na pregled zbog zamagljenja vida na jednom oku, kao i čudnih simptoma u vidu povremenih treperenja, što se uz uredan oftalmološki nalaz tumači kao retinalna migrena. Sedam meseci kasnije dolazi zbog ispada u vidnom polju na levom oku i okluzijom grane retinalne arterije, a dve nedelje kasnije sa ispadom u vidnom polju desnog oka i okluzijom grane retinalne arterije. Pacijentkinji se uvodi iv terapija Solumedrola. MR mozga ukazuje na promene u beloj masi, audiometrija pokazuje poremećaje u niskim frekvencijama što pojačava sumnju da se radi o Susakovom sindromu. Za vreme same dijagnostike, pacijentkinja ispoljava neurološke simptome tipa dizartrije, vrtoglavice, glavobolje, dezorijentacije, kao i trnjenja u ekstremitetima. Potvrđuje se dijagnoza Susakovog sindroma i započinje imunološka terapija (visoke doze kortikosteroida kao prva linija terapije, a onda metotreksat, imunoglobulini, azatioprin, rituksimab).

Zaključak. Susakov sindrom je jako retka mikroangiopatija koja daje simptomatologiju oboljenja moždanog parenhima (encefalopatija, fokalni neurološki ispadi, glavobolja), unutrašnjeg uha (pad sluha), kao i retine (rekurentne okluzije retinalnih arterija praćene ispadima u vidnom polju). Klinička trijada, tj. istovremeno ispoljavanje svih simptoma viđa se u manje od 20% obolelih što čini da je dijagnostika ove bolesti pravi izazov. Korektna i pravovremena imunosupresivna terapija dovodi do signifikantnog kliničkog i radiološkog poboljšanja i sprečava dalja oštećenja, kao i napredak bolesti koja se može manifestovati slepilom, oštećenjem sluha, kao i demencijom. Susakov sindrom zahteva interdisciplinarnu saradnju neurologa, neuroradiologa, oftalmologa i otorinolaringologa.

Ključne riječi: Susakov sindrom, okluzija retinalne arterije, encefalopatija, gubitak sluha, senzoneuralni, imunosupresivni agensi

Susac syndrome - a case report

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Introduction. Susac syndrome (SS) is an extremely rare autoimmune disease characterized by the clinical triad of encephalopathy, branch retinal artery occlusions, and sensorineural hearing loss, caused by an attack of the immune system against the patient's own endothelial cells of the small blood vessels of the brain, eye, and ear (microangiopathy). The disease was first described by John Susac in 1979. It is estimated that there are currently about 700 affected individuals worldwide – although the disease is very often misdiagnosed.

Case report. We present a case of a 33-year-old, previously healthy woman who presented with blurred vision in one eye and strange symptoms of occasional flickering, which, with a normal ophthalmological finding, was interpreted as retinal migraine. Seven months later, she presented with a visual field defect in the left eye and a branch retinal artery occlusion, and two weeks later with a visual field defect in the right eye and another branch retinal artery occlusion. Intravenous Solumedrol therapy was initiated. Brain MRI showed white matter changes, audiometry revealed low-frequency hearing loss, raising suspicion of Susac syndrome. During the diagnostic workup, the patient developed neurological symptoms including dysarthria, dizziness, headache, disorientation, and tingling in the extremities. The diagnosis of Susac syndrome was confirmed, and immunological therapy was started (high-dose corticosteroids as first-line therapy, followed by methotrexate, immunoglobulins, azathioprine, rituximab).

Conclusion. Susac syndrome is a very rare microangiopathy causing symptoms of brain parenchymal disease (encephalopathy, focal neurological deficits, headache), inner ear (hearing loss), and retina (recurrent retinal artery occlusions accompanied by visual field defects). The clinical triad, i.e., simultaneous manifestation of all symptoms, is seen in less than 20% of patients, making the diagnosis of this disease a real challenge. Correct and timely immunosuppressive therapy leads to significant clinical and radiological improvement and prevents further damage and disease progression, which can be manifested as blindness, hearing loss, and dementia. Susac syndrome requires interdisciplinary collaboration among neurologists, neuroradiologists, ophthalmologists, and otorhinolaryngologists.

Key words: Susac syndrome, retinal artery occlusion, encephalopathy, hearing loss, sensorineural, immunosuppressive agents

Procjena perfuzije mrežnjače OCTA kod pedijatrijskih pacijenata sa dijabetes melitusom tipa 1 bez dijabetičke retinopatije

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Cilj ove studije je procena perfuzije mrežnjače optičkom koherentnom tomografskom angiografijom (OCTA) kod pedijatrijskih pacijenata sa dijabetes melitusom tipa 1 (T1D) bez dijabetičke retinopatije (DR). U studiju je uključeno trideset jedan pacijent oboleo od T1D. Svi učesnici su procenjeni pomoću OCTA. Analizirane su fovealna avaskularna zona i gustina površinskih i dubokih makularnih krvnih sudova (VD). Utvrđena je korelacija ovih parametara sa indeksom telesne mase (BMI), glikovanim hemoglobinom (HbA1c) i vrstom insulinske terapije (višestruke dnevne injekcije, MDI u odnosu na kontinuiranu potkožnu infuziju insulina, CSII). Nijedan od OCTA parametara nije se značajno razlikovao između grupa. Nivo HbA1c pacijenata nije uticao ni na jedan od OCTA parametara. Upotreba MDI je težila da smanji parafovealnu i perifovealnu duboku VD u poređenju sa CSII. Povišen BMI je težio da poveća duboku VD. VD i FAZ su normalni kod pubertetske dece sa T1D bez znakova DR. Lečenje sa CSII može biti bolji izbor u poređenju sa MDI, jer CSII može biti zaštitni od oštećenja mikrovaskularnih sudova mrežnjače. Ističemo potrebu za novim kliničkim parametrima kontrole glikemije koji bi mogli da procene rizik od DR.

Ključne riječi: dijabetes melitus tip 1, dijabetička retinopatija, tomografija, optička koherentnost, retinalni sudovi, fovea centralis

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):75

Assessment of retinal perfusion by OCTA in pediatric patients with type 1 diabetes mellitus without diabetic retinopathy

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This study aims to evaluate retinal perfusion by optical coherence tomography angiography (OCTA) in pediatric patients with type 1 diabetes mellitus (T1D) without diabetic retinopathy (DR). Thirty-one patients affected by T1D were enrolled. All participants were evaluated using OCTA. The foveal avascular zone and superficial and deep macular vessel density (VD) were analyzed. The correlation of these parameters with body mass index (BMI), glycated hemoglobin (HbA1c), and the type of insulin therapy (multiple daily injections, MDI vs. continuous subcutaneous insulin infusion, CSII) was determined. None of the OCTA parameters were significantly different among the groups. The patients' HbA1c level did not influence any of the OCTA parameters. The use of MDI tended to reduce the parafoveal and perifoveal deep VD compared to CSII. An elevated BMI tended to increase the deep VD. VD and FAZ were normal in pubescent children with T1D without signs of DR. Treatment with CSII may be a better choice compared to MDI, as CSII may be protective against retinal microvascular damage. We point out the need for novel clinical parameters of glycemic control which could assess the risk of DR.

Key words: diabetes mellitus type 1, diabetic retinopathy, tomography, optical coherence, retinal vessels, fovea centralis

Kad je vreme za vitrektomiju kod Tersonovog sindroma?

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Uvod. Tersonov sindrom predstavlja intraokularno krvarenje koje može nastati kao posledica: subarahnoidalnog krvarenja, intracerebralnog krvarenja i traumatske povrede mozga. Najveći broj ovakvih intraokularnih krvarenja se spontano resorbuje, međutim kod dela ovih pacijenata potrebno je izvršiti operativno lečenje (pars plana vitrektomiju - PPV). Cilj rada je da se analiziraju klinički parametri koji ukazuju na optimalno vreme kada je indikovano hirurško lečenje pacijenata sa Tersonovim sindromom.

Metode. Prikazana je serija slučajeva pacijenata sa dijagnozom Tersonovog sindroma. Svim pacijentima je preoperativno urađen kompletan oftalmološki pregled, merenje nativne i najbolje korigovane vidne oštrine, ultrasonografija.

Rezultati. Kod pacijenata kod kojih je urađena vitrektomija via pars plana do 3 meseca od nastanka intraokularnog krvarenja nije uočena pojava epiretinalnih membrana u makuli, dok kod očiju koje su operisane nakon ovog perioda postojale su epiretinalne membrane u makuli.

Zaključak. Na optimalno vreme kada je potrebno uraditi vitrektomiju kod pacijenata sa Tersonovim sindromom utiče više faktora: opšte i neurološko stanje pacijenta, brzina resorpcije intravitrealnog krvarenja, da li je krvarenje binokularno ili monokularno i da li se ultrazvučnim pregledom uočavaju druge promene na retini.

Ključne reči: Tersonov sindrom, vitrektomija, intraokularno krvarenje, subarahnoidalno krvarenje

When is the optimal time for vitrectomy in Terson syndrome?

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Introduction. Terson syndrome is intraocular hemorrhage that can occur as a consequence of subarachnoid hemorrhage, intracerebral hemorrhage, and traumatic brain injury. Most of such intraocular hemorrhages resolve spontaneously; however, in some patients, surgical treatment (pars plana vitrectomy – PPV) is required. The aim of this work is to analyze the clinical parameters indicating the optimal time for surgical treatment of patients with Terson syndrome.

Methods. A case series of patients diagnosed with Terson syndrome is presented. Preoperatively, all patients underwent a complete ophthalmological examination, measurement of uncorrected and best-corrected visual acuity, and ultrasonography.

Results. In patients who underwent pars plana vitrectomy within three months of the onset of intraocular hemorrhage, no epiretinal membranes in the macula were observed, while eyes operated after this period had epiretinal membranes in the macula.

Conclusion. The optimal timing for vitrectomy in patients with Terson syndrome is influenced by several factors: the patient's general and neurological condition, the rate of intravitreal hemorrhage resorption, whether the hemorrhage is binocular or monocular, and whether other retinal changes are detected by ultrasound examination.

Key words: Terson syndrome, vitrectomy, intraocular hemorrhage, subarachnoid hemorrhage

BIOMEDICINSKA
ISTRAŽIVANJA
2026;17(Suppl 1):78

Primena ultrazvučne dijagnostike kod Graves orbitopatije

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Graves orbitopatija je oboljenje koje može dovesti do oštećenja vida, a javlja se kod osoba sa oboljenjem štitne žlezde. Može se javiti kod pacijenata sa hipertireoidizmom, hipotireoidizmom ili kod eutiroidnih, a posledica je pogrešno usmerenog imunološkog odgovora na tkivo orbite. Najčešće kliničke karakteristike Graves orbitopatije su retrakcija gornjeg kapka, otok i eritem kože kapaka, hiperemija konjunktive i proptoza koja nastaje zbog otoka orbitalnog tkiva uključujući ekstraokularne mišiće. Specifičan izgled pacijenata, kao i pojava duplih slika su razlozi zašto se pacijent nekad javi pre oftalmologu nego endokrinologu. Ultrazvučni pregled orbite sa verifikacijom otoka mišića, kao i masnog tkiva bude sumnju na Graves orbitopatiju, te je zadatak oftalmologa da uputi pacijenta na endokrinološko ispitivanje. Specifičan izgled otečenih mišića, njihova ultrazvučna reflektivnost uz merenje različitih preseka mišića pomaže u postavljanju dijagnoze. Po uvođenju terapije, bilo da je ona bazirana na pulsnim dozama kortikosteroida, drugoj sistemskoj imunomodulatornoj ili biološkoj terapiji, ultrazvukom se može pratiti rezolucija procesa. Tek po ultrazvučnom dokazivanju smirenja procesa, uz laboratorijske nalaze, može se po potrebi primeniti strabološka operacija ili dekompresija orbite. Prednost ultrazvučne dijagnostike u praćenju ovih pacijenata je dostupnost, lakoća primene i izbegavanje štetnih efekata u odnosu na druge dijagnostičke mogućnosti kao što su CT i NMR orbita.

Ključne reči: Gravesova oftalmopatija, bolesti štitaste žlijezde, hipertireoidizam, diplopija, egzoftalmus, orbitalni ultrazvuk

Application of ultrasound diagnostics in Graves orbitopathy

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Graves orbitopathy is a disease that can lead to vision loss occuring in people with thyroid disease. It can occur in patients with hyperthyroidism, hypothyroidism or euthyroid individuals, and it results from a misdirected immune response to orbital tissue. The most common clinical features of Graves orbitopathy are upper eyelid retraction, swelling and erythema of the eyelids, conjunctival hyperemia, and proptosis due to swelling of orbital tissue including the extraocular muscles. The characteristic appearance of patients, as well as the occurrence of diplopia, are reasons why the patient sometimes first consults an ophthalmologist rather than an endocrinologist. Orbital ultrasound examination verifying muscle and fat tissue swelling raises suspicion of Graves orbitopathy, and it is the ophthalmologist's task to refer the patient for endocrinological evaluation. The specific appearance of swollen muscles, their ultrasound reflectivity, and measurement of different muscle cross-sections help in establishing the diagnosis. After initiating therapy, whether based on pulse doses of corticosteroids, other systemic immunomodulatory or biological therapy, ultrasound can be used to monitor resolution of the process. Only after ultrasound evidence of quiescence along with laboratory findings strabismus surgery or orbital decompression can be performed if needed. The advantages of ultrasound diagnostics in monitoring these patients are its availability, ease of use, and avoidance of harmful effects compared to other diagnostic options such as CT and MRI of the orbit.

Key words: Graves ophthalmopathy, thyroid diseases, hyperthyroidism, diplopia, exophthalmos, orbital ultrasonography

Rekonstrukcija kapaka nakon ekscizije malignih tumora: funkcionalni i estetski aspekti

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Rekonstrukcija defekata kapaka nakon ekscizije malignih tumora predstavlja izazovan segment rekonstruktivne i estetske hirurgije zbog kompleksne anatomije kapaka i njihove ključne funkcionalne uloge u zaštiti oka. Cilj ovog rada je prikazati osnovne principe, hirurške opcije i rezultate rekonstrukcije kapaka nakon uklanjanja malignih kožnih tumora. U radu se analiziraju različite rekonstruktivne tehnike u zavisnosti od veličine, lokalizacije i dubine defekta, kao i stanja okolnih tkiva. Mali defekti često se mogu zatvoriti primarnim suturama ili lokalnim režnjevima, dok srednji i veliki defekti zahtijevaju kompleksnije rekonstrukcije poput Mustardeovog i Frikovog režnja. U slučajevima zahvatanja pune debljine kapka, neophodna je slojevita rekonstrukcija koja uključuje rekonstrukciju svih struktura kapka. Poseban naglasak stavljen je na očuvanje funkcionalnosti kapka, uključujući pravilno zatvaranje oka, zaštitu rožnjače i očuvanje estetske simetrije. Komplikacije poput ektropijuma, entropijuma i retrakcije kapka su razmatrane, kao i načini njihove prevencije. Rezultati pokazuju da pažljiv izbor rekonstruktivne tehnike, uz individualizovan pristup pacijentu, omogućava dobre funkcionalne i estetske ishode.

Ključne riječi: neoplazme kapaka, rekonstruktivne hirurške procedure, Mohsova hirurgija, bolesti kapaka, entropijum, ektropijum

Eyelid reconstruction after excision of malignant tumors: functional and aesthetic aspects

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Reconstruction of eyelid defects after excision of malignant tumors is a challenging segment of reconstructive and aesthetic surgery due to the complex anatomy of the eyelids and their key functional role in protecting eyes. The aim of this paper is to present the basic principles, surgical options and results of eyelid reconstruction after removal of malignant skin tumors. The paper analyzes different reconstructive techniques depending on the size, location and depth of the defect, as well as the condition of the surrounding tissues. Small defects can often be closed with primary sutures or local flaps, while medium and large defects require more complex reconstructions such as the Mustarde and Fricke flaps. In cases involving full-thickness eyelid defects, layered reconstruction including reconstruction of all eyelid structures is necessary. Special emphasis is placed on preserving eyelid functionality, including proper eye closure, corneal protection, and maintaining aesthetic symmetry. Complications such as ectropion, entropion, and eyelid retraction are discussed, as well as ways to prevent them. Results show that careful selection of reconstructive technique, with an individualized approach to the patient, enables good functional and aesthetic outcomes.

Key words: eyelid neoplasms, reconstructive surgical procedures, Mohs surgery, eyelid diseases, entropion, ectropion

Razvoj okuloplastične hirurgije u Crnoj Gori

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Okuloplastična hirurgija predstavlja supspecijalističku granu oftalmologije koja obuhvata dijagnostiku i hirurško liječenje oboljenja kapaka, suznog sistema i orbite, kao i estetske zahvate u periokularnoj regiji. U Crnoj Gori ova oblast nije bila jasno definisana do 2019. godine, kada započinje njen savremeni razvoj kroz institucionalnu podršku i međunarodnu saradnju. U radu je prikazan razvoj okuloplastične hirurgije u Kliničkom centru Crne Gore sa osvrtom na uvođenje ključnih procedura kao što su: dakriocistorinostomija (DCR), hirurgija entropijuma i ektropijuma, ptoze, rekonstruktivne tehnike kapaka, kao i savremeni pristupi u liječenju tumora i trauma periokularne regije. Poseban akcenat stavljen je na tehničke, anatomske, organizacione i edukativne izazove u implementaciji ove supspecijalnosti. Prikazani su i klinički rezultati kroz primjere prije i poslije operativnog liječenja, kao i video zapisi. Uprkos ograničenim resursima, kontinuirana edukacija i razvoj hirurških vještina doprinose unapređenju kvaliteta liječenja i smanjenju potrebe za upućivanjem pacijenata u inostranstvo.

Ključne riječi: okuloplastične hirurške procedure, bolesti kapaka, bolesti suznog aparata, bolesti orbite, entropijum, ptoza

Development of oculoplastic surgery in Montenegro

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Oculoplastic surgery is a subspecialty branch of ophthalmology including the diagnosis and surgical treatment of diseases of the eyelids, lacrimal system and orbit, as well as aesthetic procedures in the periocular region. In Montenegro, this area was not clearly defined until 2019, when its modern development began through institutional support and international cooperation. The paper presents the development of oculoplastic surgery at the Clinical Center of Montenegro with a review of the introduction of key procedures such as: dacryocystorhinostomy (DCR), surgery for entropion and ectropion, ptosis, eyelid reconstructive techniques, as well as modern approaches in the treatment of tumors and trauma of the periocular region. Special emphasis is placed on technical, anatomical, organizational and educational challenges in the implementation of this subspecialty. Clinical results are also presented through examples before and after surgical treatment, as well as videos. Despite limited resources, continuous education and development of surgical skills contribute to improving the quality of treatment and reducing the need to refer patients abroad.

Key words: oculoplastic surgical procedures, eyelid diseases, lacrimal apparatus diseases, orbital diseases, entropion, ptosis

Endoftalmitis - kako ga prepoznati, lečiti i spasiti vid?

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Uvod. Endoftalmitis predstavlja tešku intraokularnu inflamaciju staklastog tela i/ili očne vodice, povezanu sa značajnim rizikom od gubitka vida. Postoperativni endoftalmitis predstavlja najčešći oblik egzogenog endoftalmitisa i jednu od najtežih komplikacija intraokularne hirurgije. Savremeni terapijski pristup podrazumeva primenu intravitrealne, sistemske i lokalne antibiotske i antiinflamatorne terapije, dok pars plana vitrektomija (PPV) ima ključnu ulogu kod težih kliničkih oblika. Cilj rada je prikaz dijagnostičkog i terapijskog pristupa pacijentu sa postoperativnim endoftalmitisom.

Prikaz bolesnika. Pacijent se javlja na pregled zbog naglog pada vida na levom oku, 13 dana nakon operacije katarakte levog oka. Status na prijemu: VOD: 0,1 nk. VOS: L+P+; TOD: 13 mmHg, TOS: 10 mmHg; kliničkim pregledom registrovani su edem rožnjače, hipopion, fibrin u prednjoj komori i nemogućnost sagledavanja fundusa levog oka; EHO B scan levog oka pokazao je gusta zamućenja vitreusa sa membranama i trakcijom retine uz plitku ablaciju retine. Po prijemu na kliniku, sprovedena je intenzivna sistemska, kao i lokalna antibiotska i kortikosteroidna terapija, a potom PPV sa eksplantacijom intraokularnog sočiva (IOL), membranektomijom i tamponadom silikonskim uljem. Nakon stabilizacije nalaza na očnom dnu, tri meseca kasnije, učinjena je evakuacija silikonskog ulja i sekundarna implantacija IOL. U postoperativnom periodu postignuti su stabilan nalaz na očnom dnu i funkcionalni oporavak vida (VOD: 0,3 sc; VOS: 0,2–0,3 sc).

Zaključak. Pravovremeno prepoznavanje i urgentno terapijsko zbrinjavanje postoperativnog endoftalmitisa, uz ranu hiruršku intervenciju, od ključnog su značaja za povoljan anatomski i funkcionalni ishod lečenja.

Ključne reči: postoperativni, endoftalmitis, pars plana vitrektomija

Endophthalmitis - how to recognize and treat it, and save vision?

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Introduction. Endophthalmitis is a severe intraocular inflammation of the vitreous body and/or aqueous humor, associated with a significant risk of vision loss. Postoperative endophthalmitis is the most common form of exogenous endophthalmitis and one of the most serious complications of intraocular surgery. The modern therapeutic approach involves intravitreal, systemic and local antibiotic and anti-inflammatory therapy, while pars plana vitrectomy (PPV) plays a key role in more severe clinical forms. The aim is to present diagnostic and therapeutic approaches to a patient with postoperative endophthalmitis.

Case report. A patient presented with sudden vision loss in the left eye, 13 days after cataract surgery on the left eye. Admission status: VOD: 0.1 uncorrected; VOS: light perception with projection; TOD: 13 mmHg, TOS: 10 mmHg; clinical examination revealed corneal edema, hypopyon, fibrin in the anterior chamber, and inability to view the fundus of the left eye; B-scan ultrasound of the left eye showed dense vitreous opacities with membranes and retinal traction along with shallow retinal detachment. Upon admission to the clinic, intensive systemic and local antibiotic and corticosteroid therapy were administered, followed by PPV with intraocular lens (IOL) explantation, membranectomy, and silicone oil tamponade. After stabilization of the fundus findings, three months later, silicone oil removal and secondary IOL implantation were performed. In the postoperative period, a stable fundus finding and functional visual recovery were achieved (VOD: 0.3 uncorrected; VOS: 0.2–0.3 uncorrected).

Conclusion. Timely recognition and urgent therapeutic management of postoperative endophthalmitis, with early surgical intervention, are crucial for a favorable anatomical and functional outcome.

Key words: postoperative, endophthalmitis, pars plana vitrectomy

Uloga vorikonazola i keratoskleroplastike u lečenju akantameba keratitisa komplikovanog skleritisom i sekundarnim glaukomom - prikaz slučaja

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Uvod. Akantameba keratitis predstavlja retku, ali potencijalno veoma ozbiljnu infekciju rožnjače, koja se najčešće javlja kod nosilaca kontaktnih sočiva. Zbog nespecifičnih simptoma i kliničkog toka u početnim fazama bolesti, dijagnoza se često postavlja sa zakašnjenjem, što može dovesti do razvoja teških komplikacija i potrebe za hirurškim lečenjem. Cilj je da se prikaže slučaj pacijentkinje sa komplikovanim tokom akantameba keratitisa udruženog sa anteriornim i posteriornim skleritisom, kao i sekundarnim glaukomom, koji je zahtevao lečenje sklerokeratoplastikom.

Prikaz bolesnika. Pacijentkinja stara 44 godine, dugogodišnji nosilac mekih kontaktnih sočiva, primljena je na Kliniku za očne bolesti 8. aprila 2025. godine zbog apscesa rožnjače desnog oka i izraženog pada vidne oštrine, koja je na prijemu bila L+P+. Mesec dana pre hospitalizacije lečena je u privatnoj zdravstvenoj ustanovi intenzivnom topikalnom kortikosteroidnom terapijom. Po prijemu je započeta intenzivna lokalna i sistemska antiprotozoalna, antibakterijska i antimikotička terapija koja je obuhvatala PHMB, Brolen, moksifloksacin, gentamicin, meropenem, amikacin, vorikonazol i hlorheksidin. Tokom lečenja dolazi do razvoja anteriornog i posteriornog skleritisa, kao i sekundarnog glaukoma. Vorikonazol je uveden kao dodatna terapijska opcija zbog potencijalnog adjuvantnog efekta kod refraktarnih oblika akantameba keratitisa. Nakon postizanja parcijalne stabilizacije infekcije, indikovana je sklerokeratoplastika kao jedina preostala terapijska procedura.

Zaključak. Kod pacijenata sa nepravovremeno prepoznatim i neadekvatno lečenim akantameba keratitisom postoji visok rizik za razvoj ozbiljnih komplikacija. Poseban oprez potreban je kod nosilaca mekih i polutvrdih kontaktnih sočiva, imajući u vidu mogućnost teškog kliničkog toka bolesti. Rana dijagnoza i blagovremeno započinjanje terapije od ključnog su značaja za ishod lečenja. Neracionalna upotreba topikalnih kortikosteroida može dovesti do progresije bolesti, razvoja teške kliničke slike i trajnog gubitka vida. U uznapredovalim slučajevima sa zahvatanjem dubljih očnih struktura i izostankom odgovora na konzervativnu terapiju, sklerokeratoplastika predstavlja opravdan i neophodan terapijski pristup u cilju očuvanja anatomskog i funkcionalnog integriteta oka.

Ključne reči: akantameba keratitis, vorikonazol, sklerokeratoplastika, skleritis, sekundarni glaukom

The role of voriconazole and keratoscleroplasty in the treatment of acanthamoeba keratitis complicated by scleritis and secondary glaucoma - a case report

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Introduction. Acanthamoeba keratitis is a rare but potentially very serious corneal infection, most commonly occurring in contact lens wearers. Due to non-specific symptoms and clinical course in the early stages of the disease, diagnosis is often delayed, which can lead to the development of severe complications and the need for surgical treatment. The aim is to present a case of a patient with a complicated course of Acanthamoeba keratitis associated with anterior and posterior scleritis and secondary glaucoma, which required treatment with sclerokeratoplasty.

Case report. A 44-year-old female, a long-term wearer of soft contact lenses, was admitted to the Eye Clinic on April 8, 2025, due to a corneal abscess of the right eye and severe visual acuity decrease, which was light perception with projection (L+ P+) on admission. One month before hospitalization, she had been treated in a private health facility with intensive topical corticosteroid therapy. Upon admission, intensive local and systemic antiprotozoal, antibacterial and antifungal therapy was initiated, including PHMB, Brolene, moxifloxacin, gentamicin, meropenem, amikacin, voriconazole and chlorhexidine. During treatment, anterior and posterior scleritis and secondary glaucoma developed. Voriconazole was introduced as an additional therapeutic option due to its potential adjuvant effect in refractory forms of Acanthamoeba keratitis. After achieving partial stabilization of the infection, sclerokeratoplasty was indicated as the only remaining therapeutic procedure.

Conclusion. In patients with untimely recognized and inadequately treated Acanthamoeba keratitis, there is a high risk of developing serious complications. Special caution is required in wearers of soft and rigid contact lenses, considering the possibility of a severe clinical course of the disease. Early diagnosis and timely initiation of therapy are crucial for treatment outcome. Irrational use of topical corticosteroids can lead to disease progression, development of a severe clinical picture, and permanent vision loss. In advanced cases with involvement of deeper ocular structures and lack of response to conservative therapy, sclerokeratoplasty represents a justified and necessary therapeutic approach to preserve the anatomical and functional integrity of the eye.

Key words: Acanthamoeba keratitis, voriconazole, sclerokeratoplasty, scleritis, secondary glaucoma

Pioderma gangrenozum - prikaz slučaja

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Uvod. Pioderma gangrenozum je imunska, neinfektivna neutrofilna dermatoza. Bolest je retka, prevalencija iznosi svega 3–10 pacijenata na 1 milion stanovnika. Predilekciona mesta su donji ekstremiteti, kao i trup, a jako retko zahvata oko, orbitu i adnekse. U literaturi je opisan mali broj ovakvih slučajeva (20–34), a još je manji broj onih kod kojih je inflamacijom zahvaćena i orbita (5–7). Lečenje značajno otežava činjenica da je dijagnozu teško postaviti (tek isključivanjem svih drugih infektivnih, autoimunskih i malignih oboljenja koja dovode do ulceracije kože) - u literaturi postoje slučajevi kojima je dijagnoza postavljena i 5 godina po javljanju lekaru.

Prikaz bolesnika. Pacijentkinja starosti 83 godine se javlja oftalmologu zbog enoftalmusa desnog oka, bola, kao i slabijeg vida. Na CT nalazu uočen preseptalni i postseptalni sadržaj, kao i destrukcija koštanih zidova sa fistulama ka frontalnom sinusu i etmoidalnom nazalnom kavumu desno i deformisanim maksilarnim sinusom. Na ultrazvuku uočen retrobulbarno desno pojas niže reflektivnosti koji bi mogao odgovarati inflamaciji. Nakon biopsije tkiva orbite, pacijentkinji se u medijalnom uglu gornjeg desnog kapka javlja nekrotično polje. Potom biopsiju ponavlja i maksilofacijalni hirurg. Zbog brze progresije ulcerozne promene, pacijentkinja se ponovo hospitalizuje na Klinici za očne bolesti UKCS. Pacijentkinja negira prethodne, kao i slične lezije na drugim delovima tela, negira prethodne povrede regije lica (patergija). Pregledana je od strane imunologa, nalazi nisu ukazivali na postojanje sistemskih bolesti veziva, kao ni vaskulitisa. Kod 50% pacijenata nema udruženih sistemskih autoimunskih bolesti (reumatoloških, gastrointestinalnih), kao ni hematoloških, što je slučaj i kod naše pacijentkinje. Infektolog predlaže ponovnu biopsiju i dodatna bojenja, kao i mikrobiološke analize i uvođenje antibiotske terapije. Bris oka je bio pozitivan na Candidu parapsilosis, kao i na Staphylococcus epidermidis, delove fiziološke mikrobiote kože. Pacijentkinja je lečena sistemskom kortikosteroidnom, antibiotskom i antigljivičnom terapijom. Nakon više debridmana rane, u sledećem aktu je urađena enukleacija desne očne jabučice zbog atrofije. Dermatolog savetuje uvođenje Dapsona u redovnu terapiju. Naša pacijentkinja je sada na terapiji Dapsonom i nema progresije bolesti.

Zaključak. Bitan deo lečenja pioderme gangrenosum predstavlja obezboljavanje lezije. U narednom periodu planira se ugradnja očne proteze. Redovno praćenje je od ogromnog značaja jer su recidivi dosta češći kod pacijenata sa orbitalnom inflamacijom (38%). I uz sve praćenje i terapiju, krajnji ishod je neizvestan.

Ključne reči: pioderma gangrenozum, orbitalna inflamacija, biopsija, Dapson

Pyoderma gangrenosum - a case report

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Introduction. Pyoderma gangrenosum is an immune, non-infectious neutrophilic dermatosis. The disease is rare, with a prevalence of only 3–10 patients per 1 million inhabitants. Predilection sites are the lower extremities and trunk, and it very rarely involves the eye, orbit and adnexa. A small number of such cases have been described in the literature (20–34), and an even smaller number with orbital involvement (5–7). Treatment is significantly complicated by the difficulty of diagnosis (only after excluding all other infectious, autoimmune and malignant diseases that lead to skin ulceration) – there are cases in the literature where the diagnosis was made as late as five years after the patient first consulted a doctor.

Case report. An 83-year-old female patient presented to an ophthalmologist with right eye enophthalmos, pain, and reduced vision. CT scan revealed preseptal and postseptal contents, destruction of bone walls with fistulas to the frontal sinus and ethmoidal nasal cavity on the right, and a deformed maxillary sinus. Ultrasound revealed a retrobulbar band of lower reflectivity on the right that could correspond to inflammation. After orbital tissue biopsy, a necrotic area appeared in the medial corner of the right upper eyelid. Maxillofacial surgery then repeated the biopsy. Due to rapid progression of the ulcerative lesion, the patient was re-hospitalized at the Eye Clinic of the University Clinical Centre of Serbia. The patient denied previous or similar lesions on other parts of the body, also denying previous facial trauma (pathergy). She was examined by an immunologist; findings did not indicate the presence of connective tissue diseases or vasculitis. In 50% of patients, there are no associated systemic autoimmune (rheumatological, gastrointestinal) or hematological diseases, which is the case with our patient. An infectious disease specialist recommended repeating biopsy and additional staining, as well as microbiological analyses and the introduction of antibiotic therapy. The eye swab was positive for Candida parapsilosis and Staphylococcus epidermidis, components of the normal skin microbiota. The patient was treated with systemic corticosteroids, antibiotics and antifungals. After multiple wound debridements, enucleation of the right eyeball was performed due to atrophy. A dermatologist advised the introduction of Dapsone into regular therapy. Our patient is now on Dapsone therapy with no disease progression.

Conclusion. Pain management of the lesion is an important part of treating pyoderma gangrenosum. In the future, placement of an ocular prosthesis is planned. Regular follow-up is of great importance because recurrences are much more common in patients with orbital inflammation (38%). Even with all monitoring and therapy, the final outcome is uncertain.

Key words: pyoderma gangrenosum, orbital inflammation, biopsy, Dapsone

Plato iris sindrom kod pacijenta sa miopijom - prikaz slučaja

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Uvod. Plato iris sindrom predstavlja redak uzrok glaukoma zatvorenog ugla koji se češće javlja kod mlađih osoba. Karakteriše ga perzistentno sužen ili zatvoren komorni ugao uprkos prohodnoj perifernoj iridotomiji, usled anteriorno postavljenog cilijarnog tela i perifernog irisa. Rano prepoznavanje i pravovremeno lečenje su od ključnog značaja za sprečavanje trajnog gubitka vida. Cilj je prikazati klinički tok, dijagnostičke karakteristike i terapijski odgovor kod pacijenta sa plato iris sindromom.

Prikaz bolesnika. Pacijent star 45 godina primljen na Kliniku za očne bolesti UKCS, zbog dvodnevnih jakih glavobolja, bola u očima i naglog pada vida obostrano. Pacijent je miop, bez ranijih očnih bolesti. Na prijemu je vidna oštrina na oba oka bila L+P+, registrovane su izrazito visoke vrednosti intraokularnog pritiska (TOD 60 mmHg, TOS 56 mmHg), edem rožnjače, izraženiji na levom oku, plitka prednja očna komora, a goniskopski je obostrano viđen zatvoren komorni ugao. Pri pregledu očnog dna registrovana je ekskavacija papile optičkog živca 0,9 na desnom oku, dok su se detalji očnog dna na levom oku otežano sagledavali. Zbog izraženijeg edema rožnjače na levom oku, bilo je moguće uraditi samo OCT papile optičkog živca desnog oka, na kom je prosečna debljina RNFL 55 µm sa istanjenjima u svim sektorima, najmanje temporalno. Tokom hospitalizacije primao je lokalnu antiedematoznu i antiglaukomnu terapiju, kao i miotik, uz sistemsku antiglaukomnu terapiju, nakon čega je postignuta normalizacija intraokularnog pritiska. Po povlačenju edema rožnjače učinjena je obostrana YAG laser iridotomija, nakon čega je otpušten uz lokalnu i sistemsku antiglaukomnu terapiju. Na kontrolnim pregledima ustanovljeno je ponovno povećanje intraokularnog pritiska na desnom oku uprkos prohodnoj iridotomiji i antiglaukomnoj terapiji, zbog čega je indikovana hirurška intervencija (TTR). Klinički tok i refraktornost na standardno lečenje ukazali su na plato iris sindrom kao mehanizam zatvaranja ugla.

Zaključak. Plato iris sindrom može predstavljati dijagnostički i terapijski izazov, naročito kod mlađih i miopnih pacijenata kod kojih se glaukom zatvorenog ugla ređe očekuje. Perzistencija povišenog intraokularnog pritiska uprkos laserskoj iridotomiji ukazuje na potrebu za daljim praćenjem i blagovremenim hirurškim lečenjem radi očuvanja vidne funkcije.

Ključne reči: plato iris sindrom, miopija, glavobolja, intraokularni pritisak

Plateau iris syndrome in a patient with myopia - a case report

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Introduction. Plateau iris syndrome is a rare cause of angle-closure glaucoma occurring more often in younger individuals. It is characterized by persistent narrowing or closure of the chamber angle despite a patent peripheral iridotomy, due to an anteriorly positioned ciliary body and peripheral iris. Early recognition and timely treatment are crucial for preventing permanent vision loss. We aimed to present the clinical course, diagnostic features and therapeutic response in a patient with plateau iris syndrome.

Case report. A 45-year-old male patient was admitted to the Eye Clinic of the University Clinical Centre of Serbia due to two-day severe headaches, eye pain, and sudden bilateral vision loss. The patient is myopic, with no previous eye diseases. On admission, visual acuity in both eyes was light perception with projection (L+ P+); extremely high intraocular pressure values were recorded (TOD 60 mmHg, TOS 56 mmHg), as well as corneal edema, more pronounced in the left eye, shallow anterior chamber, and gonioscopically, the chamber angle was closed bilaterally. Fundus examination revealed optic disc excavation of 0.9 in the right eye, while details of the left eye fundus were difficult to visualize. Due to more pronounced corneal edema in the left eye, only OCT of the right optic nerve head was possible, which showed an average RNFL thickness of 55 µm with thinning in all sectors, least temporally. During hospitalization, he received local anti-edema and antiglaucoma therapy, as well as miotics, with systemic antiglaucoma therapy, after which intraocular pressure was normalized. After resolution of corneal edema, bilateral YAG laser iridotomy was performed, after which he was discharged on local and systemic antiglaucoma therapy. Follow-up examinations revealed a recurrent increase in intraocular pressure in the right eye despite patent iridotomy and antiglaucoma therapy, which led to the indication for surgical intervention (TTR). The clinical course and refractoriness to standard treatment indicated plateau iris syndrome as the mechanism of angle closure.

Conclusion. Plateau iris syndrome can pose a diagnostic and therapeutic challenge, especially in younger and myopic patients in whom angle-closure glaucoma is less commonly expected. Persistence of elevated intraocular pressure despite laser iridotomy indicates the need for further follow-up and timely surgical treatment to preserve visual function.

Key words: plateau iris syndrome, myopia, headache, intraocular pressure

Virus humane imunodeficijencije i uveitisi

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Uvod. Uveitis je jedna od najčešćih okularnih komplikacija kod pacijenata sa HIV. Preko 50% pacijenata sa HIV prezentuje okularne manifestacije, dok 5–6 puta češće imaju uveitis. Podjela uveitisa kod ovih pacijenata je u 4 kategorije: uveitis indukovan virusom HIV, koinfekcija povezana sa virusom HIV, uveitis imunološkog oporavka i uveitis izazvan lijekovima.

Metode. Analiza stručne literature o kliničkim znacima i terapiji uveitisa izazvanih HIV virusom. Šarolikost kliničke slike prikazujem kroz pet različitih prikaza slučajeva i kako smo ih rješavali hospitalno i ambulantno.

Rezultati. Novija istraživanja ukazuju na učestalost koinfekcije sa TBC i sifilisom. S druge strane, HIV direktno uvećava incidenciju uveitisa. Uveitis imunološkog oporavka kao entitet predstavlja dijagnozu isključenja.

Zaključak. Široka primjena antiretrovirusne terapije u posljednje dvije decenije (ART) značajno dovodi do smanjenja incidencije, izmjene dijagnoze i načina liječenja uveitisa kod ovih pacijenata. Otežavajući faktor u postavljanju dijagnoze je specifičan imunološki status. Svaki pacijent sa sumnjom na uveitis povezan sa HIV infekcijom mora proći kompletno infektološko ispitivanje, broj CD4 limfocita, koncentraciju HIV virusa u serumu, serološka testiranja, dužinu trajanja i način liječenja infekcije.

Ključne riječi: uveitis, HIV infekcije, sindrom imunološke rekonstitucije, tuberkuloza, sifilis, antiretrovirusni agensi

Human immunodeficiency virus and uveitis

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Introduction. Uveitis is one of the most common ocular complications in patients with HIV. Over 50% of HIV patients present with ocular manifestations, and they have uveitis 5–6 times more often. The classification of uveitis in these patients is divided into four categories: HIV-induced uveitis, co-infection associated with HIV, immune recovery uveitis, and drug-induced uveitis.

Methods. Analysis of the professional literature on the clinical signs and therapy of uveitis caused by HIV was done. The diversity of clinical presentation is shown through five different case reports and how they were managed in hospital and outpatient settings.

Results. Recent studies indicate a higher frequency of co-infection with tuberculosis and syphilis. On the other hand, HIV directly increases the incidence of uveitis. Immune recovery uveitis as an entity represents a diagnosis of exclusion.

Conclusion. The widespread use of antiretroviral therapy (ART) in the last two decades significantly reduces the incidence, changes the diagnosis and treatment of uveitis in these patients. A complicating factor in establishing the diagnosis is the specific immune status. Every patient with suspected HIV-related uveitis must undergo a complete infectious disease workup, including CD4 count, serum HIV viral load, serological tests, duration and type of antiretroviral therapy.

Key words: uveitis, HIV infections, immune reconstitution inflammatory syndrome, tuberculosis, syphilis, anti-retroviral agents

Duboki pad vida kao prvi simptom u seriji zanimljivih slučajeva. Šta nam to retina govori?

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Uvod. Zahvaljujući transparentnosti svojih medija, oko omogućava neinvazivno, u realnom vremenu, analiziranje očnih struktura, vaskularne mreže i optičkog nerva kao dijela centralnog nervnog sistema. Razvoj dijagnostičkih aparata omogućio je otkrivanje i suptilnih promjena u strukturi i funkciji oka. Brojna istraživanja pokazala su značaj oka, a posebno retine, u dijagnostici sistemskih oboljenja.

Metode. Prikazana su tri slučaja iz kliničke prakse u kojima je pad vida bio inicijalni simptom i ključan za pokretanje interdisciplinarnog pristupa u otkrivanju sistemske bolesti. Analizirani su dijagnostički protokoli i sprovedena terapija.

Rezultati. U našem slučaju iz kliničke prakse prva manifestacija sarkoidoze je bila bilateralni papilitis i vitritis, bez granulomatoznog uveitisa i vaskulitisa kao karakteristične kliničke slike sarkoidoze. Terapija sa oralnim kortikosteroidima je uspješno sprovedena sa povlačenjem otoka papile i za sada bez relapsa i drugih manifestacija sarkoidoze. Drugi slučaj nam je pokazao da kod prednje ishemijske optičke neuropatije kao uzročnika treba imati na umu i hematološki malignitet i da je AION rijetka, ali rješiva komplikacija HLL. Takođe, vidjeli smo da prateći tragove retine možemo otkriti do tada neprepoznate sistemske bolesti, ordinirati odgovarajuću terapiju i spriječiti komplikacije bolesti na drugim organima.

Zaključak. Retinalne strukture nam omogućavaju rano otkrivanje nekih sistemskih bolesti. Fokus novih istraživanja su retinalni biomarkeri kojima se može predvidjeti i nastanak nekih bolesti. Kako se imidžing dijagnostika neprestano razvija i vještačka inteligencija pridružuje analizi, izvjesno je da je budućnost u retini kao ogledalu opšteg zdravlja organizma.

Ključne riječi: sarkoidoza, edem papile, uveitis, optička neuropatija, ishemijska, retinalno snimanje

Severe vision loss as the first symptom in a series of interesting cases. What does the retina tell us?

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Introduction. Thanks to the transparency of its media, the eye enables non-invasive, real-time analysis of ocular structures, vascular network and optic nerve as the part of the central nervous system. The development of diagnostic devices has enabled the detection of even subtle changes in the structure and function of the eye. Numerous studies have shown the importance of the eye, especially the retina, in the diagnosis of systemic diseases.

Methods. Three cases from clinical practice are presented in which vision loss was the initial symptom and key to initiating an interdisciplinary approach to discovering systemic disease. Diagnostic protocols and administered therapy were analyzed.

Results. In our clinical case, the first manifestation of sarcoidosis was bilateral papillitis and vitritis, without granulomatous uveitis and vasculitis as characteristic features of sarcoidosis. Therapy with oral corticosteroids was successfully administered with resolution of optic disc edema and, so far, no relapse or other manifestations of sarcoidosis. The second case showed us that in anterior ischemic optic neuropathy, hematologic malignancy should also be considered as a cause, and that AION was a rare but treatable complication of CLL. Also, we saw that by following retinal traces we could discover previously unrecognized systemic diseases, prescribe appropriate therapy and prevent complications of the disease in other organs.

Conclusion. Retinal structures enable early detection of some systemic diseases. The focus of new research is retinal biomarkers that can predict the occurrence of some diseases. As imaging diagnostics continuously develops and artificial intelligence joins the analysis, it is clear that the future lies in the retina as a mirror of general health.

Key words: sarcoidosis, papilledema, uveitis, optic neuropathy, ischemic, retinal imaging

Oko kao prva manifestacija Waldenstromove makroglobulinemije

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Uvod. Bilateralna eksudativna ablacija mrežnjače dovela je do dijagnoze Waldenstromove makroglobulinemije. Odvajanje mrežnjače je bilo otporno na medikamentoznu terapiju i odlučili smo se za pars plana vitrektomiju, nakon čega je uslijedila ekscizija granuloma i gustog krvarenja u staklastom tijelu, endolaserska fotokoagulacija i tamponada silikonskim uljem. Hirurško liječenje je bilo uspješno.

Metode. Kompletan pregled oka, ultrazvuk oka, optička koherentna tomografija (OCT), ultra široko fokusna fotografija očnog dna u boji (UWF), vitrektomija pars plana, ekscizija granuloma, endolaserska fotokoagulacija i tamponada silikonskim uljem.

Rezultati. Pacijentkinja stara 62 godine javila se sa iznenadnim bilateralnim gubitkom vida. Prilikom pregleda najbolje korigovana vidna oštrina na desnom oku je bila 0,1, tj. 20/200 (ETDTS slovni rezultat 35), a lijevo osjećaj svjetlosti bez projekcije. Samo 24 h nakon prijema u bolnicu, vidna oštrina na desnom oku se smanjila na osjećaj svjetlosti (VOD: L+P+, VOS: L+P–). Pacijentkinja je podvrgnuta dodatnim hematološkim pregledima, koji su otkrili Waldenstromovu makroglobulinemiju kao uzrok. S obzirom da se vidna oštrina nije popravljala na standardni protokol liječenja WM (plazmafereza, hemoterapija), odlučili smo se za hirurško liječenje desnog oka. Vratili smo djelimičan vid slijepoj pacijentkinji i pacijentkinja je bila izuzetno zadovoljna.

Zaključak. Krvarenje u staklastom tijelu (hemoftalmus) sa ablacijom mrežnjače može biti prva manifestacija Waldenstromove makroglobulinemije i može se uspješno liječiti pars plana vitrektomijom.

Ključne riječi: Waldenstromova makroglobulinemija, ablacija retine, krvarenje u staklastom tijelu, vitrektomija, laserska koagulacija, silikonsko ulje

The eye as the first manifestation of Waldenstrom macroglobulinemia

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Introduction. Bilateral exudative retinal detachment led to the diagnosis of Waldenstrom macroglobulinemia. The retinal detachment was resistant to medical therapy, and we decided on pars plana vitrectomy, followed by excision of granuloma and dense vitreous hemorrhage, endolaser photocoagulation and silicone oil tamponade. Surgical treatment was successful.

Methods. Complete eye examination, ocular ultrasound, optical coherence tomography (OCT), ultra-widefield color fundus photography (UWF), pars plana vitrectomy, granuloma excision, endolaser photocoagulation and silicone oil tamponade were applied.

Results. A 62-year-old female patient presented with sudden bilateral vision loss. On examination, best-corrected visual acuity in the right eye was 0.1, i.e., 20/200 (ETDRS letter score 35), and light perception without projection (L+ P-) in the left eye. Only 24 hours after hospital admission, visual acuity in the right eye decreased to light perception (VOD: LP with projection, VOS: LP without projection). The patient underwent additional hematological examinations, which revealed Waldenstrom macroglobulinemia as the cause. Since visual acuity did not improve on the standard treatment protocol for WM (plasmapheresis, chemotherapy), we decided on surgical treatment of the right eye. We restored partial vision to a blind patient, and the patient was extremely satisfied.

Conclusion. Vitreous hemorrhage (hemophthalmos) with retinal detachment can be the first manifestation of Waldenstrom macroglobulinemia and can be successfully treated with pars plana vitrectomy.

Key words: Waldenstrom macroglobulinemia, retinal detachment, vitreous hemorrhage, vitrectomy, laser coagulation, silicone oil

Više od nedostatka suza: zamke prividne reumatološke dijagnoze - prikaz slučaja

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Uvod. Diferencijalna dijagnoza suvog oka najčešće se fokusira na lokalnu patologiju ili sistemske autoimune bolesti. Međutim, perzistentna hiposekrecija koja ne odgovara adekvatno na konvencionalnu terapiju zahtijeva šire kliničko sagledavanje, uključujući i rijetke neurološke uzroke koji mogu simulirati reumatološka oboljenja.

Prikaz bolesnika. Pacijentkinja B.T. (1983. godište, ženski pol) javila se oftalmologu zbog crvenila, osjećaja stranog tijela i izražene suvoće oba oka. Inicijalni pregled ukazao je na oskudan prekornealni suzni film i tačkastu keratopatiju (Fl+). Zbog izrazito niskih vrijednosti Širmerovog testa (1–2 mm) i niskog TBUT (< 5 sec), pacijentkinja je upućena reumatologu. Postavljena je radna dijagnoza Sjögrenovog sindroma (M35.0), te je uključena sistemska terapija (hidroksihlorokin 200 mg/dan) uz lokalne vještačke suze i gelove. Tokom naredne dvije godine, uprkos redovnoj terapiji, subjektivne tegobe su perzistirale uz povremene egzacerbacije keratitisa i konjunktivitisa. Postepeno se razvijaju novi simptomi: diskretna ptoza desnog oka (1 mm), poteškoće pri fokusiranju na blizinu, te povremeni prolazni gubici vida (amaurosis fugax) na desnom oku u trajanju od nekoliko sekundi. Ključni preokret nastaje na kontrolnom pregledu tri godine nakon prve posjete, kada se pregledom zadnjeg segmenta oka uočava do tada odsutni edem papile vidnog živca (PNO). Hitna MR endokranijuma otkrila je tumorsku promjenu. Pacijentkinja je podvrgnuta neurohirurškom zahvatu. Već mjesec dana nakon operacije, edem papile se povlači, a kornealni nalazi postaju uredni (Fl–). Godinu dana nakon operacije, zabilježen je dramatičan oporavak: Širmerov test se normalizovao na 14 mm, a TBUT na preko 10 sekundi, uz potpuni nestanak simptoma suvoće koji su godinama tretirani kao sistemsko reumatološko oboljenje.

Zaključak. Ovaj slučaj ilustruje klasičnu dijagnostičku zamku gdje se intrakranijalni proces godinama maskirao simptomima suvog oka. Normalizacija suzne sekrecije nakon neurohirurške intervencije dokazuje da je primarni uzrok bio prekid refleksnog luka vlaženja oka usljed tumorske kompresije. Neobjašnjiva suvoća i atipični neurološki znaci (ptoza, amauroze) zahtijevaju hitnu neuroradiološku obradu.

Ključne riječi: sindrom suhog oka, Sjögrenov sindrom, tumori mozga, edem optičkog diska, amauroza fugaks, neurooftalmologija

More than a lack of tears: the pitfalls of an apparent rheumatologic diagnosis - a case report

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Introduction. The differential diagnosis of dry eye most often focuses on local pathology or systemic autoimmune diseases. However, persistent hyposecretion that does not adequately respond to conventional therapy requires broader clinical evaluation, including rare neurological causes that can mimic rheumatologic diseases.

Case report. A female patient B.T. (born 1983) presented to an ophthalmologist with redness, foreign body sensation and marked dryness of both eyes. Initial examination revealed a scant precorneal tear film and punctate keratopathy (Fl+). Due to extremely low Schirmer test values (1–2 mm) and low TBUT (<5 sec), the patient was referred to a rheumatologist. A working diagnosis of Sjögren's syndrome (M35.0) was made, and systemic therapy (hydroxychloroquine 200 mg/day), along with local artificial tears and gels, was initiated. Over the next two years, despite regular therapy, subjective complaints persisted with occasional exacerbations of keratitis and conjunctivitis. New symptoms gradually developed: discrete ptosis of the right eye (1 mm), difficulty focusing on near vision, and occasional transient vision loss (amaurosis fugax) in the right eye lasting a few seconds. The crucial turning point occurred at a follow-up examination three years after the first visit, when examination of the posterior segment revealed previously absent optic disc edema (ODE). Emergency brain MRI revealed a tumor mass. Results. The patient underwent neurosurgery. One month after surgery, the optic disc edema resolved, and corneal findings became normal (Fl–). One year after surgery, dramatic recovery was recorded: Schirmer test normalized to 14 mm, TBUT to over 10 seconds, with complete disappearance of dryness symptoms that had been treated as a systemic rheumatologic disease for years.

Conclusion. This case illustrates a classic diagnostic pitfall where an intracranial process was masked by dry eye symptoms for years. Normalization of tear secretion after neurosurgical intervention proves that the primary cause was interruption of the reflex arc for ocular wetting due to tumor compression. Unexplained dryness and atypical neurological signs (ptosis, amauroses) require urgent neuro-radiological workup.

Key words: dry eye syndromes, Sjögren's syndrome, brain neoplasms, optic disk edema, amaurosis fugax, neuro-ophthalmology

Vaskulitis retine kao posledica sistemskih vaskulitisa

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Vaskulitis retine predstavlja inflamatorno oboljenje koje primarno zahvata komponente krvnih sudova retine i to najčešće njihov endotel, ali i druge strukture mogu biti supstrat za imuni proces. Mogu biti zahvaćene arterije (arteritisi), vene (flebitisi) ili mogu postojati mešovite forme kod kojih su zahvaćene i arterije i vene. Vaskulitis retine može biti posledica sistemskih vaskulitisa, sistemskih infekcija ili mogu postojati kao izolovan oftalmološki entitet.

Sistemski vaskulitisi predstavljaju heterogenu grupu zapaljenskih bolesti koje primarno zahvataju zidove krvnih sudova. Podela se najčešće vrši u zavisnosti od kalibra zahvaćenog krvnog suda prema Chapel Hill konsenzusu na: vaskulitis velikih (Takayasu arteritis, arteritis džinovskih ćelija), srednjih (poliarteritis nodosa, Mb. Kawasaki), malih (ANCA udruženi vaskulitis, mikroskopski poliangiitis, granulomatoza sa poliangiitisom, Churg Strauss Sy, HenochSchonlein purpura (IgA vaskulitis), esencijalna krioglobulinemija), različitog kalibra (Mb. Behcet, Coganov sindrom) i udružen sa sistemskim bolestima (sistemski lupus, reumatoidni vaskulitis, sarkoidni vaskulitis).

Nelečeni vaskulitis retine u sklopu sistemskih vaskulitisa je skopčan sa potencijalnim brojnim komplikacijama poput cistoidnog edema makule, epiretinalnih membrana, okluzije krvnih sudova, neovaskularizacije retine, katarakte, sekundarnog glaukoma i drugo.

Izuzetno je važno tačno utvrditi etiologiju vaskulitisa retine, jer je to od presudnog značaja za lečenje. Ako se dokaže sistemski vaskulitis, lečenje se obavlja u saradnji sa nadležnim lekarom (reumatologom/imunologom), a obuhvata sistemsku primenu imunosupresivne i po potrebi biološke terapije uz dodatak lokalne antiinflamatorne terapije.

U izlaganju će biti prikazani epidemiologija, kliničke manifestacije, dijagnostika, diferencijalna dijagnoza i lečenje najznačajnijih vaskulitisa retine u sklopu sistemskih vaskulitisa.

Ključne reči: vaskulitis retine, sistemski vaskulitis, ANCA udruženi vaskulitis, Behčetova bolest, imunosupresivna terapija, diferencijalna dijagnoza

Retinal vasculitis as a consequence of systemic vasculitis

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Retinal vasculitis is an inflammatory disorder primarily affecting the vascular components of the retina, most frequently targeting the endothelium, although other structural components can also serve as substrates for the immunopathogenic process. The disease can affect the retinal arteries (arteritis), veins (phlebitis), or present as mixed forms involving both vessel types. Retinal vasculitis may manifest secondary to systemic vasculitides, systemic infections, or as an isolated ocular entity.

Systemic vasculitides comprise a heterogeneous group of inflammatory diseases characterized by vessel wall inflammation. According to the Chapel Hill Consensus Conference criteria, they are predominantly classified based on the caliber of the affected blood vessels into: largevessel vasculitis (Takayasu arteritis, giant cell arteritis); mediumvessel vasculitis (polyarteritis nodosa, Kawasaki disease); smallvessel vasculitis (ANCAassociated vasculitis, microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis [ChurgStrauss syndrome], IgA vasculitis [HenochSchönlein purpura], essential cryoglobulinemic vasculitis); variablevessel vasculitis (Behçet's disease, Cogan's syndrome); and vasculitis associated with systemic diseases (systemic lupus erythematosus, rheumatoid vasculitis, sarcoid vasculitis).

Untreated retinal vasculitis secondary to systemic vasculitides is associated with numerous potential complications, including cystoid macular edema, epiretinal membranes, vascular occlusions, retinal neovascularization, cataract, and secondary glaucoma. Accurately determining the precise underlying etiology of retinal vasculitis is critical, as it dictates the therapeutic approach. When a systemic vasculitis is confirmed, management requires close collaboration with the managing specialist (rheumatologist/immunologist) and encompasses systemic immunosuppressive and, if indicated, biologic therapies, supplemented by topical antiinflammatory treatment.

This presentation will review the epidemiology, clinical manifestations, diagnostic strategies, differential diagnosis, and management of the most significant forms of retinal vasculitis associated with systemic vasculitides.

Key words: retinal vasculitis, systemic vasculitis, ANCAassociated vasculitis, Behçet's disease, immunosuppressive therapy, differential diagnosis

Sistemske bolesti i oko u Crnoj Gori

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Dijabetes melitus, hipertenzija i ateroskleroza najčešće dovode do oštećenja krvnih sudova oka. Prevalencija dijabetesa u Crnoj Gori je relativno visoka i predstavlja ozbiljan javnozdravstveni problem. Oko 50.000 osoba u Crnoj Gori ima DM. To je približno 10 posto populacije starije od 20 godina. Oko 21.600 ljudi ima dijabetes, a da ne zna. Broj oboljelih je u stalnom porastu.

Posebno zabrinjava porast dijabetesa kod mladih. Crna Gora spada među zemlje sa visokom učestalošću dijabetesa u Evropi, a razlog je loša ishrana, fizička neaktivnost, gojaznost, stres i savremen način života. Oko 30–35% osoba sa dijabetesom razvije neki oblik dijabetesne retinopatije. Rizik raste sa dužinom trajanja šećerne bolesti, lošom regulacijom šećera, visokim pritiskom i pušenjem. Visok krvni pritisak je sistemska bolest koja utiče na više organa uključujući i oči. Svaka druga odrasla osoba u Crnoj Gori ima povišen krvni pritisak (češće muškarci). Kod hipertoničara na krvnim sudovima oka može biti ispoljena hipertenzivna retinopatija. Osobe sa aterosklerozom mogu imati okluzije arterije i retinalne vene. Ove sistemske bolesti najčešće dovode do oštećenja krvnih sudova oka što posljedično oštećuje vid.

Liječenje vaskularnih bolesti oka u Crnoj Gori može biti hirurški (vitrektomije i laseri), i anti-VEGF terapijom. Pacijenti u Crnoj Gori imaju privilegiju da pod određenim uslovima primaju anti-VEGF terapiju na teret Fonda zdravstva.

Ključne riječi: dijabetes melitus, hipertenzija, ateroskleroza, dijabetesna retinopatija, hipertenzivna retinopatija, okluzija retinalne vene

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):103

Systemic diseases and the eye in Montenegro

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Diabetes mellitus, hypertension, and atherosclerosis represent the primary etiologies of ocular vascular damage. In Montenegro, the prevalence of diabetes mellitus (DM) is remarkably high, posing a critical public health challenge. Approximately 50,000 individuals—representing nearly 10% of the population over the age of 20—are affected by DM. Furthermore, an estimated 21,600 cases remain undiagnosed. The incidence of DM exhibits a continuous upward trend, with a particularly concerning rise among the younger population. Montenegro ranks among the European countries with the highest diabetes rates, heavily driven by poor dietary habits, physical inactivity, obesity, stress, and a sedentary modern lifestyle. Approximately 30% to 35% of diabetic patients develop some form of diabetic retinopathy. This risk increases progressively with longer disease duration, poor glycemic control, concomitant hypertension, and tobacco smoking. Arterial hypertension is a systemic disorder with multiorgan manifestations, significantly affecting the ocular system. Every second adult in Montenegro suffers from elevated blood pressure, with a higher prevalence observed in males. In hypertensive patients, these vascular changes manifest as hypertensive retinopathy. Concurrently, individuals with atherosclerosis are predisposed to retinal arterial and venous occlusions. Ultimately, these systemic pathologies lead to structural damage of the ocular vasculature, resulting in progressive visual impairment. Management of ocular vascular diseases in Montenegro encompasses surgical interventions—including vitrectomy and laser photocoagulation—as well as antiVEGF (vascular endothelial growth factor) therapy. Under designated clinical criteria, patients in Montenegro have the privilege of receiving antiVEGF therapy fully covered by the National Health Insurance Fund.

Key words: diabetes mellitus, hypertension, atherosclerosis, diabetic retinopathy, hypertensive retinopathy, retinal vein occlusion

Neovaskularni glaukom kod sindroma okularne ishemije

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Uvod. Neovaskularni glaukom (NVG) je težak oblik sekundarnog glaukoma koji se karakteriše razvojem neovaskularizacije irisa (NVI) i/ili ugla prednje očne komore koji dovodi do povećanja intraokularnog pritiska (IOP) i zapaljenja prednjeg segmenta oka.

Veći broj stanja kao što su: okluzija arterije centralis retine (OACR), proliferativna dijabetička retinopatija (PDR), okluzija vene centralis retine (OVCR) i okularni ishemijski sindrom (OIS) mogu dovesti do pojave NVG. Dijagnoza NVG postavlja se na osnovu pažljivog kliničkog pregleda prednjeg segmenta oka, irisa i komornog ugla. U liječenju NVG najvažnija je kontrola retinalne ishemije primjenom intravitrealnih anti-VEGF lijekova i panretinalne laserfotokoagulacije, kontrola IOP, kontrola upale primjenom lokalnih kortikosteroidnih kapi i liječenja sistemske bolesti. Cilj ovog rada je da prikaže slučaj NVG kod pacijenta starije životne dobi sa sindromom okularne ishemije lijevog oka.

Prikaz bolesnika. Pacijent, muškarac starosti 71 godinu, se javlja na pregled zbog pada vida i bola u lijevom oku. Primijetio je pad vidne oštrine unazad godinu dana na lijevom oku, izraženije u posljednjih mjesec dana. U ličnoj anamnezi navodi da se liječi zbog HTA i da je pušač. Nalaz na pregledu: VOD: 0.8 s.c.VOS:2/60 nk; TOD: 19 mmHg; TOS:35 mmHg; SpOD: početno mućenje sočiva; SpOS: NVI, početno zamućenje sočiva; FOD: F. atherosclerotic us; FOS: nejasno se sagledava. Na prethodnom nalazu oftalmologa, od prije dvije godine indikovan dopler krvnih sudova vrata, pregled vaskularnog hirurga i neurologa, zbog asimetrije nalaza na očnom dnu kada je uočena blijeda PNO OS, dilatirani venski krvni sudovi, te amaurosis fugax i tranzitorni isemijski atak (TIA). Pacijentu ordinirana lokalna terapija za lijevo oko: Sol. Cosopt 2x1, Sol. Alphagan 2x1, Sol. Atropin 1%, Sol. Prednizolon 3x1 i tbl. Diamox 1x1. Indikuje se ponovni pregled neurologa, interniste, dopler krvnih sudova vrata i pregled vaskularnog hirurga. Na kontrolnom pregledu: TOD: 18 mmg, TOS: 26 mmHg. Pacijent pregledan od strane vaskularnog hirurga: Dg. Sklerozantna karotidna bolest. Stenoza a. CCint. 70%. Pacijentu predloženo operativno liječenje.

Zaključak. Neovaskularni glaukom je teška i razarajuća bolest koja može da dovede do sljepila. Nastaje na terenu produžene ishemije zadnjeg segmenta oka ili lokalizovane hipoksije prednjeg segmenta oka sa posljedičnom fibrovaskularnom proliferacijom koja dovodi do opstrukcije trabekularne mreže komornog ugla, povećanja IOP i oštećenja optičkog nerva. Veoma je važno da se u sklopu NVG prepoznaju sistemske bolesti koje doprinose nastanku NVG, kao što je npr. stenoza karotidnih arterija jer predstavlja stanje koje može da ugrozi ne samo vid, već i život oboljele osobe. Multidisciplinarni pristup, pravovremeni i odgovarajući tretman osnovnog uzroka ishemije i kontrola IOP su ključ liječenja ovog ozbiljnog oboljenja.

Ključne riječi: neovaskularni glaukom, okularni ishemijski sindrom, multidisciplinarni pristup

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):105

Neovascular glaucoma in ocular ischemic syndrome

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Introduction. Neovascular glaucoma (NVG) is a severe form of secondary glaucoma characterized by neovascularization of the iris (NVI) and/or the anterior chamber angle, leading to elevated intraocular pressure (IOP) and anterior segment inflammation. Numerous conditions, including central retinal artery occlusion (CRAO), proliferative diabetic retinopathy (PDR), central retinal vein occlusion (CRVO), and ocular ischemic syndrome (OIS), can induce NVG. The diagnosis of NVG is established through a meticulous clinical examination of the anterior segment, iris, and chamber angle. The primary management strategies for NVG include mitigating retinal ischemia via intravitreal antiVEGF therapy and panretinal laser photocoagulation, regulating IOP, controlling inflammation with topical corticosteroid drops, and treating the underlying systemic disease. This study aims to report a case of NVG secondary to ocular ischemic syndrome in an elderly patient.

Case report. A 71yearold male presented with a decline in visual acuity and pain in his left eye. The patient reported a progressive decrease in vision over the past year, which became more pronounced during the preceding month. His medical history was significant for arterial hypertension and chronic tobacco smoking. Clinical examination findings were as follows: visual acuity of the right eye (VOD): 0.8 s.c.; visual acuity of the left eye (VOS): 2/60 n.c.; intraocular pressure of the right eye (TOD): 19 mmHg; intraocular pressure of the left eye (TOS): 35 mmHg. Slitlamp examination of the right eye (SpOD) revealed earlystage nuclear sclerosis, while the left eye (SpOS) exhibited NVI and earlystage nuclear sclerosis. Fundoscopy of the right eye (FOD) demonstrated atherosclerotic retinopathy (fundus atherosclerоticus), whereas the left fundus (FOS) was poorly visualized. A prior ophthalmological evaluation from two years earlier had recommended a carotid Doppler ultrasound, a vascular surgery consultation, and a neurological assessment due to funduscopic asymmetry characterized by a pale optic nerve head in the left eye, dilated retinal veins, along with a history of amaurosis fugax and transient ischemic attack (TIA). The patient was prescribed a local therapeutic regimen for the left eye consisting of Sol. Cosopt 2×1, Sol. Alphagan 2×1, Sol. Atropine 1%, Sol. Prednisolone 3×1, and systemic administration of Tab. Diamox 1×1. Repeat consultations with a neurologist, an internist, a vascular surgeon, and a followup carotid Doppler ultrasound were indicated. At the followup examination, IOP measurements were TOD: 18 mmHg and TOS: 26 mmHg. The vascular surgery evaluation confirmed a diagnosis of sclerotic carotid artery disease with 70% internal carotid artery stenosis, and surgical intervention was recommended.

Conclusion. Neovascular glaucoma is a severe, devastating disease that can result in irreversible blindness. It arises from prolonged ischemia of the posterior segment or localized hypoxia of the anterior segment, with subsequent fibrovascular proliferation leading to trabecular meshwork obstruction, elevated IOP, and optic nerve damage. Within the clinical spectrum of NVG, it is critical to identify contributing systemic pathologies such as carotid artery stenosis, as it constitutes a condition that threatens not only vision but also the patient's life. A multidisciplinary approach, timely and appropriate management of the underlying ischemic cause, and rigorous IOP control are paramount in treating this grave condition.

Key words: neovascular glaucoma, ocular ischemic syndrome, multidisciplinary approach

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):106

Da li je keratokonus samo bolest mladih? - prikaz slučaja

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Uvod. Keratokonus je progresivna ektatična bolest rožnjače koja najčešće napreduje u mlađem životnom dobu, dok se nakon četvrte decenije života očekuje usporavanje ili stabilizacija bolesti usled prirodnog povećanja rigidnosti kolagena rožnjače. Ipak, pojedini pacijenti mogu pokazivati progresiju bolesti i u kasnijem životnom dobu, što ukazuje na značaj dugoročnog praćenja.

Prikaz bolesnika. Prikazujemo slučaj pacijenta muškog pola M.S. kod kojeg je keratokonus dijagnostikovan u 36. godini života (OD: K1 43,7; K2 49,5; Kmax 50,6; CCT 498; OS K1 42,8 k2 45,7; Kmax 48,5; CCT 498), a nakon šestomesečnog praćenja klinički i tomografski (Wave Light Oculyzer II) otkrivena je progresija na desnom oku. Zbog dokumentovane progresije keratokonusa desnog oka, avgusta 2020. godine (VOD: 4/60 cc 0,2 OD: K1 44,0 D, K2 49,3, Kmax 54,3, CCT 503 µm, VOS: 3/60, cc 0,3, OS: K1 43,0, OS 45,3, Kmax 48,7, CCT 511 µm) urađen je crosslinking (CXL) desnog oka standardnim Drezdenskim protokolom (epioff, 0,1% riboflavin u metilcelulozi i iradijacija UV lampom 370 nm, 3 mW/cm^2 tokom 30 min, s ukupnom dozom od 5,4 J/cm^2) nakon čega je postignuta stabilizacija nalaza bez znakova dalje progresije.

Levo oko je tokom inicijalnog praćenja pokazivalo stabilne parametre, bez indikacija za CXL. Međutim, tokom daljeg praćenja, nakon 6 godina, u 42. godini života registrovani su znaci progresije bolesti u vidu povećanja keratometrijskih vrednosti, promena na tomografskim mapama i progresivnog ispupčenja zadnje strane rožnjače (OS: K1 43,6, OS 45,1, Kmax 51,6, CCT 512 µm, zbog čega je u martu 2026. godine urađen CXL i na levom oku (Drezdenski protokol). Na poslednjem kontrolnom pregledu zapažena stabilizacija tomografskih parametara.

Pacijent postiže korekciju vidne oštrine RGP kontaktnim sočivima (VOU: ccs 0,4).

Zaključak. Iako se keratokonus tradicionalno smatra bolešću mlađih osoba, ovaj slučaj potvrđuje da progresija može biti prisutna i nakon 40. godine života. Asinhrona progresija između očiju dodatno naglašava potrebu za individualizovanim pristupom i kontinuiranim praćenjem svih pacijenata sa keratokonusom, bez obzira na životnu dob. Pravovremeno prepoznavanje progresije omogućava adekvatnu indikaciju za CXL i očuvanje vidne funkcije.

Ključne reči: keratokonus, umrežavanje kolagena rožnjače (CXL), progresija bolesti, kasna progresija bolesti, tomografija rožnjače, dugoročno praćenje

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):107

Is keratoconus exclusively a disease of the youth? - a case report

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Introduction. Keratoconus is a progressive ectatic corneal disorder that characteristically advances during youth and early adulthood. Following the fourth decade of life, the disease is generally expected to decelerate or stabilize due to the natural, agerelated increase in corneal collagen rigidity. Nevertheless, certain patients may exhibit disease progression later in life, underscoring the critical clinical importance of longterm longitudinal monitoring.

Case report. We report the case of a male patient (M.S.) diagnosed with keratoconus at 36 years of age (right eye [OD]: K1: 43.7 D, K2: 49.5 D, Kmax: 50.6 D, central corneal thickness [CCT]: 498 µm; left eye [OS]: K1: 42.8 D, K2: 45.7 D, Kmax: 48.5 D, CCT: 498 µm). Following a sixmonth observation period, clinical and tomographic evaluation (WaveLight Oculyzer II) revealed disease progression in the right eye. Due to documented progression, the right eye underwent corneal collagen crosslinking (CXL) in August 2020 (preoperative findings—VOD: 4/60 c.c. 0.2; OD: K1: 44.0 D, K2: 49.3 D, Kmax: 54.3 D, CCT: 503 µm; VOS: 3/60 c.c. 0.3; OS: K1: 43.0 D, K2: 45.3 D, Kmax: 48.7 D, CCT: 511 µm). The procedure was performed utilizing the standard Dresden protocol (epioff, 0.1% riboflavin in methylcellulose, and ultravioletA irradiation at 370 nm with an irradiance of 3 mW/cm^2 for 30 minutes, delivering a total surface dose of 5.4 J/cm^2). Postoperatively, stabilization of the right eye was achieved with no signs of further ectatic progression. During the initial followup, the left eye demonstrated stable parameters, with no indication for CXL. However, during subsequent longterm monitoring six years later, at 42 years of age, signs of disease progression were recorded in the left eye, characterized by an increase in keratometric values, alterations on tomographic maps, and progressive steepening of the posterior corneal surface (OS: K1: 43.6 D, K2: 45.1 D, Kmax: 51.6 D, CCT: 512 µm). Consequently, in March 2026, CXL was performed on the left eye using the Dresden protocol. At the final followup examination, stabilization of tomographic parameters was observed. The patient achieves optimal visual acuity correction utilizing rigid gas permeable (RGP) contact lenses (VOU: c.c.s. 0.4).

Conclusion. Although keratoconus is traditionally considered a pathology of younger individuals, this case confirms that ectatic progression can persist beyond the age of 40. Furthermore, the asynchronous progression between the eyes highlights the necessity of an individualized approach and continuous monitoring for all keratoconus patients, irrespective of age. Timely identification of progression allows for the precise indication of CXL, thereby preserving visual function.

Key words: keratoconus, corneal collagen crosslinking (CXL), disease progression, late disease progression, corneal tomography, longterm monitoring

Tumor optičkog nerva

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Uvod. Tumori optičkog nerva, iako su pretežno benigni, zbog svog anatomskog položaja mogu dovesti do teškog oštećenja vida. U radu su prikazani klinički i dijagnostički nalazi intraorbitalnog tumora optičkog nerva kod muškarca starosti 64 godine.

Prikaz slučaja. Muškarac starosti 64 godine upućen je na oftalmološki pregled nakon što je magnetnom rezonancom (MR) postavljena sumnja na intraorbitalni tumor desnog optičkog nerva. Pacijent je naveo progresivno pogoršanje vida tokom prethodne godine, sa izraženim gubitkom vida u poslednjih mesec dana. U anamnezi su navedeni nedovoljno kontrolisan glaukom otvorenog ugla i arterijska hipertenzija. Oftalmološkim pregledom utvrđeni su očuvana percepcija svetlosti na desnom oku, očuvana vidna oštrina levog oka, povišen intraokularni pritisak desnog oka (24 mmHg), relativni aferentni pupilarni defekt, blaga proptoza i nepravilan položaj desne očne jabučice. Pregledom očnog dna uočeni su bledilo papile optičkog nerva i povećana ekskavacija. Optičkom koherentnom tomografijom utvrđeni su odnos ekskavacije i prečnika papile (C/D) od 0,85 i istanjenje sloja nervnih vlakana mrežnjače u gornjem i donjem kvadrantu desnog oka. Propisana je lokalna antiglaukomska terapija, a pacijent je upućen u tercijarnu zdravstvenu ustanovu radi dalje dijagnostičke obrade i lečenja.

Zaključak. Progresivan jednostrani gubitak vida praćen proptozom, poremećajem položaja očne jabučice i promenama na papili optičkog nerva zahteva detaljan oftalmološki pregled i neuroradiološku dijagnostiku orbite. Lečenje tumora optičkog nerva zahteva multidisciplinarni pristup, uzimajući u obzir karakteristike tumora, njegovu anatomsku proširenost i prognozu vidne funkcije.

Ključne reči: optički nerv, retrobulbarni tumor, gubitak vida

Optic nerve tumor

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Introduction. Optic nerve tumors, although predominantly benign, may cause severe visual impairment due to their anatomical location. This report presents the clinical and diagnostic findings of an intraorbital optic nerve tumor in a 64-year-old male patient.

Case Report. A 64-year-old man was referred for ophthalmological evaluation following magnetic resonance imaging (MRI) findings suggestive of a right intraorbital optic nerve tumor. He reported progressive visual deterioration over one year, with profound visual loss during the preceding month. His medical history included poorly controlled open-angle glaucoma and arterial hypertension. Ophthalmological examination revealed light perception in the right eye, preserved visual acuity in the left eye, elevated right intraocular pressure (24 mmHg), a relative afferent pupillary defect, mild proptosis, and abnormal positioning of the right globe. Fundoscopy demonstrated mild optic disc pallor and increased cupping. Optical coherence tomography revealed a cup-to-disc ratio of 0.85 and retinal nerve fiber layer thinning in the superior and inferior quadrants of the right eye. Topical antiglaucoma treatment was prescribed, and the patient was referred to a tertiary center for further evaluation and management.

Conclusion. Progressive unilateral visual loss accompanied by proptosis, ocular misalignment, and optic disc abnormalities warrants comprehensive ophthalmological examination and orbital neuroimaging. Management of optic nerve tumors requires a multidisciplinary approach guided by tumor characteristics, anatomical extension, and visual prognosis.

Key words: optic nerve, retrobulbar tumor, vision loss

Okulomika i okulometrija

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Od izuma oftalmoskopa 1851. godine, oftalmologija je evoluirala daleko izvan granica bolesti oka, pružajući uvid u opšte (sistemsko) zdravlje. Oko, a naročito retina (mrežnjača), pruža dragocene informacije o različitim sistemskim stanjima, omogućavajući kliničarima da prepoznaju karakteristične intraokularne znake kada se pacijenti jave sa određenim kliničkim simptomima. Još važnije, snimanje retine može otkriti subkliničke promene rane pokazatelje bolesti pre pojave simptoma. Ovo presimptomatsko otkrivanje omogućava pravovremenu intervenciju, pomažući da se spreče nepovratna oštećenja i očuva kvalitet života pacijenata.

Nedavni napredak u oblasti veštačke inteligencije (AI) transformisao je analizu slika retine identifikovanjem suptilnih retinalnih biomarkera povezanih sa sistemskim bolestima, kao što su hipertenzija i dijabetes. Ova stanja često prolaze neprimećeno tokom rutinskih pregleda, ali se sada mogu otkriti u najranijim fazama pomoću algoritama zasnovanih na veštačkoj inteligenciji.

Ovaj proboj doprinosi razvoju dve nove naučne discipline, okulomike i okulometrije, koje proučavaju odnos između očnih biomarkera i pokazatelja opšteg zdravstvenog stanja.

Integracija veštačke inteligencije u oftalmološku dijagnostiku ima duboke kliničke i ekonomske implikacije. Ranim otkrivanjem sistemskih bolesti, kliničari mogu započeti blagovremeno lečenje i sprečiti ozbiljne komplikacije, kao što su moždani i srčani udar. Ovakav proaktivan pristup ne samo da poboljšava ishode lečenja, već i značajno smanjuje troškove zdravstvene zaštite povezane sa lečenjem uznapredovalih stadijuma bolesti. Stoga se oftalmologija sve više nameće kao ključni činilac u prediktivnoj i preventivnoj medicini, pružajući dragocene informacije za upravljanje opštim zdravstvenim stanjem.

Ključne reči: oftalmoskopija, mrežnjača (retina), veštačka inteligencija, biomarkeri, hipertenzija, dijabetes melitus

Oculomics and oculometrics

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Since the invention of the ophthalmoscope in 1851, ophthalmology has evolved far beyond the boundaries of eye disease, offering a window into systemic health. The eye, particularly the retina, provides valuable insights into various systemic conditions, allowing clinicians to detect characteristic intraocular signs once patients present with particular clinical symptoms. More importantly, retinal imaging can reveal subclinical changes—early indicators of diseases before symptom onset. This presymptomatic detection enables timely intervention, helping to prevent irreversible damage and preserve patients' quality of life.

Recent advancements in artificial intelligence (AI) have transformed retinal image analysis by identifying subtle retinal biomarkers associated with systemic diseases such as hypertension and diabetes. These conditions often go unnoticed in routine examinations but can now be detected at their earliest stages through AIbased algorithms. This breakthrough contributes to the rise of two novel scientific disciplines—oculomics and oculometrics—which explore the relationship between ocular biomarkers and systemic health metrics.

The integration of AI into ophthalmic diagnostics has profound clinical and economic implications. By identifying systemic diseases early, clinicians can initiate prompt treatment and prevent severe complications such as stroke and heart attack. This proactive approach not only improves patient outcomes but also significantly reduces healthcare costs associated with managing diseases in advanced stages. Ophthalmology is therefore emerging as a key player in predictive and preventive medicine, offering valuable information for systemic health management.

Key words: ophthalmoscopy, retina, artificial intelligence, biomarkers, hypertension, diabetes mellitus

Paraneoplastični sindromi sa očnim manifestacijama: imunopatogeneza, klinička prezentacija i onkološke implikacije

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Uvod. Paraneoplastični sindromi sa očnim manifestacijama predstavljaju retka, ali klinički značajna imunski posredovana stanja koja mogu prethoditi dijagnozi maligniteta i imati važne dijagnostičke i prognostičke implikacije. Cilj ovog rada je da prikaže savremena saznanja o imunopatogenezi, kliničkim karakteristikama, dijagnostičkom pristupu i onkološkom značaju ovih sindroma.

Metode. Rad predstavlja narativni pregled literature zasnovan na analizi relevantnih publikacija dostupnih u bazama podataka PubMed, Scopus i Web of Science, objavljenih u periodu od 2000. do 2025. godine. Zbog heterogenosti u dizajnu studija i prijavljenim ishodima, podaci su sintetizovani kvalitativnim pristupom.

Rezultati. Patogeneza ovih sindroma zasniva se na unakrsnoj imunskoj reaktivnosti između tumorskih i očnih antigena, što dovodi do oštećenja retine ili optičkog živca putem autoantitela, ćelijski posredovanog imuniteta i rastvorljivih medijatora. Klinička slika najčešće obuhvata subakutno, bilateralno pogoršanje vida praćeno fotopsijama, skotomima, niktalopijom i poremećajima kolornog vida. Retinopatija udružena sa karcinomom povezuje se sa prisustvom antiretinalnih antitela i brzom disfunkcijom fotoreceptora. Retinopatija udružena sa melanomom karakteriše se povezanošću sa metastatskim melanomom, prisustvom TRPM1 antitela i elektronegativnim elektroretinogramom. Paraneoplastična optička neuropatija, uključujući CRMP5 asocirane forme, može imitirati inflamatorne i infektivne bolesti optičkog živca, što zahteva pažljivu diferencijalnu dijagnozu.

Zaključak. Pravovremeno prepoznavanje ovih stanja ima ključni značaj za rano otkrivanje maligniteta i započinjanje adekvatnog lečenja. Terapijski pristup obuhvata lečenje osnovne neoplazme uz primenu imunomodulatorne terapije prilagođene kliničkom fenotipu. Savremena onkološka terapija, uključujući inhibitore imunskih kontrolnih tačaka, dodatno usložnjava dijagnostiku i lečenje, što naglašava značaj multidisciplinarnog pristupa.

Ključne reči: paraneoplastični očni sindromi, retinopatija udružena sa karcinomom, retinopatija udružena sa melanomom, paraneoplastična optička neuropatija, antiretinalna antitela, elektroretinografija

Paraneoplastic syndromes with ocular manifestations: immunopathogenesis, clinical presentation, and oncological implications

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Introduction. Paraneoplastic syndromes with ocular manifestations represent rare but clinically significant immunemediated conditions that can precede the diagnosis of an underlying malignancy, thereby carrying critical diagnostic and prognostic implications. This study aims to review contemporary insights regarding the immunopathogenesis, clinical characteristics, diagnostic approaches, and oncological significance of these syndromes.

Methods. This study is a narrative literature review based on the analysis of relevant publications retrieved from the PubMed, Scopus, and Web of Science databases published between 2000 and 2025. Due to the heterogeneity in study designs and reported outcomes, data synthesis was performed using a qualitative approach.

Results. The pathogenesis of these syndromes is driven by immune crossreactivity between tumorspecific and ocular antigens, resulting in retinal or optic nerve damage mediated by autoantibodies, cellmediated immunity, and soluble inflammatory factors. The clinical presentation characteristically involves subacute, bilateral visual deterioration accompanied by photopsias, scotomas, nyctalopia, and dyschromatopsia (color vision disturbances). Cancerassociated retinopathy (CAR) is strongly linked to the presence of antiretinal antibodies and rapid photoreceptor dysfunction. Melanomaassociated retinopathy (MAR) is highly correlated with metastatic melanoma, the presence of antiTRPM1 antibodies, and an electronegative electroretinogram (ERG). Paraneoplastic optic neuropathy, including CRMP5associated variants, can mimic inflammatory or infectious optic nerve disorders, necessitating a meticulous differential diagnosis.

Conclusion. Timely recognition of these conditions is of paramount importance for the early detection of occult malignancies and the prompt initiation of appropriate therapy. The management strategy encompasses treating the primary neoplasm combined with immunomodulatory therapy tailored to the specific clinical phenotype. Modern oncological therapies, including immune checkpoint inhibitors, further complicate both diagnostics and treatment, thereby highlighting the absolute necessity of a multidisciplinary approach.

Key words: paraneoplastic ocular syndromes, cancerassociated retinopathy, melanomaassociated retinopathy, paraneoplastic optic neuropathy, antiretinal antibodies, electroretinography

Vasculitis retinae u sklopu morbus Takayasu: prikaz slučaja

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Uvod. Takayasu arteritis predstavlja rijedak hronični granulomatozni vaskulitis velikih krvnih sudova koji primarno zahvata aortu i njene glavne grane. Oftalmološke manifestacije bolesti mogu biti značajan pokazatelj aktivnosti bolesti, dok retinalni vaskulitis predstavlja rijetku, ali potencijalno ozbiljnu komplikaciju koja može dovesti do trajnog oštećenja vida.

Prikaz bolesnika. Kod pacijentkinje stare 52 godine ispoljio se nagli pad vida na desnom oku praćen glavoboljom i klaudikacijama gornjih ekstremiteta. Oftalmološkim pregledom registrovana je vidna oštrina desnog oka 2/60, uz prisustvo mrljastih retinalnih hemoragija i izraženih eksudativnih promjena u makularnoj regiji, dok je nalaz na lijevom oku bio uredan. Fluoresceinska angiografija ukazala je na promjene u skladu sa retinalnim vaskulitisom. Anamnestički je navodila višegodišnje smanjenje pulsa na lijevoj ruci, kao i razliku vrijednosti krvnog pritiska na desnoj i lijevoj ruci. Kliničkim pregledom registrovana je značajna razlika u arterijskom pritisku između ruku (TA desno 180/130 mmHg, lijevo 130/100 mmHg). Dopler krvnih sudova vrata pokazao je subclavian steal sindrom, dok je MSCT arteriografija verifikovala subtotalnu stenozu lijeve arterije subklavije. Laboratorijski nalazi ukazivali su na izraženu inflamatornu aktivnost (SE 53/81, fibrinogen 21,1, CRP 7,55), dok su imunološke analize bile negativne. Na osnovu kliničkih, laboratorijskih i radioloških kriterijuma postavljena je dijagnoza Takayasu arteritis. U terapiju su uvedeni pulsni ciklusi ciklofosfamida uz visoke doze glikokortikoida, a planirana je i endovaskularna implantacija stenta u lijevu arteriju subklaviju.

Zaključak. Retinalni vaskulitis sa zahvatanjem makularne regije može predstavljati značajnu oftalmološku manifestaciju Takayasu arteritisa i biti jedan od prvih znakova sistemskog vaskulitisa. Pravovremeno prepoznavanje oftalmoloških i vaskularnih simptoma omogućava rano postavljanje dijagnoze i adekvatno liječenje u cilju prevencije trajnih komplikacija i očuvanja vidne funkcije.

Ključne riječi: vaskulitis retine, Takayasu sy, fluoresceinska angiografija, MSCT arteriografija

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):115

Retinal vasculitis in Takayasu's arteritis: a case report

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Introduction. Takayasu's arteritis is a rare, chronic granulomatous largevessel vasculitis primarily affecting the aorta and its major branches. Ophthalmological manifestations of this disease can serve as a significant indicator of disease activity, while retinal vasculitis represents a rare but potentially severe complication that can result in permanent visual impairment.

Case report. A 52yearold female presented with a sudden decline in the visual acuity of her right eye, accompanied by headache and upper extremity claudication. Upon ophthalmological examination, the visual acuity of the right eye was 2/60, with the presence of blot retinal hemorrhages and pronounced exudative changes within the macular region, while the findings in the left eye were unremarkable. Fluorescein angiography demonstrated changes consistent with retinal vasculitis. Her medical history revealed a multiyear history of a diminished pulse in the left arm, as well as an asymmetry in blood pressure readings between the right and left arms. Clinical evaluation recorded a significant interarm arterial pressure discrepancy (blood pressure: right arm 180/130 mmHg, left arm 130/100 mmHg). Carotid and upper extremity Doppler ultrasound demonstrated a subclavian steal syndrome, while multislice computed tomography (MSCT) angiography verified a subtotal stenosis of the left subclavian artery. Laboratory investigations indicated highly elevated inflammatory activity (erythrocyte sedimentation rate [ESR]: 53/81 mm/h; fibrinogen: 21.1 g/L; Creactive protein [CRP]: 7.55 mg/L), whereas immunological serology yielded negative results. Based on clinical, laboratory, and radiological criteria, a diagnosis of Takayasu's arteritis was established. The therapeutic regimen was initiated with pulse cycles of cyclophosphamide combined with highdose glucocorticoids, and an endovascular stent implantation within the left subclavian artery was planned.

Conclusion. Retinal vasculitis with macular involvement can represent a prominent ophthalmological manifestation of Takayasu's arteritis and may serve as one of the sentinel signs of this systemic vasculitis. Timely recognition of both ocular and vascular symptoms facilitates early diagnosis and appropriate therapeutic intervention, which are essential for preventing permanent complications and preserving visual function.

Key words: retinal vasculitis, Takayasu's arteritis, fluorescein angiography, MSCT angiography

AMD exudativa - da ili ne?

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Uvod. Senilna degeneracija makule (AMD) predstavlja jedan od glavnih uzroka sljepila kod starije populacije. AMD se javlja u dva oblika, AMD sicca i AMD exudativa. Eksudativna ili vlažna forma bolesti se odlikuje pojavom neovaskularizacije, krvarenja i edema u makuli. Druge promjene na očnom dnu, kao što su amelanotični melanom horoideje, metastatske tumorske promjene mogu da imitiraju neobične forme AMD eksudativa. Zbog toga je kod onkoloških pacijenata i atipičnih oftalmoskopskih nalaza neophodna detaljana dijagnostička obrada. Cilj rada je bio da prikaže slučaj prominentne promjene u makuli kod onkološkog pacijenta starije životne dobi.

Prikaz slučaja. Pacijent, muškarac starosti 69 godina, se javlja na pregled zbog slabe vidne oštrine i pojave crne mrlje ispred desnog oka poslije operacije katarakte. Primijetio pad vidne oštrine unazad godinu dana na oba oka, više desno. Operisao kataraktu na desnom oku nedjelju dana prije pregleda (preoperativna VOD: L+P+). U ličnoj anamnezi navodi da se liječi zbog HTA, HLP i da je 2019. godine operisao karcinom pluća. Nalaz pri pregledu: VOD: 2/60 n.k; VOS:0,9; TOU: 15 mmHg; BMOD: IOL na mjestu, ostali nalazi uredni. BMOS: početno zamućenje sočiva, ostali nalazi uredni. FOD: PNO jasno ograničena, u ravni retine, u predjelu makule vidljiva promjena koja prominira, nejasno ograničena sa zonama hipo i hiperpigmentacije, kao i okolnim krvarenjem oko promjene. FOS: Druze u makuli. F. atherosclerotic us. Pacijentu urađena dodatna dijagnostička obrada: OCT ML, OCT PNO, foto fundus, fluoresceinska angiografija. Zbog postojanja promjena na lijevom oku koje odgovaraju AMD sicca, postavljena sumnja na AMD eksudativa na desnom oku, ali zbog podatka o liječenju karcinoma pluća, pacijent upućen na dodatnu dijagnostičku obradu: B scan, ICGA, pregled pulmologa, onkologa, kao i na konzilijarni pregled na odjeljenju za tumore oka.

Zaključak. Neobični slučajevi eksudativne senilne degeneracije makule kod starijih pacijenata mogu prikriti primarne intraokularne tumorske procese, kao i metastatske promjene na oku. Rana dijagnostika, kao i konzilijarni pristup ima veliki značaj za postavljanje tačne dijagnoze i razlikovanje benignih od malignih promjena.

Ključne riječi: AMD eksudativa, fluoresceinska angiografija, ICGA, karcinom pluća

BIOMEDICINSKA ISTRAŽIVANJA
2026;17(Suppl 1):117

Exudative AMD - yes or no?

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Introduction. Agerelated macular degeneration (AMD) represents one of the leading causes of blindness among the elderly population. AMD manifests in two clinical forms: dry AMD (AMD sicca) and exudative AMD (AMD exudativa). The exudative, or wet, form of the disease is characterized by the development of neovascularization, hemorrhages, and macular edema. Other funduscopic pathologies, such as amelanotic choroidal melanoma or metastatic tumor lesions, can mimic atypical presentations of exudative AMD. Consequently, a comprehensive diagnostic evaluation is crucial for oncological patients presenting with atypical ophthalmoscopic findings. This study aims to report a case of a prominent macular lesion in an elderly oncological patient.

Case report. A 69 year old male presented for evaluation due to poor visual acuity and the appearance of a black spot (scotoma) in front of his right eye following cataract surgery. The patient reported a progressive decline in bilateral visual acuity over the past year, which was more pronounced in the right eye. He underwent uncomplicated cataract surgery on the right eye one week prior to the examination (preoperative visual acuity of the right eye [VOD]: light perception with accurate projection [L+P+]). His medical history was significant for arterial hypertension, hyperlipidemia, and a history of lung cancer resection in 2019. Upon clinical examination, the visual acuity findings were VOD: 2/60 n.c. and visual acuity of the left eye (VOS): 0.9. Intraocular pressure was 15 mmHg bilaterally (TOU). Slitlamp biomicroscopy of the right eye (BMOD) showed a wellpositioned intraocular lens (IOL) with otherwise unremarkable findings. Slitlamp biomicroscopy of the left eye (BMOS) revealed earlystage nuclear sclerosis of the lens. Funduscopy of the right eye (FOD) demonstrated a distinct, welldefined optic disc in the retinal plane, while the macular region exhibited a prominent, poorly demarcated lesion characterized by zones of hypo and hyperpigmentation, accompanied by surrounding hemorrhage. Funduscopy of the left eye (FOS) revealed macular drusen and atherosclerotic retinopathy (fundus atherosclerоticus).

The patient underwent further diagnostic workup, including macular optical coherence tomography (OCT ML), peripapillary OCT (OCT PNO), fundus photography, and fluorescein angiography (FA). Due to the presence of changes in the left eye consistent with dry AMD, a clinical suspicion of exudative AMD in the right eye was established. However, given the patient's history of lung cancer, he was referred for additional diagnostic procedures, including Bscan ultrasonography, indocyanine green angiography (ICGA), pulmonology and oncology evaluations, as well as a multidisciplinary consultation at an ocular oncology department.

Conclusion. Atypical cases of exudative agerelated macular degeneration in elderly patients can conceal primary intraocular tumors as well as metastatic ocular lesions. Early diagnosis and a multidisciplinary team approach are paramount for establishing an accurate diagnosis and differentiating benign conditions from malignant pathologies.

Key words: exudative AMD, fluorescein angiography, ICGA, lung cancer

Hlorokinska makulopatija - novi protokoli

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Hlorokinska makulopatija predstavlja ozbiljnu, potencijalno ireverzibilnu komplikaciju dugotrajne primene hlorokina i hidroksihlorokina lekova široko korišćenih u terapiji autoimunih bolesti kao što su reumatoidni artritis i sistemski lupus eritematodes.

Toksičnost je povezana sa kumulativnom dozom, trajanjem terapije, kao i individualnim faktorima rizika poput bubrežne insuficijencije i istovremene primene drugih retinotoksičnih lekova. Patofiziološki dolazi do oštećenja retinalnog pigmentnog epitela i fotoreceptora, najčešće u parafovealnoj regiji, što klinički može dovesti do karakterističnog „bull's eye" izgleda makule u uznapredovalim stadijumima.

U ranim fazama bolest je često asimptomatska, što naglašava značaj redovnog skrininga. Savremene dijagnostičke metode, uključujući optičku koherentnu tomografiju (OCT), autofluorescenciju fundusa i multifokalnu elektroretinografiju, omogućavaju detekciju prekliničkih promena. Preporuke za skrining zasnivaju se na proceni dnevne doze u odnosu na telesnu masu i trajanje terapije. Prije svega par mjeseci objavljen je novi protokol oftalmološke evaluacije pacijenata na (hidroksi)hlorokinu, što je i jezgro ove teme.

Prekid terapije može zaustaviti progresiju, ali već nastala oštećenja su uglavnom nepovratna. Pravovremeno prepoznavanje i multidisciplinarni pristup ključni su za očuvanje vidne funkcije i smanjenje rizika od trajnog gubitka vida.

Ključne reči: hlorokinska retinopatija, hidroksihlorokin, degeneracija makule, optička koherentna tomografija, retinalna toksičnost

Chloroquine maculopathy - new protocols

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Chloroquine maculopathy represents a severe, potentially irreversible complication associated with the longterm administration of chloroquine and hydroxychloroquine—medications widely utilized in the management of autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus. Drug toxicity is closely correlated with the cumulative dose, treatment duration, as well as individual risk factors, including renal insufficiency and the concomitant use of other retinotoxic agents. Pathophysiologically, the condition induces damage to the retinal pigmen7t epithelium and photoreceptors, predominantly within the parafoveal region, which clinically manifests as the characteristic "bull'seye" maculopathy in advanced stages.

In its early phases, the disease is frequently asymptomatic, underscoring the critical importance of routine screening. Contemporary diagnostic modalities—including optical coherence tomography (OCT), fundus autofluorescence, and multifocal electroretinography—enable the detection of preclinical retinal changes. Current screening guidelines are based on the evaluation of the daily dose relative to body weight and the duration of therapy. Notably, a new protocol for the ophthalmological evaluation of patients on chloroquine and hydroxychloroquine therapy was published just a few months ago, constituting the core focus of this study.

Discontinuation of the medication can halt disease progression; however, preexisting structural damage is largely irreversible. Timely recognition and a multidisciplinary approach are paramount to preserving visual function and mitigating the risk of permanent vision loss.

Key words: chloroquine retinopathy, hydroxychloroquine, macular degeneration, optical coherence tomography, retinal toxicity

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Short summary (abstract) and keywords. In addition to the original scientific paper, an announcements, review and professional paper and a paper on the history of medicine, a short summary of up to 250 words should be attached on a separate page. It states the objectives and methods, the main results (*if possible, state the numerical data and their statistical significance*) and the basic conclusions of the paper. Finally, list keywords or shorter phrases (3 to 5) relevant to the rapid identification and classification of the article. If possible, use *Medical Subject Headings-MeSH* (http://www.nlm.nih.gov/mesh) to select keywords. It is recommended not to use the words from the title for keywords.

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On a separate page, type the title of the paper, full names and surnames of the authors, names of institutions, abstract and keywords in English, if the paper is written in Serbian. (For papers written in English, in addition to short summary in English, short summary in Serbian is also required).

Attachments are tables, figures (photographs), drawings (schemes, graphs), of which there can be a total of six. Each attachment is submitted as a separate document, marked in the same way as in the text. If tables, graphs, schemes or figures have already been published, indicate the original source and attach written authorization for their use.

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Book:

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

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Dissertation:

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Journal article in an electronic format:

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