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APRESENTAÇÃO

Prólogo à Edição Especial de Retina e Vítreo da Revista Brasileira de Oftalmologia da Sociedade Brasileira de Oftalmologia

Foi com grande honra que recebi o convite do Dr. Osvaldo Ferreira Moura Brasil, atual presidente da Sociedade Brasileira de Oftalmologia (SBO), para elaborar e coordenar esta edição especial da Revista Brasileira de Oftalmologia (RBO).

Esta edição da RBO, que será lançada no Dia Mundial da Retina, tem como objetivos homenagear os mais de 100 anos de contribuição da SBO à Oftalmologia nacional e oferecer um conteúdo de alto valor prático, mas, ao mesmo tempo, científico e focado em avanços recentes na área de retina e do vítreo.

Convidei autores de destaque no cenário nacional e internacional, verdadeiras referências em suas áreas, que gentilmente aceitaram contribuir com editorial e artigos originais, abordando temas clínicos e cirúrgicos de grande relevância. Os textos aqui reunidos representam o que há de mais atual na prática da retina e vítreo mundial, com abordagens modernas, resultados consistentes e reflexões críticas sobre o presente e o futuro da especialidade, refletindo os avanços significativos da área nos últimos anos e o comprometimento contínuo de nossos especialistas com a inovação, o rigor técnico e o cuidado humanitário com os pacientes.

A construção desta edição foi fruto de intenso trabalho e rica troca de ideias, envolvendo curadoria cuidadosa e discussões profundas sobre os rumos da especialidade em nosso país. Esperamos que o resultado seja de grande proveito para estudantes, oftalmologistas, residentes, estagiários e *fellows*. Que este número especial se torne um marco na história da SBO, simbolizando a vitalidade, a excelência e o compromisso científico da nossa comunidade.

Com apreço, entusiasmo e gratidão, agradeço a todos que contribuíram para a magnitude e a finalidade desta obra e compartilho este trabalho com todos os leitores.

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Prof. Titular, Livre-Docente e Orientador da Pós-Graduação.
Responsável pela Especialização de Retina e Vítreo do Departamento de Oftalmologia e Ciências Visuais da Escola Paulista de Medicina da Universidade Federal de São Paulo.
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Perspectives in vitreoretinal surgery: profound and continuous transformation

Perspectivas na cirurgia vitreorretiniana: transformação profunda e contínua

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Vitreoretinal surgery, which is dedicated to the management of complex disorders of the retina and vitreous, has undergone remarkable changes in the last 5 decades.[1,2] What began as a high-risk intervention with unpredictable outcomes has improved into a safe and effective approach, offering innovative therapies for previously untreatable diseases. This editorial highlights the current state of vitreoretinal surgery and explores future directions.

The journey of vitreoretinal surgery started with Machemer and Parel's pioneering introduction of pars plana vitrectomy (PPV) in 1970. As with any disruptive technology, each successive advance over the past decades has had to demonstrate superiority while overcoming practical barriers such as high cost, learning curves, and surgeons' preference for established techniques.

For more than three decades, 20-gauge PPV remained the surgical mainstay. Early in the 21st century, the advent of transconjunctival 23-gauge systems reduced surgery-related trauma, shortened operating time, lowered the risk of iatrogenic retinal breaks, and promoted faster wound healing without sacrificing efficiency.[3]

Subsequent 25- and 27-gauge systems were introduced, but early probes were compromised by slower cut rates and reduced flow. Progressive increases in cut rates – now reaching 30,000 cuts per minute – have positioned the 25-gauge system as the platform preferred by most surgeons.[4-6]

Vital dyes have become indispensable in modern chromovitrectomy because they turn transparent tissues into visible surgical targets. Brilliant blue G (BBG) remains the first-line dye used for internal limiting membrane (ILM) peeling thanks to its high affinity and favorable safety record,[7] whereas preservative-free triamcinolone acetonide is still the workhorse for highlighting the posterior hyaloid.[8] Combination preparations containing BBG and trypan blue also have improved staining of the ILM and epiretinal membranes.[9]

Two recent Brazilian contributions deserve to be mentioned: the addition of soluble lutein–zeaxanthin crystals to BBG,[10] now commercially available in Brazil, and the dye extracted from açaí (*Euterpe oleracea*), which remains under experimental investigation.[11]

The advent of three-dimensional (3D) heads-up surgery and real-time intraoperative optical coherence tomography (OCT) has set new standards for surgical precision. These systems provide unparalleled visualization, enabling surgeons to make real-time decisions based on live data.[12,13] In Brazil, two heads-up platforms are currently marketed: Alcon Ngenuity® and Carl Zeiss Artevo 800.

Emerging platforms include the Bausch & Lomb SeeLuma™ heads-up system, which integrates the Heidelberg OCT technology. The Beyeonics One exoscope from Israel goes a step further, replacing the traditional tower and monitor with a lightweight augmented-reality headset and eliminating the need for external 3D monitors.[14]

Gene therapy represents a major milestone in the treatment of inherited retinal diseases. Voretigene neparvovec-rzyl (Luxturna®, Novartis), targeting *RPE65*-mutated retinal dystrophies, is the first ocular gene therapy approved by the US Food and Drug Administration (FDA).[15] Brazilian groups have already treated patients with this therapy, demonstrating both its feasibility and associated challenges.[16] Numerous clinical trials are currently underway for a variety of retinal conditions, including degenerative macular diseases such as wet age-related macular degeneration, which have a promising therapeutic frontier, although high costs and complex technical-logistical demands remain major barriers.

In addition, therapies using embryonic stem-cell–derived retinal pigment epithelium cells show encouraging potential for visual improvement in dystrophic and degenerative diseases.[17]

Although current anti-vascular endothelial growth factors agents and corticosteroids have greatly improved the management of many retinal disorders, the substantial treatment burden underscores the need for longer lasting, more efficient therapies. Multiple studies are investigating implants and/or sustained-release systems, such as the Port Delivery System (Susvimo, Genentech), a refillable ranibizumab reservoir, to reduce injection frequency and enhance adherence and efficacy. The remaining challenges include the implant size, leakage rates, infection risk, and refill difficulties; however, phase 3 results have been encouraging.[18,19] This approach is likely to gain prominence in the coming years and may be incorporated into routine clinical practice.

Surgical simulators have advanced significantly in recent years, allowing for frequent use in training and enabling a better understanding of surgical techniques. Platforms, such as EYESi (VRmagic, Mannheim, Germany), allow residents and fellows to practice complex maneuvers in a controlled, repeatable, and risk-free setting, improving both dexterity and decision-making.[20] Beyond technical skill acquisition, these simulators enable researchers to evaluate how external factors – such as caffeine intake, alcohol consumption, tremor, sleep deprivation, and even pharmacologic modulation – affect surgical performance.[21-23] Such insights would be ethically and logistically unfeasible to obtain in real-life operating rooms. As a result, virtual reality simulators not only enhance the preparation of new surgeons but also serve as valuable tools for studying human performance and optimizing intraoperative behavior in ways that directly impact patient outcomes. Their practicality and relevance continue to grow, and they are expected to become an increasingly integral part of surgical training and research.

Despite noteworthy progress, several challenges persist. High equipment costs still restrict access to state-of-the-art care, especially in resource-limited environments. Clinically, proliferative vitreoretinopathy and the absence of an ideal vitreous substitute continue to challenge surgeons, while each new generation of instruments lengthens the learning curve and demands ongoing investment in training.

Looking into the future, the field's trajectory will be shaped by the convergence of artificial intelligence, surgical robotics, personalized gene-based therapies, and next-generation imaging and vitrectomy platforms. These technologies promise unprecedented precision and efficiency.

Vitreoretinal surgery now exists in a transformative era. Recent advances have expanded the range of treatable diseases and elevated both anatomic and functional outcomes, ultimately improving patients' quality of life. As the field continues to evolve, ensuring the accessibility of these innovations is essential so that patients worldwide can benefit from the remarkable progress achieved. Through sustained research, cross-disciplinary collaboration, and a commitment to global equity, the future of vitreoretinal surgery can be as inclusive as it is extraordinary.

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Terapia gênica para doenças da retina

Gene therapy for retinal diseases

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Retinal dystrophies; rare diseases; Choroid diseases; Gene therapy

RESUMO

Este artigo de atualização tem como objetivo discutir as principais terapias genéticas em estudo para uso nas doenças da retina, principalmente entre as diferentes distrofias hereditárias da retina. As distrofias hereditárias da retina são consideradas doenças raras e algumas ultrarraras. O uso do Luxturna, que foi aprovado pela *Food and Drug Administration*, em 2017, e pela Agência Nacional de Vigilância Sanitária, em 2020, mudou a história natural da doença da retinopatia associada a variantes bialélicas no gene *RPE65* e foi uma grande conquista para a oftalmologia. Há ainda muitos desafios para essa nova modalidade terapêutica que abrange diferentes estratégias que vem sendo estudadas nas diferentes áreas da medicina.

ABSTRACT

This update article aims to discuss gene therapies under study for retinal diseases, mainly among the different inherited retinal dystrophies. Inherited retinal dystrophies are considered rare diseases, some are ultra-rare. The use of Luxturna, which was approved by the FDA in 2017 and by Anvisa in 2020, changed the natural history of the retinopathy associated with biallelic variants in *RPE65* gene and was a major milestone in ophthalmology. There are still many challenges for this new therapeutic modality, which encompasses different strategies being studied in different areas of medicine.

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INTRODUÇÃO

A oftalmologia se destaca no campo da terapia gênica e está na vanguarda dos avanços dessa modalidade terapêutica. A primeira terapia de adição de material genético *in vivo* aprovada pela *Food and Drug Administration* (FDA) foi para o tratamento da retinopatia relacionada a mutações bialélicas no gene *RPE65*. A primeira terapia de edição gênica humana usando a tecnologia CRISPR/Cas9 (do inglês *Clustered Regulation Interspaced Short Palindromic Repeats*, *CRISPR and Associated Proteins, Cas*) foi usada em estudo clínico em paciente com retinopatia relacionada a uma mutação intrônica específica no gene *CEP290*.[1,2] Há novos tratamentos em estudo para mais doenças oftalmológicas, em especial para doenças da retina.

Na terapia gênica, o gene pode ser introduzido na célula-alvo *in vivo* ou *in vitro* (ou *ex vivo*). Na técnica *in vivo*, o gene é introduzido diretamente no organismo, enquanto na técnica *ex vivo*, as células são removidas do indivíduo e, então, reintroduzidas no organismo após serem geneticamente modificadas. Além disso, a introdução de genes nas células não ocorre espontaneamente. Para a entrada do material genético através da membrana plasmática, é necessário um veículo chamado "vetor". Existem três classes principais de vetores: plasmídeos, vetores nanoestruturados e vírus. Entre os vírus que podem ser utilizados, estão os retrovírus, os lentivírus e os adenovírus, vírus adenoassociados (AAV), que não são patogênicos para humanos, entre outros.[3-6]

Em dezembro de 2017, o FDA aprovou o Luxturna (*voretigeno neparvoveque-rzyl*), que também foi aprovado pelas agências regulamentárias da Europa e pela Agência Nacional de Vigilância Sanitária (Anvisa) no Brasil. Esse medicamento consiste em um vetor AAV carregando o material genético que é introduzido no espaço sub-retiniano por meio de cirurgia retiniana e tem como objetivo tratar a distrofia progressiva associada a mutações bialélicas no gene retinoide isomeroidrolase, o *RPE65*. Nesses casos, o aumento de sua produção restabelece uma função enzimática específica no ciclo visual.[7,8]

O Luxturna é considerado um produto de terapia avançada pela Anvisa (Registro 1.0068.1173.001-2). Além dele, outros medicamentos compõem a lista, como Carvykti®, Elevidys®, Kymriah®, Roctavian, Tecartus®, Upstaza®, Yesarta® e Zolgensma, para tratamento de diferentes doenças, como mieloma múltiplo recidivante, distrofia muscular de Duchenne, hemofilia A, entre outros.[9] A terapia gênica é considerada opção no tratamento de algumas doenças e classicamente consiste na introdução de material genético em uma célula-alvo para alcançar um benefício terapêutico. Além das terapias de adição existem as terapias avançadas que se baseiam na edição gênica e nos mecanismos de RNA.

Este artigo de atualização teve por objetivo discutir os principais avanços da terapia gênica para o tratamento de retinopatias, abordando o gene que possui terapia gênica aprovada, o *RPE65* e alguns dos genes que possuem estudos clínicos em andamento, como o *CEP290*, o *RPGR*, o *CHM*, o *CNGA3*, o *RS1*, o *USH2A* e *ABCA4*.

RPE65

Variantes bialélicas no gene *RPE65* podem causar amaurose congênita de Leber, distrofia retiniana de início precoce (EOSRD, do inglês *early-onset severe retinal dystrophy*), distrofia retiniana grave de início na infância (SECORD, do inglês *severe early-childhood-onset retinal dystrophy*), retinose pigmentar que pode se apresentar com cegueira noturna (nictalopia), alterações no campo visual, baixa visão, cegueira legal e nistagmo.[10,11] Além disso, o gene *RPE65* também pode causar uma distrofia com padrão de herança autossômico dominante (apenas uma mutação em um alelo pode causar as manifestações clínicas) com atrofia coriorretiniana macular.[10,12,13] Esse gene está localizado no braço curto do cromossomo 1 (1p31.3). Os estudos de história natural de pacientes com retinopatia por mutações bialélicas no gene *RPE65* demonstraram que os pacientes apresentam perda progressiva grave da visão sem o tratamento.[11]

A presença de modelos animais murino e, posteriormente, canino com cegueira noturna devido a mutação no gene *RPE65* permitiu os primeiros estudos de terapia gênica nesses animais.[14,15] Os resultados da primeira terapia gênica em três pacientes humanos foram publicados em 2008.[16] O ensaio clínico de fase 3 foi iniciado em 2012 na Universidade da Pensilvânia, nos Estados Unidos, incluindo pacientes com mais de 3 anos de idade, visão entre 20/60 ou pior com mutações bialélicas no gene *RPE65* que fossem capazes de realizar o teste de mobilidade multiluminância (MLMT). Durante o estudo, 21 participantes foram submetidos a tratamento cirúrgico e 10 foram randomizados como controles e não receberam a terapia gênica. Os resultados subsequentes demonstraram melhora no desempenho dos pacientes do grupo tratado no MLMT em comparação ao grupo controle, atingindo o desfecho primário.[17] Em 2017, essa terapia foi aprovada pela FDA e, em 2020, pela Anvisa. O Luxturna necessita ser manipulado em uma farmácia com cabine de fluxo laminar, respeitando-se normas de biossegurança, antes de ser entregue ao cirurgião. O medicamento é

injetado no espaço sub-retiniano após cirurgia de vitrectomia posterior via *pars plana* com descolamento da hialoide posterior, criando um descolamento de retina que se resolve espontaneamente nas primeiras 24 horas. O espaço sub-retiniano apresenta algumas vantagens, como pouca resposta imunológica, além de permitir o contato do material injetado com as células fotorreceptoras e do epitélio pigmentado da retina. Além da melhora no teste MLMT, outros estudos também descreveram melhora da sensibilidade no campo visual,[18,19] melhoras nas medidas do teste de limiar de sensibilidade à luz de campo total (FST, do *inglês full-field stimulus testing*) e também na acuidade visual,[20] A primeira cirurgia usando o Luxturna no Brasil foi realizada em maio de 2021, e a paciente apresentou melhora da cegueira noturna e do campo visual.[18] O tratamento é indicado para pacientes com diagnóstico clínico e molecular conclusivos e pela presença de células retinianas viáveis.

Após liberação dos resultados da fase 3 e aprovação do Luxturna, iniciou a fase 4, cujo objetivo é identificar algum efeito terapêutico ou colateral que pode não ter sido observado nas fases anteriores dos estudos. A identificação da atrofia coriorretiniana como efeito colateral após cirurgia de terapia gênica foi reportada por diferentes autores de diferentes instituições, sem prejuízo funcional aos pacientes, como demonstrado nos exames de acuidade visual, FST e campo visual.[21]

CEP290

De acordo com o OMIM (do inglês, *Online Mendelian Inheritance in Man*), o gene *CEP290* está associado a diferentes quadros clínicos, como amaurose congênita de Leber (OMIM 611755), síndrome de Bardet-Biedl (OMIM 615991), síndrome de Joubert (OMIM 610188), síndrome de Meckel (OMIM 611134) e síndrome de Senior-Loken (OMIM 610189).[10] Esse gene está localizado no braço longo do cromossomo 12 (12q21.32). Em março de 2020, a tecnologia CRISPR-Cas9 foi usada pela primeira vez para editar o genoma humano.[2] Foi realizada uma cirurgia de vitrectomia posterior via *pars plana* com descolamento da hialoide posterior e descolamento de retina para injeção do CRISPR-Cas9 no espaço sub-retiniano para editar uma mutação específica no íntron 26 do *CEP290*. Essa variante intrônica é comum entre pacientes com retinopatia associada ao *CEP290* (c.2991+1655A>G) e ela gera um *splicing* aberrante e um códon de parada prematura da proteína (p.Cys998*). Os resultados da fase 1/2 foram publicados recentemente em maio de 2024 e demonstraram segurança dessa terapia.[22]

Essa mesma mutação intrônica também é alvo de outra terapia usando um oligonucleotídeo antisense, que é uma molécula sintética de fita simples de 15 a 35 nucleotídeos que podem hibridizar com sequências específicas da molécula de pré-RNA mensageiro (RNAm) para melhorar a leitura e, consequentemente, produzir uma proteína mais funcional. O oligonucleotídeo antisense, *sepofarseno* (QR-110), liga-se a uma região específica do pré-RNAm do CEP290 para bloquear o *splicing* aberrante. Os resultados da fase 1/2 foram publicados em 2018. Essa terapia envolveu injeções intravítreas a cada seis meses não sendo necessário cirurgia retiniana.[23]

RPGR

De acordo com o OMIM, o gene *RPGR* está associado a diferentes fenótipos como a retinose pigmentar (OMIM 300029), distrofia de cones e bastonetes (OMIM 304020), atrofia macular (OMIM 300834).[10] O gene *RPGR* está situado no braço curto do cromossomo X, na posição Xp11.4. A proteína codificada por esse gene faz parte da constituição e formação do cílio conector dos fotorreceptores. Mutações no gene *RPGR* são responsáveis por aproximadamente 70% dos casos de retinose pigmentar ligada ao X (XLRP).[24] Outros genes que também causam XLRP são *OFD1*, *RP2* e o RP6.[10,25]

Atualmente, há estudos em fase 3 (conduzidos pela *Beacon Therapeutics* e pela Janssen/Meira GTx) para pacientes com retinose pigmentar associada ao gene *RPGR* que consistem em cirurgia de retina com adição do material genético no espaço sub-retiniano. Os resultados parciais da fase 2 (NCT04850118) mostraram melhorias promissoras na microperimetria, FST e testes de mobilidade.[26]

Além desses estudos, a empresa 4D Molecular Therapeutics está conduzindo um estudo de terapia com a administração intravítrea do 4D-125, dose única em fase1/2 (NCT04517149).[27]

CHM

De acordo com o OMIM, o gene *CHM* está associado a coroideremia (OMIM 303100).[10] Esse gene está localizado no braço longo do cromossomo X na posição Xq21.2, seguindo um padrão de herança recessiva ligado ao cromossomo X e afetando cerca de 1 a cada 50 mil homens. O gene *CHM* é o único associado à coroideremia e ele codifica a enzima REP1 (do inglês *Rab escort protein 1*) que se liga a proteína Rab, permitindo sua ligação nas organelas para regular o transporte vesicular intracelular. O transporte de proteínas dentro dos fotorreceptores, a regulação da fagocitose e a degradação das membranas dos segmentos externos dos

fotorreceptores pelo epitélio pigmentado da retina são dependentes da proteína Rab escoltada pela REP1.[28]

Mais de 330 variantes já foram descritas no gene *CHM* associadas à coroideremia que leva à atrofia coriorretiniana, que evolui centriptamente.[28,29]

Estudos para tratamento da coroideremia com terapia gênica por meio de cirurgia retiniana foram conduzidos, mas não atingiram o desfecho primário desejado e não tiveram suas terapias aprovadas para uso comercial. Atualmente, a empresa *4D Molecular Therapeutics* está conduzindo estudo fase 1 para injeção intravítrea do REP1 (4D-110) (NCT04483440) em dose única.[30]

CNGA3 e CNGB3

De acordo com o OMIM, os genes *CNGA3* (localizado no cromossomo 2q11.2) e *CNGB3* (localizado no cromossomo 8q21.3) estão associados à acromatopsia (OMIM 216900/ OMIM 262300).[10] Outros genes, como *GNAT2*, *PDE6C*, *PDE6H* e *ATF6*, também estão associados à acromatopsia, que é caracterizada principalmente por perda de discriminação de cores de forma completa ou incompleta, acuidade visual reduzida e fotofobia.[31]

Estudos fase 1/2 foram conduzidos para avaliar segurança e tolerabilidade da terapia gênica com adição de material genético para os genes *CNGA3* e *CNGB3*, responsáveis por aproximadamente 90% dos casos de acromatopsia.[31]

A STZ eyetrial, da Alemanha, também está conduzindo estudo de terapia gênica para avaliar a segurança e a eficácia de uma única injeção sub-retiniana bilateral de rAAV.hCNGA3 em pacientes com acromatopsia ligada ao gene *CNGA3* (NCT02610582).[32]

RS1

O gene *RS1* é o único associado à retinosquise juvenil ligada ao X (OMIM 312700),[10] levando à separação das camadas da retina devido à disfunção da proteína retinosquisina, proteína envolvida na adesão intercelular. O principal sinal é a maculosquise, devido à separação das camadas da retina, e o aspecto ao fundo de olho é descrito como "roda de carroça". O exame de tomografia de coerência óptica macular demonstra a separação principalmente na camada nuclear interna. A camada nuclear externa e a plexiforme externa podem estar envolvidas. Pode haver acometimento das camadas de fibras nervosas e de células ganglionares. Esse gene está localizado no braço curto do cromossomo X (Xp22.13), e a retinosquise juvenil apresenta prevalência de 1:15 mil a 1:30 mil entre os nascidos vivos.[6,33]

Já foram realizados estudos de terapia gênica em humanos por meio de injeções intravítreas, porém não atingiram resultados significativos, não sendo aprovados.[6] Atualmente, há estudos em andamento de terapia gênica, por meio da injeção sub-retiniana ATSN-201 (clinicaltrials.gov ID: NCT05878860), sendo necessário cirurgia retiniana.[34]

USH2A

De acordo com o OMIM, o gene *USH2A* localizado no braço longo do cromossomo 1 (1q41) está associado à retinose pigmentar isolada (OMIM 613809) e à síndrome de Usher do tipo 2A (OMIM 276901).[10] Dentre as síndromes oftalmológicas, a síndrome de Usher é a mais frequente, sendo o gene *USH2A* o mais prevalente seguido do gene *MYO7A*, que está associado à síndrome de Usher tipo 1B. A síndrome de Usher é uma ciliopatia com comprometimento dos fotorreceptores e das células ciliadas da cóclea e dos canais semicirculares.[35]

Há estudo clínico do uso de oligonucleotideo antisenso, *ultevurseno*, (NCT06627179) em fase 2 pela empresa Sepul Bio para mutações especificas no éxon 13 do gene *USH2A*. O estudo consiste em injeções intravítreas seriadas do medicamento em pacientes com retinose pigmentar.[36]

ABCA4

De acordo com o OMIM, o gene *ABCA4* (OMIM 601691) está localizado no braço longo do cromossomo 1 (1p22.1) e está relacionado aos fenótipos de doença de Stargardt, SECORD, retinose pigmentar, distrofia de cones e bastonetes, *fundus flavimaculatus* e degeneração macular relacionada à idade. Esse gene se expressa fortemente nos fotorreceptores e codifica um transportador transmembrânico no segmento externo dessas células importante para o ciclo visual.[37]

Uma das limitações da terapia gênica para o gene *ABCA4* é seu tamanho. O vetor AAV tem capacidade menor que o tamanho desse gene, por isso, diferentemente das outras terapias apresentadas neste artigo, o vetor *lentivirus equine infectious anemia virus* foi utilizado.[38] Outra estratégia consiste em usar duplo vetor para carrear o gene *ABCA4*.[39] Uma abordagem agnóstica da Ocugen (NCT05956626) e outra abordagem optogenética da *Nanoscope Therapeutics* (NCT05417126) estão em andamento para retinopatia pelo *ABCA4*.[40,41]

DEGENERAÇÃO MACULAR RELACIONADA A IDADE

Além da terapia gênica aprovada e em desenvolvimento para as diferentes distrofias hereditárias da retina

existem também estudos do uso da terapia gênica para doenças mais prevalentes, como a degeneração macular relacionada à idade (DMRI). Estudos de terapia gênica para DMRI demonstram o interesse de ampliar o uso dessa modalidade terapêutica em doenças mais prevalentes e multifatoriais.[42] O medicamento ABBV-RGX-314 injetado no espaço sub-retiniano tem por objetivo inibir o fator de crescimento endotelial vascular A (VEGF-A), evitando o crescimento anormal de neovascularização macular.[43] Foi demonstrado que a medicação foi bem tolerada e sem repostas imunológicas clinicamente reconhecidas.[43] São necessários mais estudos antes da sua aprovação.

CONCLUSÃO

A terapia gênica é considerada opção no tratamento de algumas doenças oftalmológicas, contudo, são necessários os estudos clínicos para avaliar a resposta estrutural, funcional e sua aprovação. Além da terapia gênica aprovada e das outras citadas nesse artigo, existem estudos clínicos em andamento para outros genes e doenças. O uso da terapia gênica na oftalmologia está constantemente evoluindo, sendo prática constante em alguns centros pelo mundo, seja pelo uso em protocolos de estudos clínicos ou do tratamento aprovado com o Luxturna.

CONTRIBUIÇÃO DOS AUTORES

Palma MP contribuiu na concepção e delineamento do artigo, redação e revisão crítica do conteúdo do manuscrito. Salles MV e Sallum JMF contribuíram também na redação e revisão crítica do conteúdo do manuscrito. Todos os autores aprovaram a versão final do manuscrito e são responsáveis por todos os seus aspectos, incluindo a garantia de sua precisão e integridade.

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Current evidence-based treatments for diabetic retinopathy: a comprehensive review for ophthalmologists

Tratamentos atuais baseados em evidências para a retinopatia diabética: uma revisão abrangente para oftalmologistas

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ABSTRACT

Diabetic retinopathy and diabetic macular edema are leading causes of preventable vision loss, with a rising global impact due to the increasing prevalence of diabetes mellitus. This review article synthesizes current evidence regarding the management of diabetic retinopathy, addressing pathophysiological mechanisms and evidence-based therapeutic recommendations from major clinical trials. Key topics include screening strategies, updated classification systems, systemic control, and ocular therapies such as anti-vascular endothelial growth factor (anti-VEGF) agents, corticosteroids, laser photocoagulation, and vitrectomy. Emerging medication approaches, sustained-release drug delivery systems, gene therapy, Artificial Intelligence (AI) and telemedicine are also discussed. Special considerations are highlighted for specific populations, including pregnant women and young individuals with type 1 diabetes. The review highlights the importance of individualized, multidisciplinary and evidence-based management to optimize visual outcomes and the quality of life for patients with diabetic retinopathy.

RESUMO

A retinopatia diabética e o edema macular diabético constituem importantes causas de perda visual potencialmente evitável, com impacto global crescente em decorrência da elevação da prevalência do diabetes mellitus. Este capítulo revisa criticamente as evidências atuais relacionadas ao manejo da retinopatia diabética, abordando os mecanismos fisiopatológicos envolvidos e as principais recomendações terapêuticas baseadas em estudos clínicos de grande porte. São discutidos tópicos fundamentais como estratégias de rastreamento, atualizações nos sistemas de classificação, controle sistêmico rigoroso e terapias oculares, incluindo agentes antifator de crescimento endotelial vascular (anti-VEGF), corticosteroides, fotocoagulação a laser e vitrectomia. Abordam-se ainda abordagens terapêuticas emergentes, sistemas de liberação prolongada de fármacos, terapia gênica, inteligência artificial e telemedicina. Considerações específicas são destacadas para subgrupos populacionais como gestantes e indivíduos jovens com diabetes tipo 1. Reforça-se, ao final, a relevância de uma abordagem individualizada, multidisciplinar e fundamentada em evidências para otimização dos desfechos visuais e da qualidade de vida de pacientes com retinopatia diabética.

INTRODUCTION

Epidemiology and socioeconomic impact of diabetic retinopathy in Brazil and worldwide

Diabetic retinopathy (DR) is one of the most prevalent and disabling complications of diabetes mellitus (DM), representing an important cause of avoidable blindness in the working-age population. Globally, recent estimates suggest that approximately 22.3% of individuals with DM have DR, totaling around 103 million people in 2020, with projections reaching 160.5 million by 2045.[1] This increasing global burden reflects population aging, increased life expectancy among people with diabetes, and lifestyle changes associated with urbanization. Ocular complications of diabetes account for up to 2.6% of global blindness cases and about 4.8% of moderate to severe visual impairment, according to the Global Burden of Disease.[2] This burden is disproportionately higher in low- and middle-income countries, where screening and treatment programs are often structurally deficient.

In Brazil, the scenario is equally concerning: the prevalence of DM is estimated at 9.4%, with significant underreporting (42.5%) and low frequency of ophthalmic exams. Only 41% of diagnosed individuals underwent a fundus examination in the past year, and approximately 20% have never had one. These gaps in screening and disease control lead to increased morbidity, hospitalizations, and healthcare costs, in addition to significant socioeconomic losses related to visual disability.[3]

Pathophysiology of diabetic retinopathy: key mechanisms

The pathophysiology of DR is multifactorial and complex, involving interactions between metabolic, inflammatory, oxidative, and angiogenic pathways, primarily triggered by chronic hyperglycemia. This condition initiates a cascade of cellular and molecular changes, resulting in dysfunction and damage to the retinal microvasculature, which progressively compromises retinal integrity.

Hyperglycemia is the primary factor that promotes oxidative stress, mitochondrial damage, and the activation of inflammatory and apoptotic mediators. It also induces basement membrane thickening and pericyte loss, events that lead to microaneurysm formation, increased vascular permeability, and breakdown of the blood-retinal barrier.[4-6]

Among the angiogenic mediators, vascular endothelial growth factor (VEGF) plays a prominent role. It is upregulated by retinal hypoxia and promotes increased capillary permeability and pathological neovascularization. Other mediators, such as angiopoietin-2 and interleukin 6, are also involved in vascular destabilization and act synergistically with VEGF in the progression to proliferative DR and diabetic macular edema (DME). The study of these mediators has expanded as targets for new DME treatments.[5,6]

More recently, retinal neurodegeneration has been recognized as an early event in DR, even preceding microvascular alterations. The ganglion cell loss and thinning of the retinal nerve fiber layer have been observed even in the absence of overt clinical lesions, suggesting that DR also constitutes a sensory neuropathy associated with diabetes.[6,7]

Updated classification of diabetic retinopathy

The current classification of DR is based on clinical and imaging findings (Figure 1), with the International Clinical Diabetic Retinopathy (ICDR) system being the gold standard in clinical research (Table 1). This system evaluates seven standard retinal photographic fields to provide a detailed assessment.[8,9]

Table 1. Clinical classification of diabetic retinopathy according to severity. The progression from mild non-proliferative to proliferative diabetic retinopathy reflects increasing microvascular damage and risk of vision loss. Criteria are based on fundoscopic findings and guide the timing of referral and therapeutic intervention

Stage	Clinical criteria	Risk of progression / considerations
Mild NPDR	Presence of microaneurysms only	Typically asymptomatic. Low short-term risk of progression
Moderate NPDR	Microaneurysms, dot-blot hemorrhages, and hard exudates. It does not meet criteria for severe NPDR	Requires closer monitoring. Moderate risk of progression
Severe NPDR	Presence of at least one of the following: • More than 20 intraretinal hemorrhages in all four quadrants • Venous beading in ≥ 2 quadrants • IRMA in ≥ 1 quadrant	Up to 50% risk of progression to proliferative DR within one year. Referral to retina specialist is recommended
Very severe NPDR	Any two of the three criteria for severe NPDR, without neovascularization	High risk of rapid progression to proliferative DR. It requires intensive follow-up.
PDR	Neovascularization of the optic disc (NVD) and/or elsewhere in the retina (NVE), vitreous hemorrhage	High risk of severe vision loss. Treatment with panretinal photocoagulation and/or anti-VEGF therapy is typically indicated

NPDR: non-proliferative diabetic retinopathy; IRMA: intraretinal microvascular abnormalities; DR: diabetic retinopathy; PDR: proliferative diabetic retinopathy; VEGF: vascular endothelial growth factor.

The advent of ultra-widefield (UWF) imaging has challenged the limitations of the ETDRS seven-field assessment (Figure 2). Comparative studies have shown that, although discrepancies in severity grading occur in less than 6% of cases, UWF imaging can reveal vision-threatening lesions such as neovascularization and

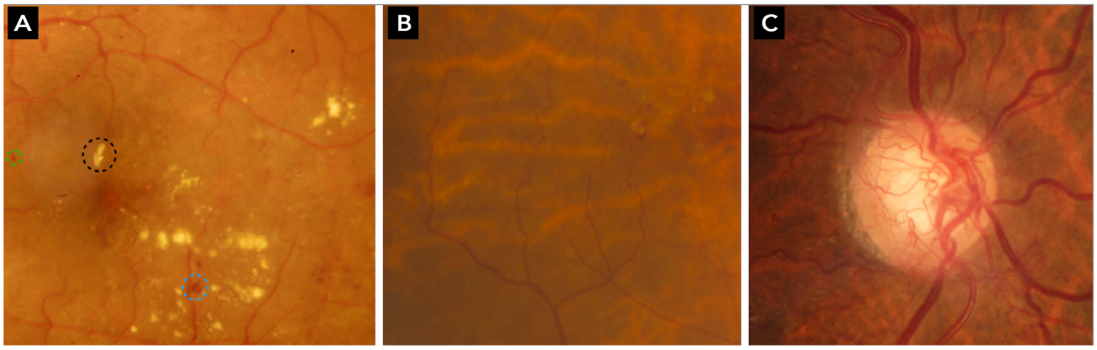

Figure 1. Color fundus photographs illustrating key features of diabetic retinopathy. (A) shows microaneurysms (green circle), intraretinal hemorrhages (blue circle) and hard exudates (black circle); (B) highlights intraretinal microvascular abnormalities; (C) displays neovascularization of the optic disc.

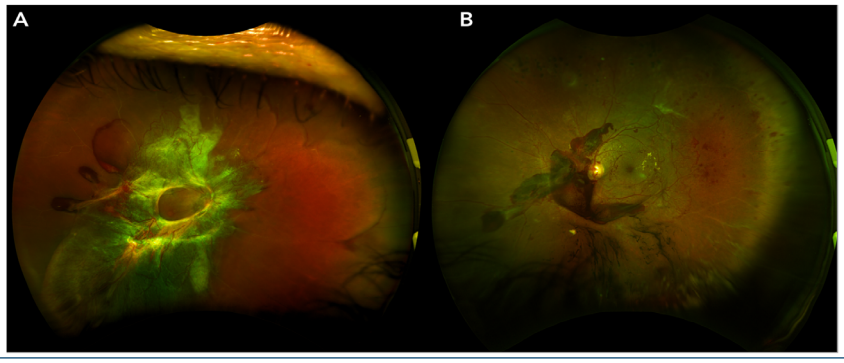

Figure 2. Ultra-widefield fundus images illustrating bilateral high-risk proliferative diabetic retinopathy. The right eye (A) presents a complex tractional retinal detachment, while the left eye (B) shows a pre-retinal hemorrhage.

pre-retinal hemorrhages located in the peripheral retina, beyond the ETDRS fields.[10]

Diabetic macular edema: pathophysiology, classification, and relationship with diabetic retinopathy stages

Diabetic macular edema is the leading cause of vision loss in patients with DM and may occur at any stage of DR, whether non-proliferative or proliferative. The pathophysiology of DME is multifactorial, involving breakdown of the blood-retinal barrier, oxidative stress, chronic inflammation, vascular dysfunction, and neurodegeneration.[11,12]

Diabetic macular edema can be classified according to different criteria. Morphologically, it is described as focal when localized leakage areas are associated with microaneurysms, or diffuse when the macular thickening is more extensive and uniform. Another classification is based on central involvement, dividing DME into center-involving and non-center-involving types, as determined by optical coherence tomography (OCT) imaging. Additionally, DME may be described as cystoid when intraretinal fluid filling spaces are observed on OCT.[12]

The development of DME is closely related to DR progression. Although it can occur at any stage, its prevalence and severity increase with DR severity. Macular involvement, particularly when central, is associated with more significant visual loss.[11,12]

Critical importance of systematic screening and early diagnosis: current recommendations

Systematic DR screening is a key public health strategy to reduce the incidence of preventable blindness in people with DM. Organized screening programs allow for early identification of retinal lesions, risk stratification, and timely therapeutic interventions. According to the guidelines of the *Sociedade Brasileira de Diabetes* (SBD), ophthalmological examinations should begin five years after the diagnosis of type 1 diabetes and at the time of diagnosis for patients with type 2 diabetes, due to the possibility that DR may already be present in this population due to the frequent absence of precise onset of the disease.

Screening can be performed by clinical examination with pupillary dilation or through imaging methods

such as fundus photography. The latter has gained prominence, especially when associated with telemedicine, allowing trained technicians to capture retinal images for remote analysis by ophthalmologists in specialized centers. Fundus photography combined with automated AI algorithms has proven effective and feasible, even in regions with a shortage of specialists. Artificial Intelligence use is in an advanced validation stage and has already shown high diagnostic performance in international studies.[9]

The recommended screening interval is based on the DR stage. For patients with no DR or mild NPDR, annual exams are sufficient. For moderate or advanced cases, the interval should be reduced to six months or less, as determined by clinical judgment. Patients with PDR or center-involving DME should be referred immediately to a specialist for treatment initiation.[9]

MANAGEMENT OF NON-PROLIFERATIVE DIABETIC RETINOPATHY

Optimized systemic control as a therapeutic foundation: glycemic, blood pressure, and lipid targets

Optimized systemic control is a cornerstone in managing non-proliferative diabetic retinopathy (NPDR), as demonstrated by landmark clinical trials such as DCCT/EDIC, UKPDS, and ACCORD-Eye. Intensive glycemic control, particularly maintaining a glycated hemoglobin (HbA1c) below 7%, significantly reduces the risk of DR onset and progression. In the DCCT and its long-term follow-up EDIC, patients with type 1 diabetes who received intensive glycemic treatment had up to 76% reduction in DR progression over 6.5 years, with sustained benefits despite later convergence of HbA1c levels—an effect known as "metabolic memory". Likewise, the UKPDS demonstrated that 0.9% reduction in HbA1c among individuals with type 2 diabetes led to 25% decrease in microvascular complications, including DR. Furthermore, tight blood pressure control led to 37% reduction in the risk of vision-threatening events.[13,14]

However, rapid and intensive glycemic control—particularly in patients with poor baseline metabolic control or advanced retinopathy—has been associated with early worsening of DR. This paradoxical effect, first observed in the DCCT and confirmed in subsequent studies such as ACCORD-Eye, is thought to result from abrupt changes in retinal blood flow, oxygenation, and osmotic gradients, potentially exacerbating ischemic and inflammatory responses in the retina. Therefore, glycemic targets should be approached gradually in high-risk individuals, with close ophthalmologic monitoring to mitigate the risk of early retinal deterioration during initial metabolic adjustment.[13,15]

In addition to glycemia and blood pressure, lipid control has emerged as an important modifiable factor in DR progression. Fenofibrate, a peroxisome proliferator-activated receptor-alpha (PPAR-α) agonist with lipid-modulating and anti-inflammatory effects, has shown consistent retinal protective effects across multiple trials. The FIELD study [16] demonstrated a reduction in the need for laser therapy for both proliferative DR and macular edema in patients with type 2 diabetes treated with fenofibrate, regardless of baseline lipid levels. Similarly, the ACCORD-Eye study found that fenofibrate added to statin therapy reduced the risk of DR progression by 40% over four years, supporting its retinal benefit.

Most recently, the LENS trial (2024) further substantiated the protective role of fenofibrate in a real-world population enrolled in the Scottish Diabetic Eye Screening program. Among 1,151 participants with early, non-referable DR or maculopathy, those randomized to receive 145 mg of fenofibrate daily experienced a 27% reduction in the composite endpoint of progression to referable disease or need for ocular treatment (hazard ratio [HR]: 0.73; 95% of confidence interval [95%CI] 0.58-0.91). The drug also halved the risk of developing macular edema and showed favorable effects on overall DR progression, without significant impact on visual acuity or quality of life. These findings reinforce the role of fenofibrate as a systemic adjunct in the early stages of DR, especially in patients not yet requiring ophthalmologic intervention.[17]

Mild to moderate non-proliferative diabetic retinopathy: strategy of active surveillance and systemic optimization

The management of mild to moderate NPDR primarily involves active surveillance paired with rigorous systemic control. At these early stages, patients are generally asymptomatic, and the main recommendation is periodic monitoring to detect early progression.

This conservative strategy is supported by evidence indicating that early invasive or pharmacological interventions, such as anti-VEGF injections, are not indicated for mild to moderate NPDR, except when center-involving DME is present.[6,12,18]

Severe and very severe non-proliferative diabetic retinopathy

Panretinal photocoagulation: indications based on ETDRS, optimal timing (early *versus* deferred), controversies, and current role

Panretinal photocoagulation (PRP) is traditionally reserved for PDR but plays a role in severe and very severe NPDR, although this remains controversial. The ETDRS showed that early PRP in eyes with very severe NPDR reduced the risk of progression to high-risk PDR, particularly in cases with poor follow-up reliability or imminent loss to follow-up. However, it also demonstrated that early PRP in NPDR did not confer a significant visual benefit over deferred treatment and was associated with adverse effects, including reduced visual field and impaired dark adaptation.[4,18,19]

Thus, treatment decisions should be individualized, especially in public health systems with limited access and adherence.

Intravitreal anti-vascular endothelial growth factor therapy: evidence for prevention of progression to proliferative diabetic retinopathy and development of diabetic macular edema

Intravitreal anti-VEGF therapy has been studied as a means of preventing progression from NPDR to PDR and the onset of DME, even in the absence of visual symptoms. Studies such as PANORAMA, Protocol W, and Protocol V[20, 21, 22] have provided strong evidence.

The PANORAMA trial evaluated aflibercept in patients with severe to very severe NPDR, showing 79% reduction in progression to PDR or DME compared to observation, with sustained benefit up to 100 weeks.[20] Protocol W, conducted by the DRCR Retina Network, demonstrated that early treatment with aflibercept in patients with moderate to severe NPDR without baseline DME significantly reduced the risk of vision-threatening complications, including progression to proliferative DR and the need for vitrectomy. These findings support the role of anti-VEGF therapy as a preventive strategy in carefully selected patients at high risk of disease progression.[21]

In contrast, Protocol V evaluated patients with center-involving DME and good baseline visual acuity. The study found no meaningful advantage of immediate anti-VEGF treatment over observation with deferred therapy. These results emphasize the importance of individualized treatment decisions, suggesting that close monitoring may be a safe and effective approach for patients with preserved vision at presentation.[22]

Comparative analysis: panretinal photocoagulation versus anti-vascular endothelial growth factor in severe non-proliferative diabetic retinopathy

In severe NPDR, the choice between PRP and anti-VEGF must balance efficacy, safety, cost-effectiveness, and patient adherence. Anti-VEGF requires frequent, costly injections and visits, while PRP, though less protective of central vision and peripheral field, often requires only one or a few sessions, favoring adherence and lower cost.[18,21,23]

MANAGEMENT OF PROLIFERATIVE DIABETIC RETINOPATHY

Panretinal photocoagulation

PRP remains a mainstay treatment for PDR (Figures 3 and 4) and has been considered the historical standard since the Diabetic Retinopathy Study (DRS), which demonstrated a

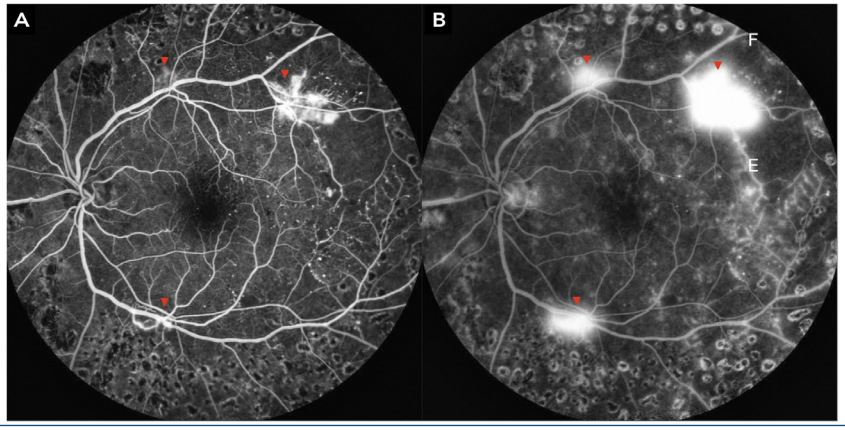

Figure 3. Fluorescein angiography showing mid-phase (A) and late-phase (B) images, highlighting characteristic leakage from neovascularization elsewhere (red triangle).

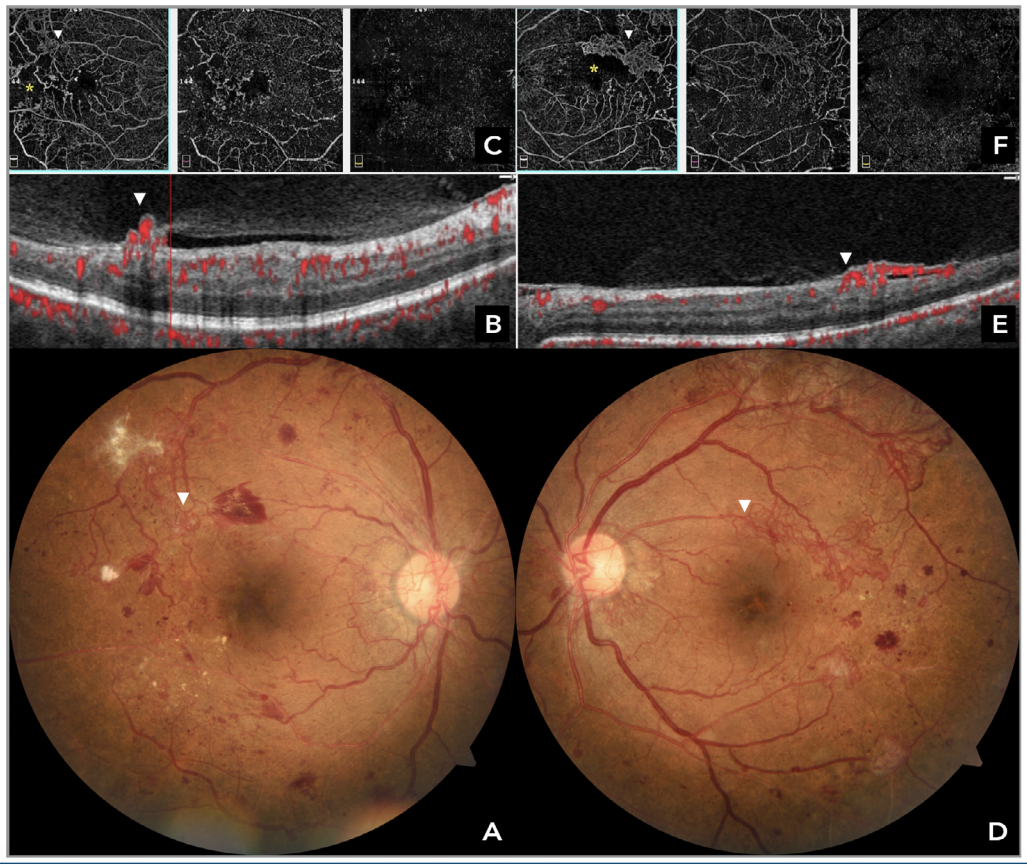

Figure 4. Color fundus photographs (A, D) showing proliferative diabetic retinopathy with neovascularization elsewhere (white triangle). Corresponding optical coherence tomography angiography B-scans (B, E) demonstrate the decorrelation signal and internal limiting membrane disruption caused by the NVE. Structural optical coherence tomography-angiography images (C, F) depict the NVE and associated areas of capillary nonperfusion (yellow asterisk).

50% reduction in the risk of severe vision loss in eyes treated with PRP compared to observation.[24] The ETDRS further supported early PRP benefits in high-risk PDR cases. The technique involves applying laser burns to the peripheral ischemic retina to reduce the angiogenic stimulus. Despite its proven efficacy, PRP is associated with adverse effects, including peripheral visual field loss, impaired night vision, and the potential exacerbation of macular edema.[4]

Nevertheless, PRP continues to play an essential role, particularly in patients with poor adherence to continuous intravitreal therapies.

Intravitreal anti-vascular endothelial growth factor therapy as primary or adjunctive option

Anti-vascular endothelial growth factor monotherapy

Intravitreal anti-VEGF agents have emerged as effective alternatives to PRP for PDR. The DRCR.net Protocol S showed that ranibizumab was non-inferior to PRP in terms of visual acuity over two years, with a lower risk of developing DME and better preservation of visual field.[25] The CLARITY study confirmed these findings, demonstrating superior efficacy of aflibercept compared to PRP for visual improvement and neovascular regression.[26]

Treatment regimens vary and include monthly loading doses followed by PRN (pro re nata) or Treat-and-Extend maintenance. Among the available agents, bevacizumab, ranibizumab, and aflibercept are all effective, with aflibercept offering superior outcomes in patients with worse baseline visual acuity.[27]

Combination therapy (anti-vascular endothelial growth factor + panretinal photocoagulation)

Combining anti-VEGF with PRP has shown advantages in specific subgroups, particularly those at risk of treatment discontinuation. Initial anti-VEGF therapy facilitates rapid neovascular regression, allowing for more targeted and less aggressive PRP. This strategy is especially beneficial in cases with vitreous hemorrhage or optic disc neovascularization, where prompt angiogenic suppression is required.[6]

Advantages and disadvantages: anti-vascular endothelial growth factor versus panretinal photocoagulation

Anti-VEGF agents have emerged as a frontline treatment option in proliferative diabetic retinopathy (PDR), offering not only superior anatomical outcomes but also improved visual acuity and preservation of peripheral vision when compared to traditional laser therapy. These benefits are particularly evident in patients with concurrent DME, where anti-VEGF therapy addresses both situations simultaneously. Additionally, studies have shown a lower incidence of vitrectomy and neovascular complications with anti-VEGF treatment, reinforcing its efficacy as a disease-modifying intervention.[25,26]

However, the success of anti-VEGF therapy is highly dependent on patient adherence to a regimen of frequent intravitreal injections and long-term follow-up, which may pose challenges in real-world settings. The cumulative financial burden—both for healthcare systems and for patients—can be substantial, particularly in countries with limited access to biologics or reimbursement barriers.

On the other hand, PRP, a time-tested and widely available intervention, requires significantly fewer clinical visits and has a lower overall cost. While PRP does not typically improve central visual acuity and may result in peripheral visual field loss, night vision impairment, and exacerbation of DME in some cases, it remains an effective strategy for inducing regression of retinal neovascularization and reducing the risk of severe vision loss. In healthcare settings where patient compliance, access to specialized care, or logistical support are limited, PRP continues to play a critical role in managing PDR.[25,26]

Thus, the choice between anti-VEGF therapy and PRP should be individualized, balancing the patient's clinical profile, visual demands, systemic comorbidities, and the capacity for sustained treatment adherence within the healthcare system.

Pars plana vitrectomy for complicated proliferative diabetic retinopathy

Classical and Contemporary Indications

Pars plana vitrectomy (PPV) is indicated for complicated PDR cases, such as dense and persistent vitreous hemorrhage, tractional retinal detachment with or without rhegmatogenous component, tractional macular edema, and extensive fibrovascular membranes. The Diabetic Retinopathy Vitrectomy Study (DRVS) demonstrated the visual benefits of early PPV in eyes with recent vitreous hemorrhage, especially in patients with type 1 diabetes.[28]

Timing of surgical intervention

The optimal timing for PPV depends on vitreous opacity severity and risk of permanent retinal damage. DRVS findings showed that early PPV (within six months) resulted in better final visual acuity compared to that of patients with bilateral vitreous hemorrhage and no useful vision.[28] Factors such as glycemic control, cardiovascular stability, and tractional detachment extent including or close to the macula influence the surgical decision.

Advanced surgical techniques

Advances in surgical technology have improved PPV safety and efficacy using smaller-gauge instruments (23G, 25G, 27G), reducing operating time and postoperative inflammation. Dyes assist in identifying epiretinal membranes (ERM) and the internal limiting membrane. Intraoperative moderate intensity endolaser is widely used, and preoperative anti-VEGF injections decrease active neovascularization, facilitating dissection and minimizing intraoperative bleeding.[6]

The development of 3D electronic visualization screen systems, per operative OCT, high-speed cutters (up to 30,000 cpm), and efficient fluidics has expanded surgical indications, including previously inoperable cases, and supports safer and faster visual recovery.[29]

Visual and anatomic outcomes, complications, and postoperative management

Visual outcomes after PPV in complicated PDR are generally favorable when performed before macular involvement. Complications include recurrent hemorrhage, secondary rhegmatogenous retinal detachment, and ocular hypertension. Postoperative care requires close monitoring of intraocular pressure, retinal integrity, and adjunctive treatments (anti-VEGF or PRP) when indicated. Visual rehabilitation may be prolonged, especially in cases with residual edema, retinal atrophy or significative macular damage.

MANAGEMENT OF DIABETIC MACULAR EDEMA

Diagnostic assessment and monitoring

The diagnostic assessment of DME is primarily based on OCT, the gold standard for measuring central macular thickness and identifying structural abnormalities such as intraretinal cystoid spaces, neurosensory detachment, and vitreomacular traction (VMT). Fluorescein angiography (FA) remains useful for evaluating capillary perfusion and identifying leakage sites, although its use has been partially replaced by OCT-angiography (OCT-A), a

non-invasive technique that provides high-resolution images of the retinal vascular plexuses. Technological advancements have made OCT-A increasingly integrated into routine clinical practice.

The combination of these tools allows for precise characterization of DME phenotypes and longitudinal therapeutic response monitoring. The presence of macular ischemia, often identified by enlargement of the foveal avascular zone (FAZ) on FA or OCT-A, serves as a prognostic marker for poor functional outcomes.[30]

First-line anti-vascular endothelial growth factor therapy

Intravitreal anti-VEGF agents (bevacizumab, ranibizumab, aflibercept and faricimab) are the first-line treatment for center-involving DME with decreased visual acuity. The RISE and RIDE studies demonstrated the efficacy and safety of ranibizumab, showing significant improvements in visual acuity and macular thickness.[31] Similarly, the VIVID and VISTA trials validated the use of aflibercept, particularly in patients with poorer baseline vision.[32]

DRCR.net Protocol T compared all three agents and found that aflibercept offered superior outcomes in patients with baseline vision of 20/50 or worse, while the agents were comparable in other subgroups.[27] Treatment regimens include monthly loading doses followed by PRN or Treat-and-Extend approaches.

Intravitreal corticosteroids

Intravitreal corticosteroids are indicated in cases that are refractory to anti-VEGF, pseudophakic patients, or when an inflammatory component is prominent. The dexamethasone implant (Ozurdex®) showed visual benefits and edema control lasting 4 to 6 months in the MEAD study.[33] The fluocinolone acetonide implant (Iluvien) was evaluated in the FAME study and provided sustained efficacy for up to 36 months in chronic cases.[34] Triamcinolone acetonide, although effective, is off-label and associated with a higher risk of intraocular pressure elevation and cataract formation. DRCR.net Protocol U showed that combining anti-VEGF with dexamethasone improves anatomy but not visual outcomes.[35]

Focal/grid laser photocoagulation

Laser photocoagulation was a mainstay treatment for DME before the anti-VEGF era. The ETDRS demonstrated reduced risk of visual loss using focal laser in clinically significant macular edema. Today, laser plays an adjunctive role, indicated for non-center-involving DME, isolated leaking microaneurysms, or as a complement to other therapies. DRCR.net Protocol I showed that combining laser with ranibizumab offered no additional benefit over anti-VEGF monotherapy, supporting its selective use.[24]

Diabetic macular edema without center involvement or with good visual acuity

In patients with non-center-involving DME and good visual acuity, observation may be a safe and effective option. DRCR.net Protocol V demonstrated that active monitoring without immediate treatment did not result in significant visual decline over two years, representing a valid alternative to early intervention.[36] Treatment decisions should consider anatomical features, follow-up feasibility, and progression risk.

Surgical approach in diabetic macular edema

Pars plana vitrectomy plays an important role in the management of selected cases of DME, particularly when there is a prominent mechanical component contributing to retinal thickening. Surgical intervention is primarily indicated in the presence of VMT, taut or thickened ERM, or in cases refractory to optimized pharmacologic therapy, including repeated anti-VEGF or corticosteroid injections. In such scenarios, PPV can alleviate the anteroposterior or tangential tractional forces exerted on the macula, promoting retinal reattachment and improved oxygenation of the inner retina.[37]

Several studies have shown that the surgical release of vitreomacular adhesion and peeling of ERM can lead to significant anatomical improvement and, in select cases, meaningful functional recovery—particularly in patients where traction is the predominant pathogenic mechanism. However, visual prognosis depends on multiple factors, including the chronicity of the edema, the degree of photoreceptor damage, and integrity of the ellipsoid zone on spectral-domain OCT (SD-OCT). Therefore, surgical indication should be individualized and based on detailed multimodal imaging, with OCT findings playing a central role in evaluating the presence and extent of traction, foveal architecture, and surgical accessibility. The decision to proceed with PPV must also consider systemic factors such as glycemic control, ocular comorbidities, and the patient's overall visual potential.[37]

In summary, while PPV is not the first-line therapy for most cases of DME, it remains a valuable option in cases with tractional pathology or treatment-resistant edema, offering anatomical stability and, in selected patients, functional improvement when pharmacologic options are insufficient.

Biomarkers and predictive factors for treatment response

Optical coherence tomography-derived biomarkers, such as large intraretinal cysts, neurosensory detachment, and intraretinal hyperreflective foci, have been associated with a suboptimal anti-VEGF response.[38] Additionally, thickening of the inner plexiform layer and loss of the ellipsoid zone are correlated with a poorer visual prognosis. Emerging studies suggest that intraocular inflammatory profiles and cytokine levels, including VEGF, may help tailor personalized treatment strategies.

Treatment algorithm and management of refractory or suboptimal cases

Managing refractory DME requires an individualized approach. Patients unresponsive after 3 to 6 anti-VEGF injections may benefit from switching agents or adding corticosteroids.[35] Anatomical assessment with OCT and identification of tractional or structural abnormalities guide the decision for surgical intervention. An effective treatment algorithm should consider DME phenotype, systemic comorbidities, and treatment adherence, integrating pharmacologic, surgical, and intensive follow-up strategies.[12]

EMERGING THERAPIES AND PERSPECTIVES

Novel pharmacological agents

Several novel pharmacological agents are being developed to improve the durability and efficacy of DR and DME treatment. Faricimab stands out as a bispecific antibody targeting both VEGF-A and angiopoietin-2 (Ang-2), approved for intravitreal use. Clinical trials such as YOSEMITE and RHINE demonstrated their non-inferiority to aflibercept with longer dosing intervals, offering promise to reduce treatment burden.[39]

Sustained drug delivery systems

Sustained-release systems aim to reduce the frequency of intravitreal injections. The Port Delivery System (PDS), a surgically implanted, refillable reservoir delivering ranibizumab, showed non-inferior results to monthly injections in the Archway trial.[40] Additionally, technologies involving nanoparticles and hydrogels are under investigation for controlled, less invasive drug release over weeks or months.

Non-invasive or minimally invasive therapeutic approaches

Non-invasive and minimally invasive therapies, such as eye drops and oral medications, are in development for DR and DME. Oral tyrosine kinase inhibitors and PPAR agonists have demonstrated effects on inflammatory and vascular pathways in preclinical and early human studies.[41] However, phase III trials are needed to confirm efficacy and safety.

Gene therapy

Gene therapy represents an innovative strategy to treat retinal diseases by enabling prolonged expression of therapeutic proteins following a single administration. Approaches under investigation involve subretinal or intravitreal delivery of viral vectors for sustained anti-VEGF expression. Early studies with RGX-314 and ADVM-022 have shown safety and durable protein expression, though challenges remain regarding immunogenicity, response variability, and target tissue access.[42]

Artificial Intelligence and telemedicine

The integration of AI into teleophthalmology has emerged as a promising strategy to expand DR screening, particularly in regions with limited access to ophthalmic care. AI-assisted systems can automate the analysis of retinal fundus images, identifying referable DR and vision-threatening disease with high sensitivity and specificity. In conjunction with telemedicine, these tools enable the remote capture, triage, and interpretation of retinal images, reducing the need for in-person evaluation and increasing screening coverage (Figure 5). Food and Drug Administration (FDA)-approved systems such as IDx-DR, EyeArt, and AEYE demonstrate that AI-based screening can be effectively implemented in clinical settings, with performance comparable to human graders when detecting more-than-mild DR.

Despite these advancements, significant challenges remain in the deployment of AI-assisted telemedicine programs. Many studies reviewed focus on high-income countries, with limited representation from low- and middle-income countries (LMICs), where the need for scalable screening tools is greatest. Moreover, the lack of transparency regarding dataset composition, model architecture, and bias mitigation strategies raises concerns about generalizability and fairness. Biases in training data can result in inequitable performance across demographic groups, and the absence of post-deployment monitoring may allow these disparities to persist. Effective implementation requires not only technical validation but also ethical oversight, ongoing recalibration, and integration with existing healthcare workflows.[43]

Economic evaluations suggest that AI-assisted DR screening can reduce costs compared to traditional

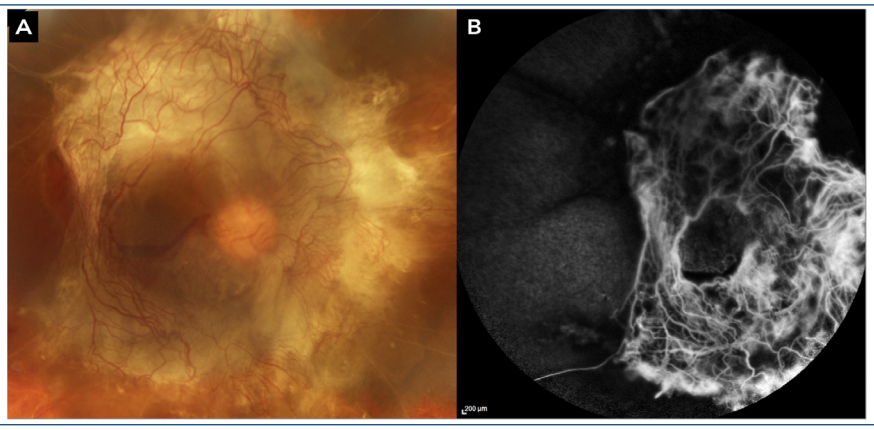

Figure 5. Color fundus image (A) acquired using a portable handheld camera (Eyer, Phelcom, Brazil), and corresponding Artificial Intelligence interpretation with a map overlay (B).

human-based approaches, particularly when using semi-automated models. However, the cost-effectiveness of these systems depends heavily on contextual factors such as greater salaries, IT infrastructure, and screening uptake. Moreover, the success of implementation relies on adequate internet access, training of local personnel, and patient engagement with digital platforms—factors that may vary widely across healthcare systems. Therefore, broader adoption of AI in telemedicine must be guided by robust evidence, inclusive development practices, and policies that promote equitable access to screening and treatment.[44]

SPECIAL CONSIDERATIONS IN CLINICAL PRACTICE

Management of diabetic retinopathy and diabetic macular edema during pregnancy

Pregnancy increases the risk of DR progression in women with preexisting diabetes, making ophthalmologic screening in the first trimester essential, followed by quarterly or severity-based monitoring. Although tight glycemic control is beneficial for the fetus, it may transiently worsen DR, requiring specialized vigilance.[45] The use of anti-VEGF agents is generally contraindicated because of limited safety data for the fetus. In severe cases, corticosteroids may be cautiously considered.

Specific aspects of diabetic retinopathy in pediatric and young adult patients (type 1 diabetes)

Young patients with type 1 diabetes are at cumulative risk of developing DR over their lifetime, typically after five years of disease duration. Strict glycemic control from childhood, as demonstrated in the DCCT/EDIC study, is crucial to delay DR onset and progression.[46] However, adherence to ophthalmologic follow-up in this population can be challenging and incorporating psychosocial and educational support is key to effective care.

Interaction between cataract surgery and diabetic retinopathy/ diabetic macular edema

Cataract surgery in patients with DR or DME requires careful planning due to the risk of postoperative retinal decompensation. Phacoemulsification-induced inflammation may exacerbate DME, particularly in moderate to severe NPDR. Studies indicate that prophylactic intravitreal anti-VEGF or corticosteroids in the perioperative period can reduce this risk and improve both anatomical and visual outcomes.[47]

Importance of a multidisciplinary approach

The management of DR and DME extends beyond the domain of ophthalmology and requires coordinated, multidisciplinary care. Optimal control of disease progression is closely tied to systemic metabolic regulation, which underscores the essential role of endocrinologists in achieving and maintaining glycemic control, as well as in adjusting antidiabetic therapies based on disease severity and comorbidities. In patients with concurrent diabetic nephropathy, nephrologists are crucial for managing fluid balance, blood pressure, and renal function—factors that significantly influence retinal vascular homeostasis. Cardiologists contribute by addressing systemic hypertension, dyslipidemia, and macrovascular complications that are known risk factors for the progression of DR. Furthermore, primary care physicians and diabetes educators play a central

role in coordinating patient follow-up, reinforcing lifestyle modifications, and ensuring long-term adherence to treatment plans.[14,15,48]

Growing evidence supports that interprofessional collaboration improves not only visual outcomes but also systemic disease markers, enhances patient satisfaction, and increases adherence to both ophthalmologic and systemic treatments. Studies have shown that patients managed within integrated care networks—where communication among specialties is standardized—are more likely to receive timely referrals, benefit from early detection of retinopathy, and demonstrate improved control of HbA1c, blood pressure, and lipid profiles. Therefore, the implementation of structured care pathways in diabetes centers, involving ophthalmologists as part of a broader chronic disease management team, is essential to address the multifactorial nature of DR and DME. This holistic approach is particularly important in preventing irreversible vision loss and reducing the overall burden of diabetes-related complications.[14,15,48]

CONCLUSION

Summary of current evidence-based recommendations for the management of diabetic retinopathy and diabetic macular edema

Current recommendations for managing DR and DME are supported by evidence from major clinical trials. For mild to moderate NPDR, close surveillance with strict systemic control is recommended. In cases of proliferative DR, both PRP and anti-VEGF therapies are effective, with the choice depending on individual patient profiles. These therapies may also be indicated for patients with severe or very severe NPDR. For center-involving DME, anti-VEGF agents are the first-line treatment, while corticosteroids are reserved for refractory cases or when anti-VEGF is contraindicated.

Major ongoing challenges

Despite therapeutic advances, several challenges remain. These include low adherence to treatment, limited access to intravitreal therapies in underserved regions, and high medication costs. Additionally, approximately 40% of DME patients do not respond satisfactorily to initial anti-VEGF therapy, requiring alternative approaches.[27] Educational initiatives, population-based screening strategies, and the incorporation of technologies such as AI may help overcome these barriers.

Future directions to optimize visual outcomes and quality of life in diabetic retinopathy

The future of DR and DME management is moving toward longer-lasting, personalized, and less invasive therapies, along with the integration of AI to predict risk and treatment response. Gene therapy and long-acting delivery systems promise to reduce treatment burden, while multidisciplinary, patient-centered care approaches can improve adherence and functional outcomes.[38] Investment in public health policies and equitable access to treatment will also be essential.

AUTHOR'S CONTRIBUTION

Clara Elisa Castro Tavares: Writing – original draft; Lucas Zago Ribeiro: Writing – review, editing & visualization; Fernando Korn Malerbi: Writing – review & editing ;Luis Filipe Nakayama: Writing – review & editing; Caio Vinicius Saito Regatieri: Conceptualization & supervision.

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Updated review of the pachychoroid spectrum and central serous chorioretinopathy

Revisão atualizada do espectro paquicoroide e da coriorretinopatia serosa central

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ABSTRACT

The pachychoroid disease spectrum (PDS) encompasses a range of chorioretinal disorders characterized by increased choroidal thickness, dilated Haller's layer vessels (pachyvessels), and choroidal hyperpermeability, often associated with retinal pigment epithelium (RPE) alterations. This review synthesizes current evidence on pachychoroid pigment epitheliopathy (PPE), central serous chorioretinopathy (CSC), pachychoroid neovasculopathy (PNV), and polypoidal choroidal vasculopathy (PCV), emphasizing their shared pathophysiological mechanisms, multimodal imaging features, and clinical implications. Enhanced depth imaging optical coherence tomography (EDI-OCT) and widefield indocyanine green angiography (ICGA) have been crucial in identifying vortex vein congestion and segmental choroidal drainage anomalies as central pathogenic drivers. Clinically, this framework supports a phenotype-based approach, where anti-VEGF therapy is prioritized for neovascular phenotypes (PNV, PCV) and photodynamic therapy (PDT) is effective for chronic, hyperpermeable non-neovascular CSC. Despite advances, challenges remain regarding standardized diagnostic thresholds, early phenotype detection, and the influence of systemic factors. The integration of hemodynamic concepts, vascular anatomy, and advanced imaging is key to developing personalized management strategies across the pachychoroid spectrum.

RESUMO

O espectro das doenças paquicoroides (PDS) abrange um conjunto de distúrbios coriorretinianos caracterizados por aumento da espessura coroidal, dilatação dos vasos da camada de Haller (paquivasos) e hiperpermeabilidade coroideana, frequentemente associados a alterações do epitélio pigmentar da retina (EPR). Esta revisão sintetiza as evidências atuais sobre a paquicoroidopatia epitelial pigmentar (PPE), a coriorretinopatia serosa central (CSC), a neovasculopatia paquicoroide (PNV) e a vasculopatia coroideana polipoidal (PCV), destacando seus mecanismos fisiopatológicos comuns, achados de imagem multimodal e implicações clínicas. A tomografia de coerência óptica com profundidade aumentada (EDI-OCT) e a angiografia com indocianina verde de campo amplo (ICGA) têm sido fundamentais para identificar a congestão das veias vorticosas e as anomalias segmentares de drenagem coroideana como principais fatores patogênicos. Do ponto de vista clínico, este modelo apoia uma abordagem baseada no fenótipo, em que a terapia anti-VEGF é priorizada para fenótipos neovasculares (PNV, PCV) e a terapia fotodinâmica (PDT) é eficaz para CSC crônica não neovascular com hiperpermeabilidade coroideana. Apesar dos avanços, persistem desafios quanto à padronização de critérios diagnósticos, à detecção precoce de fenótipos iniciais e à compreensão da influência de fatores sistêmicos. A integração de conceitos hemodinâmicos, anatomia vascular e imagem avançada é fundamental para o desenvolvimento de estratégias de manejo personalizadas em todo o espectro paquicoroide.

INTRODUCTION

Choroid is a primarily vascular layer found between the sclera and the retina, responsible for blood supply to the outer retina.[1] Anatomically, the choroid is divided into the avascular Bruch's membrane and the vascular choriocapillaris, Sattler's and Haller's layers.[2] Since 2012, when it became possible to visualize the choroid on optical coherence tomography (OCT), researchers recognized that there is a common disease spectrum of choroidal thickening, including dilated choroidal vessels in Haller's layer, thinning of the choriocapillaris and Sattler's layer, and abnormalities of the retinal pigment epithelium (RPE) over the pachyvessels.[3-5] These choroidal changes are believed to play an important pathogenic role in the development of the following clinical manifestations that occur in the pachychoroid disease spectrum: central serous chorioretinopathy (CSC), pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy (PNV), polypoidal choroidal vasculopathy (PCV), focal choroidal excavation (FCE) and peripapillary pachychoroid syndrome (PPS).[3-8]

Recently, the following diagnosis criteria were proposed for pachychoroid: reduced fundus tessellation; pachyvessels, defined as dilated choroidal vessels seen on OCT or indocyanine green angiography (ICGA), extending the entire length of the vessel to the vortex vein ampullae, causing choriocapillaris and Sattler layer attenuation; and a lack of soft drusen (an exception is made for pachydrusen, which are irregular, scattered yellow-white deposits across the posterior pole), and the presence of CSCR characteristics, such as RPE abnormalities, choroidal vascular hyperpermeability (CVH) or a prior CSCR diagnosis.[9]

Pang et al. reported ultra-widefield ICGA allowing the entire vortex vein in CSC to be visualized. The affected vortex veins showed dilatation and hyperpermeability, converging to the dilated ampulla. These findings indicate that the dilated choroidal veins of the posterior fundus, as seen on conventional ICGA, are in fact branches of the vortex vein. The dilated ampulla suggests stasis of the vortex vein to be caused by an obstruction to its passage through the sclera.[10]

The dilatation of vortex veins occurs at their distal ends, suggesting that the elevated retrograde venous pressure is transmitted to the beginning of vortex veins. Hence, dilatation is marked at the level of vortex veins and moderate at the Sattler layer, without any dilatation involving the choriocapillaris.[10]

Hayreh described that the venous outflow tract of the choroid is divided into four quadrants on the basis of a horizontal and a vertical watershed zone and noted that one or two vortex veins are independently responsible for the venous drainage in each of these quadrants.[11] In eyes with CSC, venous anastomosis occurs between the superior and inferior vortex veins at the watershed zone. The anastomotic vessels were dilated, and dilatation of Haller vessels was observed on OCT B scans. Comparison of acute CSC and chronic CSC revealed the macular choroid to be significantly thinner in eyes with chronic CSC.[12]

Therefore, venous congestion has been highlighted as a potential mechanism of pachyvessel and pachychoroid formation. Obstruction of vortex veins, especially the dominant vortex vein, which drains the macula, may contribute to the engorgement of Haller vessels and the development of subretinal fluid.[13,14]

In this review, our objective was to perform an update of the pachychoroid spectrum and central serous chorioretinopathy.

LITERATURE REVIEW

This comprehensive literature review was conducted through a systematic search of peer-reviewed articles published in English available in the PubMed database. The search was conducted since the inception of the database until April 2025. The inclusion criteria were original studies, reviews and relevant articles that addressed the pachychoroid spectrum in relation to neuroimaging, clinical manifestations and pathophysiology, or that were related to the topic. The selection of studies was performed independently by two reviewers through analysis of titles and abstracts, followed by full reading of potentially eligible articles. Discrepancies were resolved by consensus or by a third reviewer.

Data extraction was conducted using a standardized form, including information from the authors, year of publication, study focus, and main findings related to pachychoroid spectrum and its association with central serous retinopathy. The methodological quality of the studies was assessed, if applicable, using standard tools, such as the observational study assessment tool, to ensure the validity of the evidence.

The collected data were qualitatively synthesized, highlighting the most recent advances in the understanding of the spectrum, pathophysiological mechanisms, imaging findings and clinical implications associated with central serous retinopathy within the pachychoroid spectrum.

Table 1 shows that subfoveal choroidal thickness (SFCT) was frequently increased, with values between 315 and 625 μm across cases.[4,5,9] However, thickening of

Haller's layer and the presence of dilated outer choroidal vessels were also observed in some eyes with SFCT below 200 µm,[3,4] challenging the notion that only elevated total SFCT is indicative of pachychoroid disease.

Treatment strategies varied between observation, intravitreal anti-VEGF therapy and photodynamic therapy (PDT).[13,14] Functional outcomes were generally favorable, with final visual acuities ranging from 20/25 to 20/40, even in cases presenting with chronic structural abnormalities.[3,9,13]

Comparisons between eyes with SFCT greater or less than 200 µm revealed significant structural differences. Eyes with thicker choroids tended to show greater contribution from Haller's layer and a reduced relative thickness of the choriocapillaris/Sattler's layer.[3,6] Despite these differences, central retinal thickness and final visual acuity were largely similar between groups.[4]

Table 1. Clinical characteristics and subfoveal choroidal thickness in pachychoroid spectrum diseases

Study	Entity	Age (mean)	Sex	Risk factors	SFCT (µm)
Warrow et al.[3]	PPE	54	Female predominance	Corticosteroids, stress	315-460
Pang et al.[4]	PNV	56	Male predominance	CSC history	> 300
Lee et al.[5]	PCV	65	Mixed	Hypertension	386-625

SFCT: subfoveal choroidal thickness; PPE: pachychoroid pigment epitheliopathy; PNV: pachychoroid neovasculopathy; CSC: central serous chorioretinopathy; PCV: polypoidal choroidal vasculopathy.

Table 2 shows that OCT revealed serous pigment epithelial detachments (PEDs), outer retinal changes and prominent dilation of outer choroidal vessels.[3,7] Autofluorescence imaging showed mottled hyperautofluorescence, occasionally with gravitational tracts.[6] Indocyanine green angiography demonstrated dilated vortex veins and focal areas of hyperpermeability, often corresponding to zones of RPE disturbance.[3,5,6] Indocyanine green angiography frequently showed delayed choroidal arterial filling and lobular hyperperfusion, reinforcing the concept of venous outflow impairment.[3,10]

These findings overlapped with zones of PED and RPE damage, which strengthens the hypothesis of choroidal congestion as a driving mechanism.[3,4,10] Pachychoroid pigment epitheliopathy was identified by RPE mottling over choroidal thickening without fluid.[3,4,7] Acute CSC was characterized by subretinal fluid with relatively rapid resolution.[4,13] Chronic CSC featured RPE degeneration and risk of type 1 neovascularization.[4,9] PCV was categorized into an AMD-like thin choroid variant and a pachychoroid variant with choroidal hyperpermeability.[5,6]

Table 2. Imaging findings in pachychoroid spectrum diseases

Study	Modality	Findings
Pang et al.[7]	EDI-OCT	Pachyvessels, outer retinal changes
Margolis et al.[8]	EDI-OCT	Thick choroid, dilated Haller's layer vessels
Kishi et al. [12]	ICGA, EDI-OCT	Vortex vein asymmetry with delayed choriocapillaris filling, suggesting venous outflow impairment.
Spaide et al.[14]	ICGA	Dilated vortex veins, delayed filling, hyperpermeability

EDI: Enhanced Depth Imaging Optical Coherence Tomography; OCT: optical coherence tomography; ICGA: indocyanine green angiography; OCT-A: optical coherence tomography angiography.

The literature reviewed supports the hypothesis of choroidal venous overload as a unifying mechanism. Impaired vortex vein outflow results in increased hydrostatic pressure, choroidal hyperpermeability and subsequent outer retinal injury.[3,4,10] Segmental variations in vascular anatomy likely explain lesion topography.[3,11]

Table 3 shows that most cases had favorable outcomes with appropriate therapy. PDT was especially effective for chronic CSC and pachychoroid PCV,[9,10] while anti-VEGF therapy was preferred in neovascular cases.[4,5] PPE generally remained stable under observation.[1,7]

Table 3. Treatment strategies and visual outcomes

Study	Entity	Treatment	Response	Final VA
Lee et al.[5]	PCV	Anti-VEGF	Variable by phenotype	Improved or stabilized
Prünte et al. [13]	CSC	Half-dose PDT	Effective and safe	20/30 average
Spaide et al. [14]	Chronic CSC	PDT	Fluid resolution	20/25–20/40

VA: visual acuity; CSC: central serous chorioretinopathy; PDT: photodynamic therapy; PCV: polypoidal choroidal vasculopathy; VEGF: Vascular Endothelial Growth Factor; PPE: pachychoroid pigment epitheliopathy.

DISCUSSION

The pachychoroid spectrum encompasses a group of macular disorders united by structural and hemodynamic alterations in the choroid, particularly involving thickening and vascular congestion.[1,2,4] Conditions such as PPE, CSC, PNV and PCV are now seen as stages or variations of a broader phenotype driven by chronic choroidal stress.[4,5,9]

Spaide et al. proposed the concept of "venous overload choroidopathy," highlighting the central role of impaired vortex vein drainage.[14] Anatomical studies confirmed that the choroid is organized into non-overlapping drainage territories, meaning any obstruction or inefficiency in venous outflow causes localized venous hypertension.[3,11] This leads to dilation of pachyvessels, increased permeability and ultimately RPE dysfunction and serous detachment.[3,4,6]

This venous-centric model explains why lesions often cluster in specific areas, especially where drainage territories overlap or where collateral formation is insufficient.[3,11] The spatial distribution of leakage on ICGA correlates with this anatomical framework.[3,6] Furthermore, this helps reinterpret the traditional separation between PPE, CSC and PNV: rather than distinct diseases, they represent

stages of compensation and decompensation in choroidal outflow.[3,4,9]

Advanced imaging has been instrumental in characterizing these stages. EDI-OCT and SS-OCT can detect subtle Haller's layer dilation and early neovascularization, while OCT-A aids in identifying subclinical type 1 neovascular networks.[4,6,7] Widefield ICGA further delineates venous drainage territories and supports this sectoral model of congestion.[3,6]

From a therapeutic standpoint, this paradigm has practical implications. PDT has been shown to reduce choroidal hyperpermeability and vascular dilation, making it effective in CSC and some PCV cases.[9,10] Anti-VEGF therapy remains first-line for neovascular phenotypes but may be insufficient alone in pachychoroid-driven PCV.[4-6] The choice of therapy must consider phenotype, imaging biomarkers and individual disease trajectory.[4,5,9]

Despite these advances, several challenges remain. No universal definition of "pachychoroid" exists, and quantitative thresholds for SFCT or pachyvessel dilation vary across studies.[2,4] Furthermore, systemic contributors such as cortisol, stress or autonomic imbalance may modulate disease activity but remain underexplored.[7-9]

Pachychoroid disease spectrum has redefined the understanding of several chorioretinal disorders, uniting them under a common pathophysiological framework centered on chronic choroidal venous overload and impaired vortex vein drainage. Multimodal imaging techniques, particularly enhanced-depth imaging OCT and widefield ICGA, have played a pivotal role in uncovering the structural vascular features underlying these entities, facilitating more precise phenotypic classification and disease staging.[3-7] The model of venous overload choroidopathy proposed by Spaide et al. emphasizes the segmental nature of choroidal outflow and its link to localized hyperpermeability and remodeling, thus shifting diagnostic emphasis from purely morphological patterns to vascular and hemodynamic alterations.[3,11,14]

This framework has also influenced therapeutic paradigms, promoting a phenotype-guided approach. Anti-VEGF therapy remains essential for neovascular manifestations such as PNV and PCV,[4,5] whereas PDT has demonstrated significant efficacy in non-neovascular yet hyperpermeable forms such as CSC, improving anatomical and visual outcomes when guided by imaging features.[7,9,10,13]

Recognition of early phenotypes such as PPE remains limited in clinical practice despite their potential role as precursors in the disease continuum.[3,4,6,7] Nevertheless, substantial challenges persist. There is a lack of consensus on diagnostic thresholds for choroidal thickness and vascular morphology, and the systemic, genetic and anatomical factors influencing phenotypic expression and progression are not fully elucidated.[4-6,8,9]

Longitudinal studies are required to clarify transitions between phenotypes and to identify reliable prognostic markers for chronicity and treatment response. Future research should focus on standardizing diagnostic criteria, integrating systemic risk profiling and validating staging systems to enable more personalized and effective management strategies across the pachychoroid spectrum.[3,5,6,9,14]

The pachychoroid disease spectrum reframes chorioretinal disorders as manifestations of chronic choroidal venous overload, supported by multimodal imaging, particularly EDI-OCT and widefield ICGA, which elucidate the role of vortex vein congestion in disease pathophysiology. This understanding reinforces a phenotype-guided therapeutic approach. Anti-VEGF agents for neovascular variants and PDT for chronic non-neovascular CSC have demonstrated improved outcomes when tailored to imaging findings. Despite these advances, consistent diagnostic criteria and recognition of early disease expression remain limited, and some associated systemic and anatomical factors are still unknown.

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Biomarcadores de tomografia de coerência óptica em degeneração macular relacionada a idade

Optical coherence tomography biomarkers in age-related macular degeneration

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RESUMO

A tomografia de coerência óptica é uma técnica de imagem amplamente utilizada no diagnóstico e acompanhamento de pacientes com degeneração macular relacionada à idade, sendo crucial para a diferenciação entre as formas seca e exsudativa da doença. O reconhecimento e a interpretação dos diversos biomarcadores de degeneração macular relacionada à idade na tomografia de coerência óptica desempenham papéis fundamentais na identificação de sinais de atividade, cronicidade, evolução da doença e, principalmente, no monitoramento da resposta ao tratamento e ao prognóstico. Conhecer os biomarcadores permite que o oftalmologista otimize sua conduta, oferecendo a melhor orientação e o tratamento mais apropriado ao seu paciente. Dessa forma, este artigo tem como objetivo apresentar e destacar a relevância dos mais importantes biomarcadores presentes nas formas seca e exsudativa da degeneração macular relacionada à idade.

ABSTRACT

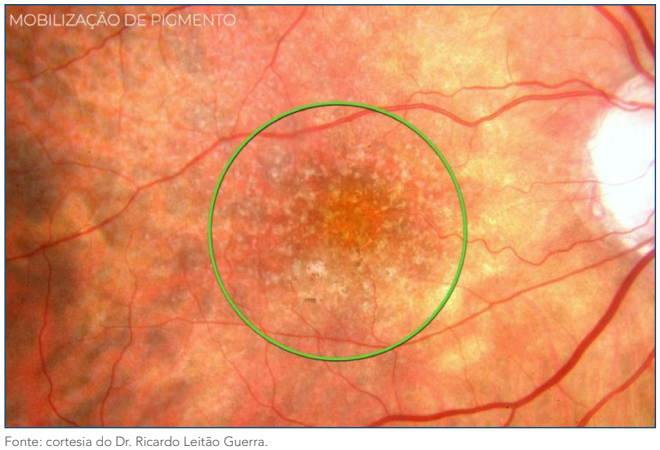
Optical coherence tomography is an imaging technique widely used in the diagnosis and monitoring of patients with age-related macular degeneration, being crucial for differentiating between the dry and exudative forms of the disease. The recognition and interpretation of various age-related macular degeneration biomarkers in optical coherence tomography play a key role in identifying signs of activity, chronicity, disease progression, and, most importantly, in monitoring the response to treatment and prognosis. Understanding the biomarkers enables the ophthalmologist to optimize their approach, providing the best guidance and treatment to the patient. Therefore, this article aims to present and highlight the relevance of the most important biomarkers present in both the dry and exudative forms of age-related macular degeneration.

INTRODUÇÃO

A degeneração macular relacionada à idade (DMRI) é uma condição prevalente, de desenvolvimento gradual e início tardio, que globalmente representa uma das principais causas de cegueira irreversível em pessoas idosas.[1-9]

A DMRI é uma doença multifatorial, na qual diversos fatores de risco interagem para seu desenvolvimento. A idade avançada é o principal fator de risco,[10,11] enquanto a etnia caucasiana e o sexo feminino também desempenham papéis importantes.[12,13] Fatores genéticos têm impacto significativo, sendo que indivíduos com histórico familiar apresentam risco três vezes maior de desenvolver a doença.[14] Entre os fatores modificáveis, o tabagismo, a obesidade e o acúmulo de gordura abdominal aumentam o risco de desenvolvimento da doença.[15,16] Por outro lado, a suplementação com vitaminas e a prática de atividades físicas oferecem proteção contra ela.[17,18]

Os achados clínicos e o padrão de progressão da DMRI podem ser classificados em três estágios distintos: inicial, intermediário e avançado.[19] A DMRI em seu estágio inicial é caracterizada pela presença de drusas de tamanho médio (variando de 63 µm a 125 µm), sem alterações pigmentares. Já na forma intermediária, observam-se drusas grandes (maiores que 125 µm) (Figura 1), com ou sem alterações pigmentares, ou, ainda, drusas médias associadas à presença de anomalias pigmentares[19,20] (Figura 2).

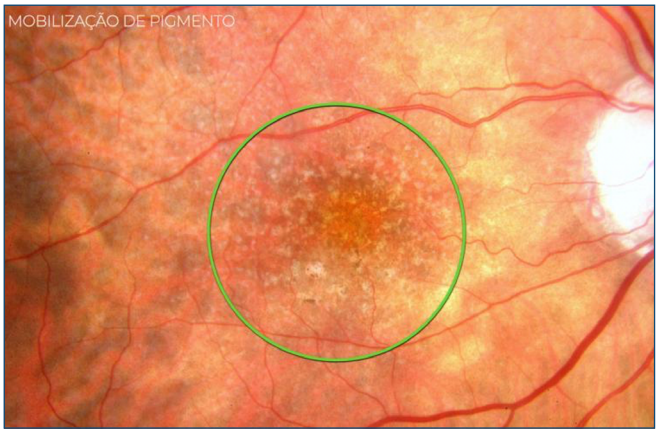


Fonte: cortesia do Dr. Ricardo Leitão Guerra.

Figura 1. Retinografia destacando drusas dos diferentes tamanhos.

A forma avançada pode ser dividida em dois tipos: a forma seca ou atrófica, que é a mais prevalente, correspondendo a 85 a 90% dos casos, e a forma neovascular ou exsudativa, menos frequente (10 a 15%), mas responsável por mais de 80% dos casos de perda de visão grave.[21]

A tomografia de coerência óptica (OCT) é um exame fundamental para diagnóstico e acompanhamento da DMRI, tanto da forma seca quanto exsudativa, devendo ser sempre complementada por um detalhado mapeamento de retina. Os recentes avanços dessa tecnologia, incluindo a melhoria na qualidade do sinal, o aumento da resolução de imagens, a maior rapidez na aquisição e a implementação da tecnologia de rastreamento ocular (*eye tracking*), estabeleceram a OCT como exame de referência nessa doença.[22]



Fonte: cortesia do Dr. Ricardo Leitão Guerra.

Figura 2. Retinografia destacando alteração de pigmento na região macular associado à drusas.

FISIOPATOLOGIA DA DEGENERAÇÃO MACULAR RELACIONADA À IDADE NEOVASCULAR

As diversas mudanças nos componentes da retina, como redução no número de fotorreceptores, acúmulo de lipofuscina no epitélio pigmentado (EPR), espessamento da membrana de Bruch e afinamento da coriocapilar, são alterações fisiológicas do envelhecimento que se intensificam significativamente em paciente com DMRI.[23,24]

Uma das principais alterações histológicas da doença é o espessamento da membrana de Bruch e o surgimento de depósitos, como as drusas. Essas alterações comprometem o transporte de oxigênio e nutrientes entre a coriocapilar e a retina, criando um ambiente favorável à formação de neovasos. O fator de crescimento do endotélio vascular (VEGF) é o principal envolvido na formação desses novos vasos, que crescem, na maioria das vezes, da coriocapilar em direção à retina e podem levar a extravasamento de fluido e sangramento. No entanto, esses vasos "anormais" também podem se originar da retina. Com o tempo, essa rede neovascular é seguida de proliferação de fibroblastos com subsequente formação de tecido fibroso e cicatrização, resultando em perda de visão irreversível, se não tratada.[23,24]

Na fundoscopia é possível identificar uma elevação da retina com coloração acinzentada, indicativa de hiperplasia do EPR em resposta ao complexo neovascular, sendo mais comum em pacientes jovens. Em indivíduos mais idosos, é mais frequente observar fluido sub-retiniano ou intrarretiniano, hemorragia sub-retiniana e/ou depósitos lipídicos. Além disso, o descolamento do EPR (DEP) pode ser sinal de neovascularização, mesmo na ausência de fluido sub-retiniano.

BIOMARCADORES DA TOMOGRAFIA DE COERÊNCIA ÓPTICA PARA A DEGENERAÇÃO MACULAR RELACIONADA À IDADE EXSUDATIVA

A forma exsudativa caracterizada pela presença da membrana neovascular sub-retiniana (MNVSR) pode ser identificada e classificada pela OCT.

A MNVRS tipo 1, forma mais comum do paciente com DMRI, é caracterizada pela presença de neovasos, originados da coriocapilar, que se localizam entre a membrana de Bruch e o EPR (espaço sub-EPR). Na OCT, essa condição é frequentemente associada ao DEP, que pode ser classificado em diferentes padrões.[25,26]

Descolamento do Epitélio Pigmentado da Retina

Representa elevações do EPR em formato de cúpula, superfície lisa e bordas demarcadas. Pode ser avasculare, exibindo conteúdo homogêneo de baixa refletividade, com a membrana de Bruch visível como uma fina linha hiperrefletiva em sua face externa. Em casos vasculares, observam-se pequenas coleções de material sólido no interior do DEP, correspondendo à proliferação fibrovascular, frequentemente associadas à presença de líquido intrarretiniano ou sub-retiniano adjacente[27] (Figura 3).

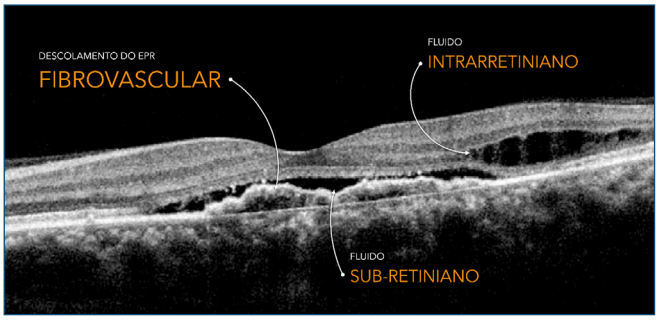
Descolamento fibrovascular do Epitélio Pigmentado da Retina

É uma elevação irregulare do EPR, causada pelo crescimento de vasos sanguíneos neovasculares entre a membrana de Bruch e o EPR.[28] Essas lesões variam em forma, reflectividade e bordas, dependendo da presença de fluido e/ou hemorragia. Em geral, são mais baixas e irregulares do que os DEPs serosos e hemorrágicos. Sua estrutura interna é heterogênea, com camadas de material de refletividade média separadas por áreas hiporreflexivas (Figura 4). Nos casos crônicos, apresentam aparência multilaminada, conhecida como "sinal da cebola", devido à deposição de cristais de colesterol.[29]

Fonte: arquivo dos autores.

EPR: epitélio pigmentado.

Figura 3. Descolamento seroso do epitélio pigmentado da retina.



Fonte: arquivo dos autores.

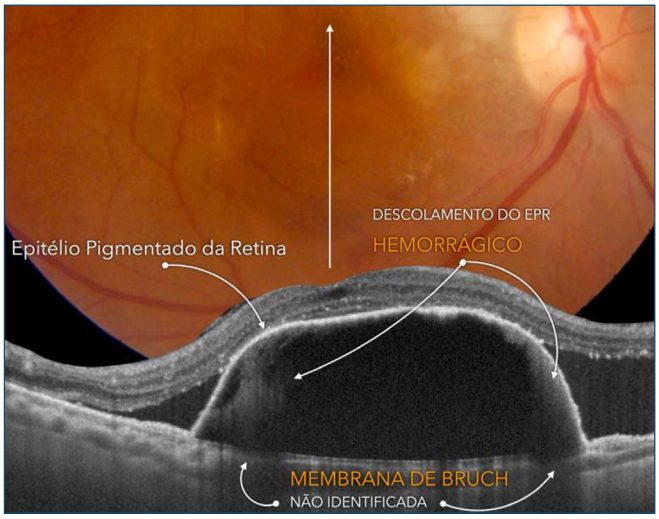
Figura 4. Descolamento fibrovascular do epitélio pigmentado da retina. É possível notar a heterogeneidade da refletividade interna.

Descolamento hemorrágico do Epitélio Pigmentado da Retina

Apresenta formato semelhante ao dos DEPs serosos, mas com bordas geralmente mais inclinadas. Além disso, a membrana de Bruch geralmente não é visível sob o DEP hemorrágico (Figura 5), devido ao sombreamento abaixo do EPR. Eles surgem a partir de sangramentos originados do complexo neovascular localizado no espaço sub-EPR ou devido a rupturas do EPR.[30]

Double-layer sign

Caracterizado por duas linhas hiperrefletivas: a superior, que representa o EPR, e a inferior, que corresponde à membrana de Bruch. O espaço entre elas indica o complexo neovascular em desenvolvimento (Figura 6). Esse

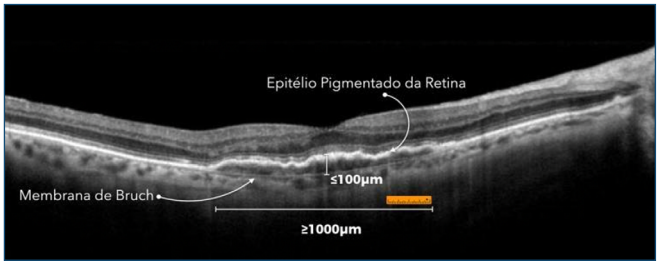


Fonte: arquivo dos autores.

EPR: epitélio pigmentado da retina.

Figura 5. Descolamento hemorrágico do epitélio pigmentado da retina. Não é possível visualizar a membrana de Bruch devido ao bloqueio do sinal pelo sangue.

sinal é um marcador precoce da MNVRS tipo 1, permitindo sua detecção nas fases iniciais, antes do surgimento de exsudação.[31]



Fonte: arquivo dos autores.

Figura 6. *Double layer sign*. Presença de elevação do epitélio pigmentado da retina com refletividade heterogênea, sem sinais de exsudação. Quando apresenta altura ≥ 100 µm e largura ≥ 1.000 µm, é denominado elevação irregular superficial do epitélio pigmentado.

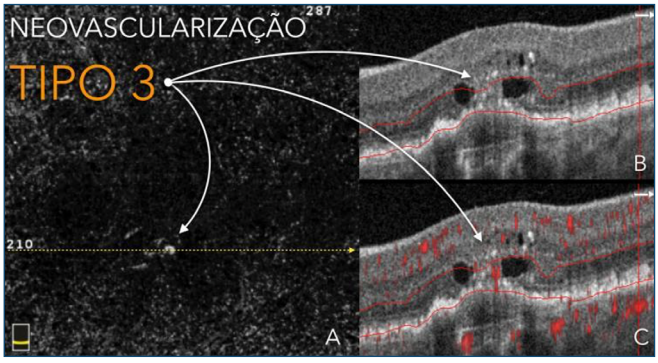
Elevação irregular superficial do epitélio pigmentado

Corresponde à elevação plana do EPR com alta probabilidade de indicar uma neovascularização não exsudativa, assim como o"*double-layer-sign*. Porém a elevação irregular superficial do epitélio pigmentado (SIRE, do inglês *shallow irregular RPE elevation)* apresenta critérios específicos: comprimento superior a 1.000 µm, altura geralmente inferior a 100 µm, irregularidade do EPR e reflectividade interna heterogênea (Figura 6). Essas características ajudam a diferenciar DEPs com maior chance de envolver neovascularização subclínica de outros, como os DEPs drusenoides ou serosos avasculares.[32]

A MNVRS tipo 2, embora menos frequente do que a neovascularização tipo 1, também pode ser observada em pacientes com DMRI. Caracteriza-se pela formação de uma banda ou placa hiperreflexiva no espaço sub-retiniano (entre a retina neurossensorial e o EPR), frequentemente acompanhada de fluido sub-retiniano e/ou intrarretiniano.

Condições que causam defeitos adquiridos no complexo EPR-membrana de Bruch reduzem a resistência para o crescimento de neovasos, permitindo que eles se expandam para o espaço sub-retiniano. Alguns exemplos são: estrias angioides, *lacquer cracks* (em miopia patológica), coriorretinites, tumores de coroide, traumas e anomalias do disco óptico.

Na MNVRS tipo 3, diferente dos tipos 1 e 2, os neovasos crescem a partir do plexo capilar profundo da retina em direção à retina externa, podendo estender até a coroide e formar anastomoses coriorretinianas (Figura 7). Focos de hemorragia intrarretiniana, localizados fora da área avascular foveal, associados ao DEP com áreas cistoides adjacentes, são os principais achados dessa condição.[33]



Fonte: arquivo dos autores.

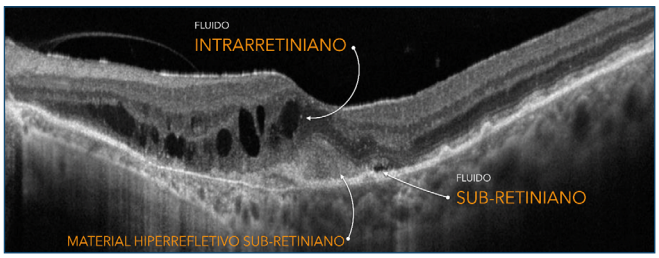
Figura 7. Membrana neovascular do tipo 3. (A) Angiograma *en face* 3 x 3 com presença de fluxo. (B) Tomografia de coerência óptica B-scan evidenciando cisto intrarretiniano e neovascularização tipo 3 como material hiperrefletivo intrarretiniano em contato com o epitélio pigmentado (anastomose coriorretiniana). (C) Tomografia de coerência óptica B-scan com sinal de decorrelação sobreposto destacando o fluxo positivo na região da neovascularização.

SINAIS DE ATIVIDADE DAS MEMBRANAS NEOVASCULARES

Fluidos sub-retiniano e intrarretiniano

São considerados os principais parâmetros da OCT para avaliar a atividade da doença e guiar o tratamento. O fluido sub-retiniano aparece como espaços hiporrefletivos localizados entre o EPR e a retina (Figuras 4 e 8). Quando

associado a sangue e/ou fibrina, o aspecto torna-se mais heterogêneo e hiperrefletivo.[34] A fisiopatologia envolve o aumento da permeabilidade vascular mediada pelo VEGF, a redução da capacidade de drenagem do EPR e a disrupção do complexo fotorreceptores-membrana limitante externa.[25,35]



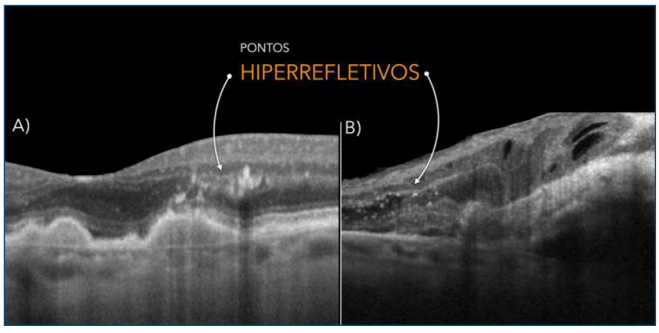
Fonte: arquivo dos autores.

Figura 8. Membrana neovascular do tipo 2 com material hiperrefletivo sub-retiniano. Presença de líquido intra e sub-retiniano.

No caso da neovascularização intrarretiniana, o fluido intrarretiniano inicialmente causa espaços cistoides hiporrefletivos na camada nuclear externa, evoluindo para as camadas nuclear e plexiforme externas da retina, e até camadas internas, quando em maior quantidade.[36]

Focos hiperrefletivos

Localizam-se principalmente nas camadas plexiforme externa e nuclear externa e representam migração de células do EPR (Figura 9A), lipídios ou exsudatos duros (Figura 9B). Eles estão relacionados com o extravasamento vascular crônico.[25]



Fonte: arquivo dos autores.

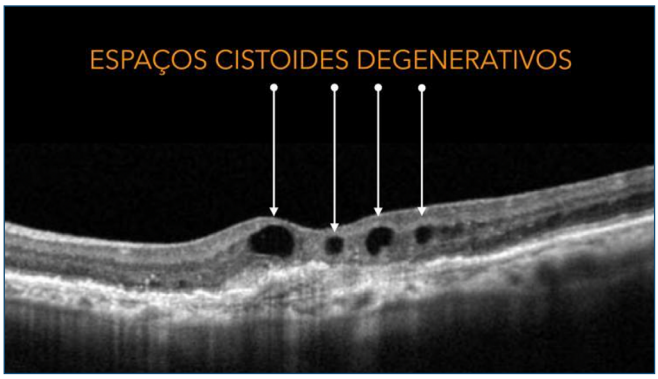
Figura 9. Pontos hiperrefletivos. (A) Migração de células do epitélio pigmentado da retina em direção a retina interna. (B) Prováveis lipídios ou exsudatos duros.

Material hiperrefletivo sub-retiniano

Na OCT, aparece como uma área homogênea de refletividade aumentada (Figura 8) e é hipoautofluorescente na autofluorescência. Ele resulta da exsudação de vários componentes séricos, como fibrina, células inflamatórias ou sangue.[25] Esse achado está relacionado a piores resultados visuais e fibrose.[37] O reaparecimento do material hiperrefletivo sub-retiniano pode indicar recorrência da atividade neovascular.[38]

É importante diferenciar os sinais de atividade da presença algumas alterações como:

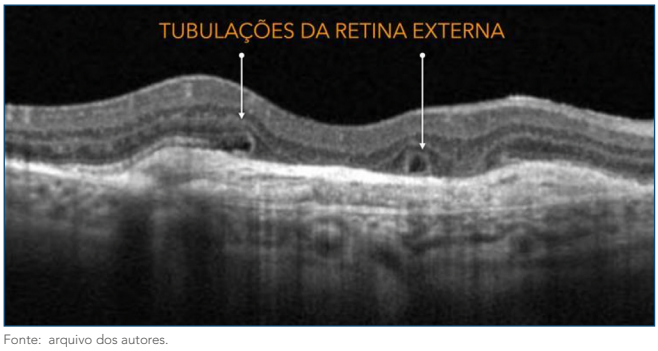
- Degeneração cistoide: ocorre por falência da bomba do EPR e perda de tecido intrarretiniano, estando presente em casos crônicos. É caracterizada pela persistência de cistos sem vazamento, que não respondem ao tratamento com agentes anti-VEGF (Figura 10).[39]



Fonte: arquivo dos autores.

Figura 10. Degeneração cistoide. Repare que os espaços hiporrefletivo não causam aumento da espessura retiniana ou alteração do contorno foveal.

- Tubulações de retina externa: presentes nos pacientes com DMRI neovascular ou atrófica avançada, correspondem ao rearranjo dos fotorreceptores em resposta à injúria local. Na OCT transversal, apresentam-se como espaços hiporrefletivos de forma redonda ou oval, com bordas hiperrefletivas, localizadas na camada nuclear externa (Figura 11). Na imagem em face, nota-se a formação de canais sub-retinianos.[39]

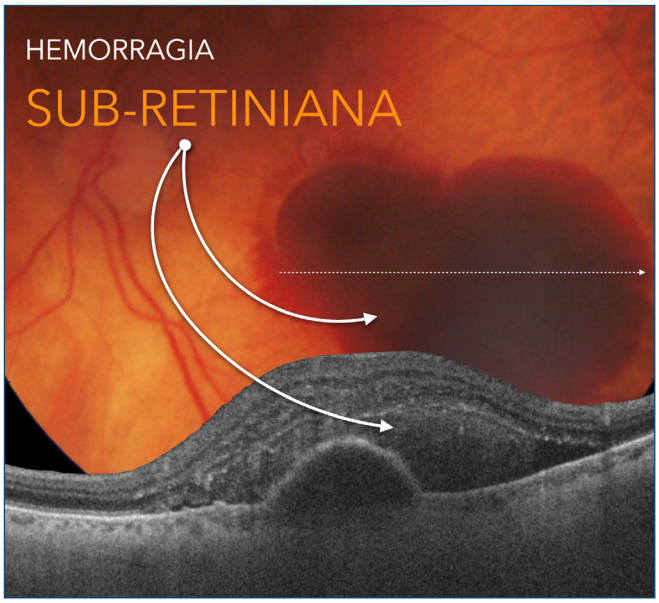


Fonte: arquivo dos autores.

Figura 11. Tubulação da retina externa.

Outras alterações que interferem no prognóstico do paciente com DMRI exsudativa:

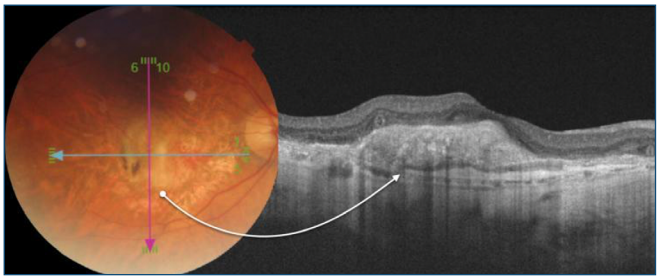
- Hemorragia: na OCT, a hemorragia aparece como um material denso e hiperrefletivo, podendo estar localizada nos espaços sub-EPR, sub-retiniano (Figura 12), intrarretiniano e, ocasionalmente, pré-retiniano. Sua presença representa que houve extravasamento de sangue do complexo neovascular.[25]



Fonte: arquivo dos autores.

Figura 12. Hemorragia sub-retiniana (retinografia). Note o material hiperrefletivo localizado entre a retina neurossensorial e o epitélio pigmentado da retina.

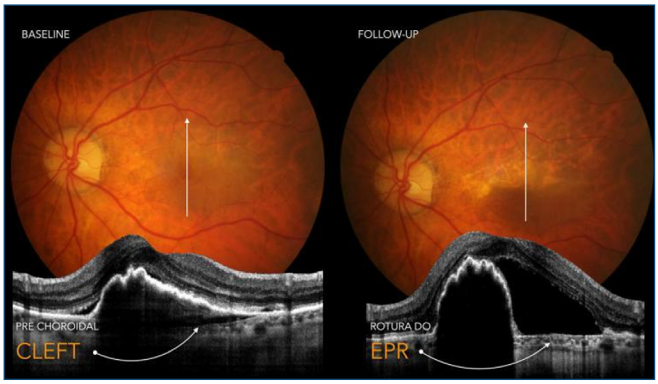
- Fibrose: é a formação de tecido rico em colágeno, que pode depositar em diversas camadas da retina, no espaço sub-retiniano, no EPR ou no espaço sub-EPR (Figura 13). É composta de colágeno tipo 4, fibroblastos, miofibroblastos, células do EPR e tecido neovascular.[40] Os complexos neovasculares jovens e ativos têm predominância vascular e são visíveis na OCT como lesões mal definidas, com refletividade média a alta. Com o tempo, o componente vascular é substituído por tecido fibrótico, formando a cicatriz disciforme, uma lesão de alta refletividade associada à atrofia dos fotorreceptores e perda visual irreversível.[41]
- *Prechoroidal cleft*: descrito pela primeira vez em 2014, corresponde à presença de um espaço hiporrefletivo encontrado entre a membrana de Bruch e o material hiperrefletivo aderido ao EPR, dentro de DEPs (Figura 14). Sua origem é atribuída a um possível acúmulo do fluido gerado pelo tecido fibrovascular. Inicialmente denominado simplesmente *"cleft"*, foi posteriormente caracterizado em DEP fibrovascular crônico, definido como *prechoroidal cleft*.[42,43] A presença desse biomarcador está associada a pior prognóstico visual a longo prazo, DEPs elevados e maior risco de rotura do EPR.[44]



Fonte: arquivo dos autores.

Figura 13. Fibrose sub-retiniano / cicatriz disciforme. A seta branca destaca lesão de alta refletividade associada à atrofia dos fotorreceptores.

- Rotura do EPR: na OCT, apresenta-se como a perda de continuidade do EPR em grandes DEPs. A rotura causa o encolhimento ou dobras do EPR com aumento do sinal dos vasos coroideanos na área afetada, devido à ausência do EPR. Com a evolução, a rotura é substituída por atrofia (Figura 14) ou cicatriz disciforme. A presença de fatores como elevada altura do DEP e irregularidade de superfícies aumenta o risco de ruptura.[45]



Fonte: arquivo dos autores.

Figura 14. *Baseline*: presença de descolamento do epitélio pigmentado com sinal de mau prognóstico do biomarcador *pre choroidal cleft*. *Follow-up*: evolução para rotura do epitélio pigmentado com hipertransmissão do sinal para coroide.

FISIOPATOLOGIA DA DEGENERAÇÃO MACULAR RELACIONADA À IDADE ATRÓFICA

A forma avançada da DMRI seca manifesta-se com atrofia geográfica, uma condição caracterizada por lesões bem definidas na mácula, envolvendo a perda progressiva de fotorreceptores. Os mecanismos fisiopatológicos da

DMRI atrófica ainda são pouco compreendidos, com discussões sobre a origem do dano retiniano, se nos fotorreceptores, no EPR ou na coriocapilar.[46]

A doença tem sido associada a um processo imunológico envolvendo a desregulação da cadeia alternativa do complemento, principalmente na via do C3 e C4.[47,48]

Inicialmente, as lesões atróficas afetam a periferia da fóvea, mas, com a progressão da doença, expandem-se para o centro da fóvea, resultando em perda gradual da visão.[22]

Na fundoscopia, as lesões de atrofia geográfica são caracterizadas por áreas de hipopigmentação do EPR, com bordas bem delimitadas, permitindo a visualização detalhada dos vasos da coroide subjacentes.

A OCT estrutural é considerada a melhor ferramenta de imagem para o diagnóstico precoce e o monitoramento detalhado de lesões subclínicas da DMRI atrófica, permitindo a visualização precisa das alterações retinianas, incluindo integridade das camadas da retina, ajudando na avaliação da progressão da doença.

CLASSIFICAÇÃO DA DEGENERAÇÃO MACULAR RELACIONADA À IDADE ATRÓFICA

O *Classification of Atrophy Meeting* (CAM) propôs uma atualização no esquema de classificação clínica da DMRI com base na OCT, amplamente utilizada em estudos clínicos atuais. Esse modelo permite uma descrição detalhada dos estágios de progressão da doença, identificando biomarcadores prognósticos e pacientes em maior risco. O CAM introduziu quatro novos biomarcadores para a progressão da forma atrófica da DMRI: atrofia incompleta da retina externa (iORA), atrofia completa da retina externa (cORA), atrofia incompleta do EPR e retina externa (iRORA), e atrofia completa do EPR e retina externa (cRORA) (Figura 15).[49]

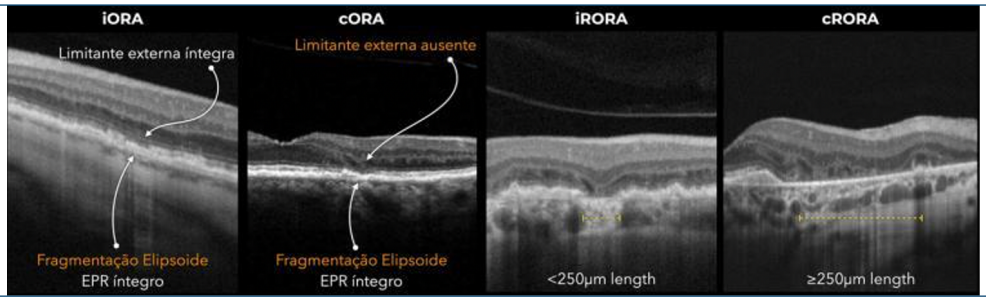
Na evolução da DMRI intermediária para a forma avançada de atrofia geográfica, as alterações observadas na OCT surgem antes das lesões clinicamente detectáveis. iRORA e cRORA são utilizados, na maioria dos estudos clínicos recentes, como biomarcadores precoces de dano tecidual retiniano:

- iRORA: são caracterizadas pela presença simultânea de certos achados na OCT. Estes incluem: degeneração das camadas nuclear interna e plexiforme externa da retina, com afinamento dessas camadas, lesão hiperrefletiva em cunha na camada de Henle, e possíveis alterações na membrana limitante externa ou na zona elipsoide; atenuação ou interrupção do EPR, com ou sem depósitos persistentes na membrana basal laminar; e sinal de hipotransmissão da coroide, geralmente abaixo de 250 µm na OCT transversal. Quando nem todos os três critérios estão presentes, os pacientes são considerados de alto risco para o desenvolvimento de iRORA.[50]
- cRORA: são identificadas pela presença de três achados na OCT: degeneração dos fotorreceptores na área afetada; evidenciada por perda da zona de interdigitação, desaparecimento da zona elipsoide, destruição da membrana limitante externa e redução da espessura da camada nuclear externa; atenuação ou interrupção do EPR, com diâmetro de 250 µm ou mais na OCT transversal; e sinal de hipertransmissão da coroide de 250 µm ou mais na OCT transversal.[49]

BIOMARCADORES DE MAIOR RISCO DE PROGRESSÃO DA DEGERANERAÇÃO MACULAR RELACIONADA À IDADE ATRÓFICA

A presença de determinados biomarcadores identificados por meio da OCT está associada a um maior risco de progressão da DMRI intermediária para forma avançada de atrofia geográfica:[51]

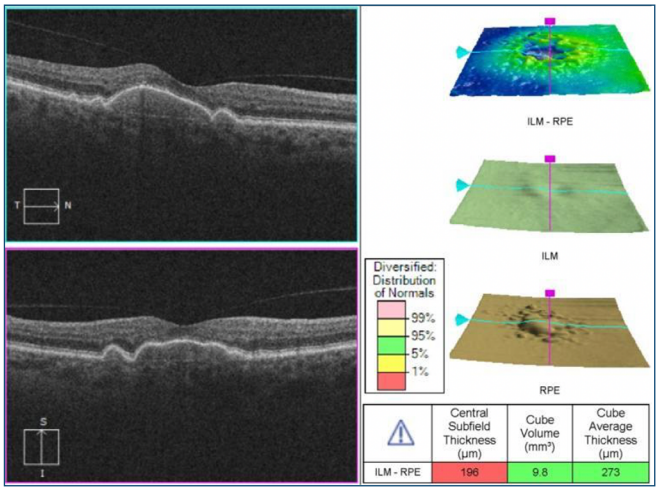
- Volume de drusas moles confluentes na OCT: os dados do *estudo Age-Related Eye Disease Study* (AREDS) indicam que a presença de drusas moles grandes e



Fonte: arquivo dos autores.

Figura 15. *Classification of Atrophy Meeting* para atrofia do epitélio pigmentado e retina externa na degeneração macular relacionada à idade.

confluentes, com alterações no EPR, está associada a maior risco de evolução para atrofia geográfica (Figura 16). Estudos recentes utilizando OCT também correlacionaram o volume dessas drusas com a progressão da atrofia geográfica.[52-55]



Fonte: arquivo dos autores.

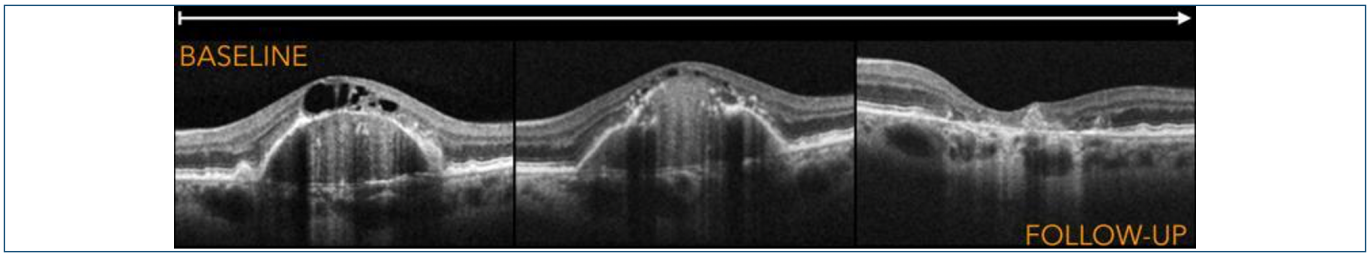
ILM: membrana limitante interna; RPE: epitélio pigmentado da retina

Figura 16. Medição automática do volume de drusas.

- Drusas de refletividade interna heterogênea: o AREDS2 e outros estudos clínicos analisaram como a refletividade tomográfica das drusas está associada à progressão da DMRI atrófica. As drusas, compostas de lipídios, carboidratos e proteínas, apresentam padrões variados de refletividade interna na OCT. Tipos diferentes de drusas, com variados padrões de refletividade, estão ligados a um maior risco de avanço para atrofia geográfica. A presença dessas subestruturas com refletividade interna variada foi associada a um maior risco de progressão para atrofia geográfica (Figura 17), tanto no estágio intermediário da DMRI quanto no aumento mais rápido da área de atrofia.[56]

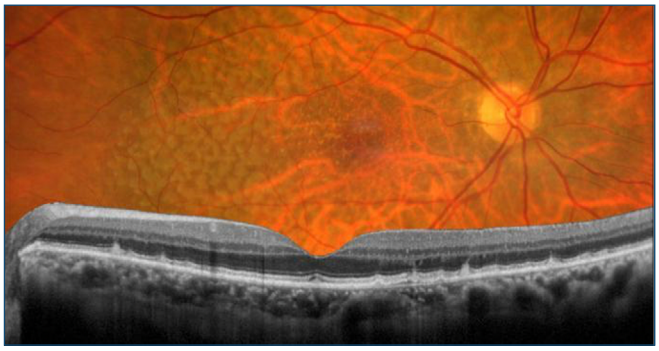
Além disso, estágios terminais das drusas podem incluir cristais de colesterol ou fibrose avascular, ambos visíveis como linhas hiperrefletivas próximas à membrana de Bruch.[57]

- Focos retinianos hiperrefletivos: estudos longitudinais indicam que os focos hiperrefletivos na retina estão relacionados a um aumento do risco de progressão da DMRI intermediária para atrofia geográfica.[56] Esses focos têm sido associados à ativação e à migração de células do EPR para a retina neurossensorial (Figura 9A),[58] embora também possam envolver outros tipos celulares. Isso torna a interpretação clínica desses achados complexa, sendo necessário considerar a análise multimodal de imagens e o histórico clínico do paciente. Além disso, esses focos podem estar ligados a depósitos de macrófagos, células microgliais, exsudatos proteicos ou lipídios.[59]
- Pseudodrusas reticulares: as pseudodrusas reticulares, também conhecidas como depósitos sub-retinianos drusenoides, são visualizadas na OCT como pequenas lesões entre o EPR e a retina neurossensorial (Figura 18). Inicialmente, esses depósitos estão localizados entre o EPR e a junção dos segmentos internos e externos dos fotorreceptores. Com o tempo, evoluem para pequenos depósitos elevados que ultrapassam os limites dos fotorreceptores.[60,61] Esses depósitos podem se estender por toda a região macular e até as áreas nasais do nervo óptico e o polo posterior. Histologicamente, estão associadas à degeneração dos fotorreceptores e à dismorfia do EPR e contêm material denso, colesterol não esterificado e depósitos inflamatórios.[57,60] Embora estejam relacionadas ao espessamento da membrana de Bruch e a alterações na circulação coroidiana, a fisiopatologia das pseudodrusas reticulares ainda não é totalmente compreendida.[62]
- Outros biomarcadores prognósticos: o DEP drusenoide e o espessamento do EPR, além de alterações na zona elipsoide, estão relacionados à evolução da DMRI intermediária para suas formas mais



Fonte: arquivo dos autores.

Figura 17. Descolamento drusenoide do epitélio pigmentado evoluindo para atrofia completa da retina externa e epitélio pigmentado.



Fonte: cortesia do Dr. Ricardo Leitão Guerra.

Figura 18. Retinografia colorida evidenciando pseudodrusas retinianas com padrão reticular. OCT demonstrando o acúmulo de material hiperrefletivo apiculado acima do EPR. Este padrão está associado a maior risco de progressão para formas avançadas de DMRI.

avançadas, incluindo tanto a forma atrófica quanto a neovascular.[63]

Lesões hiporrefletivas em forma de cunha na camada de fibras de Henle surgem como um biomarcador precoce para a atrofia geográfica (Figura 15), geralmente nas bordas da lesão.[64,65]

O aumento da refletividade nas camadas de fibras de Henle e nuclear externa, possivelmente por gliose, indica maior risco de expansão da atrofia. Além disso, alterações, como a interrupção da membrana limitante externa e a diminuição da refletividade na zona elipsoide, podem prever a direção da progressão da atrofia (Figura 15).[66]

COMENTÁRIOS FINAIS

A tomografia de coerência óptica tem se consolidado como ferramenta essencial no diagnóstico e no acompanhamento da degeneração macular relacionada à idade, sendo capaz de fornecer informações detalhadas sobre os diferentes estágios da doença, desde suas formas intermediárias até as avançadas. O conhecimento dos biomarcadores observados na tomografia de coerência óptica é crucial para a identificação precoce de sinais de progressão, como a transição da degeneração macular relacionada à idade intermediária para a forma avançada de atrofia geográfica e neovascularização. As alterações observadas nas imagens de tomografia de coerência óptica, como o iRORA, cRORA, e outras evidências de degeneração nas camadas retinianas, ou sinais de atividade de membranas neovasculares, são fundamentais para um prognóstico mais preciso e uma abordagem terapêutica mais eficaz.

A identificação precoce de alterações, como os tipos de drusas e seus padrões de refletividade, bem como os focos hiperrefletivos, desempenha papel decisivo no acompanhamento da evolução da doença e no planejamento de estratégias de tratamento personalizadas. Esses biomarcadores não apenas contribuem para a compreensão dos mecanismos patológicos da DMRI, mas também ajudam a otimizar o tratamento, permitindo intervenções mais rápidas e eficazes.

Além disso, a utilização da tomografia de coerência óptica na detecção precoce das lesões subclínicas, como as alterações nas camadas retinianas e na coroide, propicia um monitoramento contínuo e detalhado, oferecendo uma visão mais abrangente da dinâmica da doença e proporcionando aos oftalmologistas a capacidade de ajustar as abordagens terapêuticas de acordo com a evolução de cada paciente. Essa abordagem personalizada é essencial para melhorar os desfechos visuais e proporcionar uma melhor qualidade de vida para os pacientes.

Em suma, os biomarcadores de tomografia de coerência óptica estão desempenhando papel cada vez mais significativo na abordagem da degeneração macular relacionada à idade, destacando-se como um recurso valioso na detecção precoce, no acompanhamento da progressão e na avaliação de resposta terapêutica. O avanço contínuo das tecnologias de imagem, como a tomografia de coerência óptica, associada ao crescente entendimento dos biomarcadores da doença, representa um marco importante para o futuro do manejo da degeneração macular relacionada à idade, oferecendo aos oftalmologistas ferramentas mais precisas e eficientes para o acompanhamento e o tratamento dessa condição devastadora.

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Proliferative vitreoretinopathy: update in prevention and treatment

Atualizações na prevenção e tratamento da vitreorretinopatia proliferativa

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ABSTRACT

Proliferative vitreoretinopathy remains the leading cause of anatomical failure after rhegmatogenous retinal detachment repair, affecting 5 to 12% of primary detachment and up to 75% of redetachments. Although small-gauge vitrectomy, chromovitrectomy, high-definition intraoperative viewing systems and advanced preoperative imaging have revolutionized retinal surgery, the incidence of proliferative vitreoretinopathy has not decreased significantly over the past two decades. It represents a maladaptive wound-healing response in which inflammatory and fibrogenic pathways drive the formation of contractile preretinal, intraretinal, and subretinal membranes. This process typically occurs within 6 to 8 weeks after surgery, making timely prophylaxis critical. Surgical management of established proliferative vitreoretinopathy involves meticulous removal of the posterior hyaloid, residual vitreous and tractional epiretinal and subretinal membranes. The use of perfluorocarbon liquids (PFCL) and chandelier-assisted bimanual dissection improves visualization and membrane control. Brilliant blue dye enhances internal limiting membrane (ILM) identification, particularly when used under air to achieve negative staining. Small-gauge vitrectomy systems (23 to 27G) offer less invasive access, improved fluids and reduced postoperative inflammation. In complex cases, adjuvant techniques such as scleral buckling, retinectomy, and silicone oil tamponade are often required to achieve anatomical reattachment and prevent recurrence. Prophylactic therapies targeting the molecular drivers of proliferative vitreoretinopathy – such as corticosteroids, anti-inflammatory agents, anti-proliferative drugs, and biologics against cytokines, including tumor necrosis factor-alpha – are under investigation. Together, the integration of refined surgical technique, appropriate use of intraoperative adjuvants and emerging pharmacologic prophylaxis holds the potential to significantly improve anatomical and functional outcomes in patients with or at risk of proliferative vitreoretinopathy.

RESUMO

A vitreorretinopatia proliferativa (PVR) continua sendo a principal causa de insucesso anatômico após a cirurgia para descolamento de retina regmatogênico, afetando de 5 a 12% dos casos primários e até 75% das recidivas. Apesar dos avanços na cirurgia vitreorretiniana — como a vitrectomia de *gauge* reduzido, uso de corantes (cromovitrectomia), sistemas de visualização intraoperatória em alta definição e exames de imagem pré-operatórios sofisticados, a incidência de PVR não diminuiu significativamente nas últimas duas décadas. A condição representa uma resposta de cicatrização desadaptativa, em que vias inflamatórias e fibrogênicas promovem a formação de membranas contráteis preretinianas, intrarretinianas e subrretinianas. Esse processo geralmente ocorre entre 6 a 8 semanas após a cirurgia, tornando a profilaxia precoce essencial. O tratamento cirúrgico da PVR estabelecida exige remoção cuidadosa a hialoide posterior, do vítreo residual e das membranas tracionais epirretinianas e subrretinianas. O uso de perfluorcarbono e dissecção bimanual com auxílio de endoiluminação tipo "*chandelier*" melhora a visualização e o controle das proliferações. O corante azul brilhante facilita a identificação da membrana limitante interna (MLI), especialmente quando aplicado sob ar, permitindo visualização por coloração negativa. Sistemas de vitrectomia de pequeno calibre (23 a 27G) proporcionam acesso menos invasivo, melhor dinâmica de fluidos e menor inflamação pós-operatória. Em casos complexos, técnicas adjuvantes como introflexão escleral, retinotomia e tamponamento com óleo de silicone são frequentemente necessárias para o sucesso anatômico da cirurgia e prevenção de recidivas. Terapias profiláticas que visam os mediadores moleculares da PVR — como corticosteroides, agentes anti-inflamatórios, drogas antiproliferativas e biológicos contra citocinas, incluindo o fator de necrose tumoral alfa (TNF-α) — estão em investigação. A combinação de técnicas cirúrgicas aprimoradas, uso adequado de adjuvantes intraoperatórios e profilaxia farmacológica emergente tem o potencial de melhorar significativamente os desfechos anatômicos e funcionais em pacientes com PVR ou de alto risco.

INTRODUCTION

Proliferative vitreoretinopathy (PVR) is a term established by the Retina Society Terminology Committee in 1983 to describe the main complication associated with rhegmatogenous retinal detachment.[1] It denotes an active remodeling process triggered by retinal injury[2,3] and represents the leading cause of surgical failure, with an estimated prevalence of 5 to 12% of primary detachments.[4-6] It is characterized by the formation of proliferative fibrotic membranes in the posterior vitreous, located on the epi-, intra- or subretinal surfaces.

PATHOGENESIS

Initial retinal injury disrupts the blood-retinal barrier, activating cell populations that include retinal pigment epithelial (RPE) cells, glial cells (astrocytes and Müller cells) and macrophages.[7-9] Following retinal detachment, the exposure of the subretinal space to plasma proteins such as fibrinogen creates a pro-fibrotic microenvironment in which RPE cells play a central role.[8] These cells undergo epithelial-mesenchymal transition (EMT), shifting from an epithelial phenotype to a highly migratory, contractile, fibroblastic phenotype that produces extracellular matrix.[7-9] Through this process, they become myofibroblasts, which are responsible for the formation of fibrotic membranes and subsequent retinal contraction.[7]. Table 1 summarizes these pathophysiological elements. Among the molecular mediators, transforming growth factor beta (TGF-β) is considered a key driver of the EMT process. Other relevant factors include PDGF, vascular endothelial growth factor (VEGF), CTGF, interleukin (IL) 1, IL-6, tumor necrosis factor-alpha (TNF-α) and MCP-1.[7-9] Once activated, the involved cell populations start to produce their own growth factors, thereby amplifying the inflammatory response. The importance of autocrine and paracrine signaling is emphasized, with factors acting both on the originating cells and on neighboring cells.[7-9] During EMT, cells upregulate the expression of proteins such as alpha smooth muscle actin (α-SMA) and produce extracellular matrix components including fibronectin and type I collagen.[8] This leads to the formation of contractile membranes that induce retinal wrinkling and traction, ultimately resulting in redetachment.

Glial cells are co-protagonists in the initiation, progression and maintenance of PVR (Table 2). When activated following trauma or retinal detachment, they undergo a reactive gliosis process and shift their phenotype toward a more migratory and secretory state. In this state, they produce cytokines such as IL-6 and TNF-α, pro-fibrotic factors such as TGF-β, and extracellular matrix proteins including fibronectin and collagen. Their active role in fibrotic matrix production, sustained inflammation and retinal contraction expands the understanding of PVR beyond the exclusive involvement of RPE cells. Additionally, glial cells modulate intercellular signaling, promoting the migration and proliferation of RPE cells, macrophages, and fibroblasts, thus creating a self-perpetuating cycle that exacerbates fibrosis and retinal traction.[7-9]

Table 1. Summary of the main early cellular mechanisms involved in the pathogenesis of proliferative vitreoretinopathy, highlighting the central role of retinal pigment epithelial cell epithelial-mesenchymal transition, the inducing factors and the implications for anti-fibrotic therapeutic strategies

Aspects	Detail
Central event	Epithelial-mesenchymal transition of retinal pigment epithelial cells
Primary inducer	TGF-β
Celullar consequences	Migration, extracellular matrix production, contraction
Pro-fibrotic microenvironment	Inflammation plus exposure to plasma proteins
Proposed therapeutic target	Inhibition of TGF-β and blockade of epithelial-mesenchymal transition

TGF-β: transforming growth factor beta.

Table 2. Highlight of glial cells in the context of proliferative vitreoretinopathy, emphasizing their activation, mediation of inflammatory signaling and role in fibrosis, as well as identifying gliosis as a relevant therapeutic target

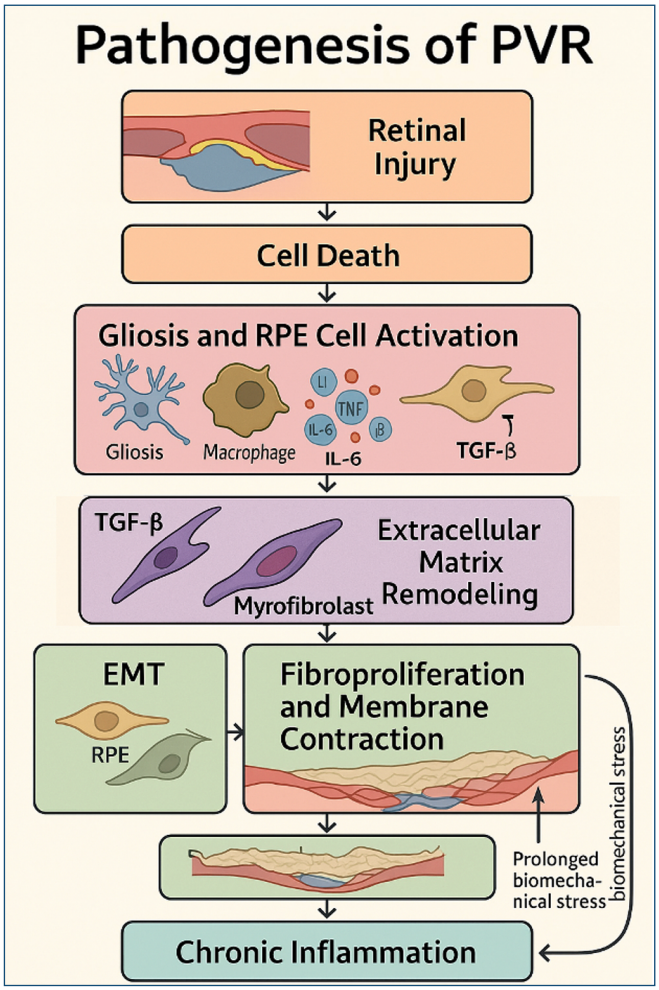
Aspects	Role of glial cells in PVR
Initial activation	Inflammatory response to retinal injury
Factor production	Secretion of inflammatory cytokines, pro-fibrotic factors and extracellular matrix proteins
Fibrosis contribution	Promotion of membrane formation and retinal contraction
Cellular interaction	Communication with retinal pigment epithelial cells, macrophages and fibroblasts
Therapeutic target	Modulation of gliosis to prevent PVR progression

PVR: proliferative vitreoretinopathy.

Vitreous cortex remnants represent another critical element that facilitates adhesion of inflammatory, glial and transformed RPE cells, as well as their migration along the retinal surface. Acting as a biological scaffold for the formation of epiretinal and subretinal membranes, the remnants support the persistence of proliferative stimulus.[7-10] The adherent cortex hinders normal regeneration of the vitreoretinal interface by concentrating cytokines and growth factors locally, thereby perpetuating an environment conducive to aberrant scarring. For this reason, complete removal of the posterior vitreous during surgery is considered a protective factor against the recurrence or worsening of PVR.[7]

Charteris et al. propose a paradigm shift in which PVR is conceptualized not merely as an exaggerated fibrotic response but rather as a failure of retinal regeneration. In this context, Müller cell transdifferentiation

is considered as pivotal as the EMT of RPE cells in the pathogenesis of fibrotic membrane formation. Upon activation, Müller cells acquire a myofibroblast-like phenotype, enabling them to generate contractile forces and secrete profibrotic mediators such as TGF-β, CTGF and key components of the extracellular matrix as well. The remodeled matrix – mechanically stressed and enriched in fibronectin and collagen – is not simply a downstream consequence but an active driver of disease progression. Within the self-sustaining cycle of PVR, this altered biomechanical environment imposes mechanical stress on retinal cells, upregulates TGF-β expression and perpetuates fibrogenesis.[10]



PVR: proliferative vitreoretinopathy; RPE: retinal pigment epithelial; TNF: tumor necrosis factor; IL: interleukin; TGF-β: transforming growth factor beta; EMT: epithelial-mesenchymal transition.

Figure 1. Schematic flowchart illustrating the pathophysiology of proliferative vitreoretinopathy. Illustration created with the assistance of an AI-based tool (ChatGPT, Open AI) and reviewed by the authors.

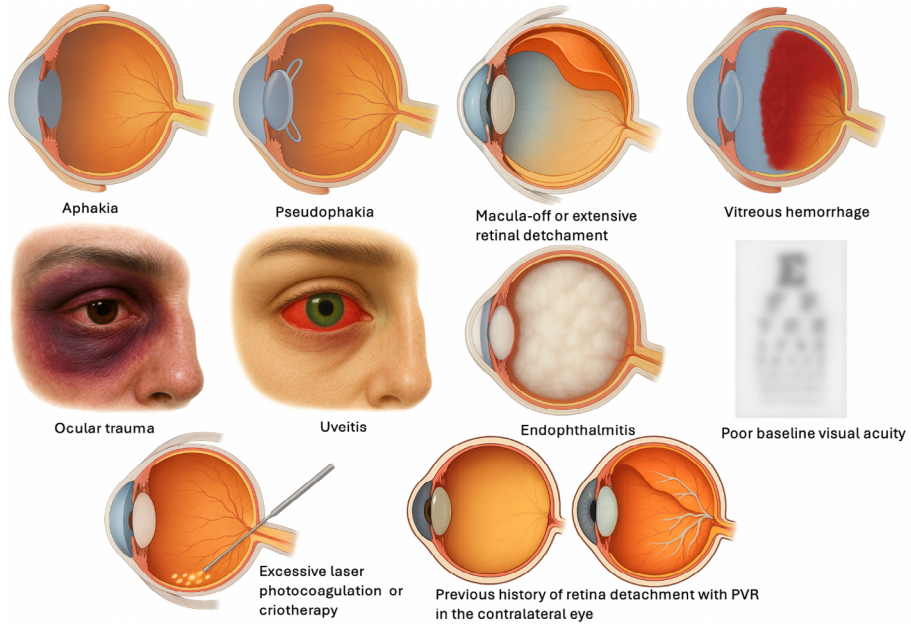
RISK FACTORS

Pro-inflammatory states occurring in the pre-, intra-, and postoperative periods have long been recognized as classical contributors to the development of PVR (Figure 2). In a comprehensive systematic review including 13,875 patients, Xiang et al. identified key ocular risk factors such as aphakia and pseudophakia, the presence of preoperative PVR, vitreous hemorrhage and retinal detachments involving the macula or with extensive spread. Systemic factors intrinsic to the patient have also been implicated, with older age and smoking being frequently associated with increased risk.[11] However, a recent review published in 2025 encompassing data from 57,264 eyes pointed to a distinct pattern, where younger patients and those with systemic hypertension exhibited higher susceptibility to PVR – a finding that underscores an age-related dichotomy in the current literature. Additional clinical predictors include poor baseline visual acuity, a history of ocular trauma, uveitis, choroidal detachment and endophthalmitis.[12] Notably, a prior episode of rhegmatogenous retinal detachment complicated by PVR in the contralateral eye increases the likelihood of PVR by 3.5 times in individuals aged 18 years and older.[13]

Intraoperative cryotherapy has been identified as an independent risk factor for the development of severe (PVR).[14] Similarly, pars plana vitrectomies performed using larger gauge instruments (20G or 23G) have been associated with a 3.6-fold increased risk of PVR development when compared to procedures conducted with 25G systems.[15] Additional intraoperative contributors include excessive panretinal photocoagulation, vitreous loss, incarceration of retinal tissue during subretinal fluid drainage and incomplete tamponade of retinal breaks. These conditions establish a permissive microenvironment for cellular migration and subsequent formation of contractile fibrotic membranes.[16] Notably, despite significant improvements in vitreoretinal surgical methods, the overall incidence of PVR has remained stable over recent years, as consistently demonstrated across the literature.[17]

Genetic background

The genetic susceptibility to PVR is not attributed to a single gene but rather to the combined influence of multiple genetic variants involved in inflammatory regulation, apoptosis and fibrogenesis.[17] Pastor et al. have proposed that polymorphisms in IL-6 and TNF-α may modulate the inflammatory response, suggesting that genetic background is a key factor when combined with environmental triggers such as surgery or intraocular inflammation.[18] Supporting this, a multicenter European study analyzed 224 single nucleotide polymorphisms (SNPs) across 30



PVR: proliferative vitreoretinopathy.

Figure 2. Major risk factors associated with the pathophysiology of proliferative vitreoretinopathy, including predisposing inflammatory, anatomical and surgical conditions. Illustration created with the assistance of an artificial intelligence tool (ChatGPT, Open AI) and reviewed by the authors.

inflammation-associated genes in patients with retinal detachment – with and without PVR – and reported significant associations between PVR and polymorphisms in the TNF, SMAD7 and PI3KCG genes.[19]

CLASSIFICATION OF PROLIFERATIVE VITREORETINOPATHY

The classification of PVR was first proposed in 1983 by the Retina Society Terminology Committee, focusing on morphological features and dividing the disease into four stages (A to D). This system was later refined by the Silicone Oil Study in 1989[20] and by Machemer et al. in 1991[21], who introduced a more detailed framework based on anatomical location and extent of disease, particularly within stage C. These updates, as presented in Table 3, aimed to improve standardization of surgical indications, technical approaches and prognostic evaluation.

In its simplified form, PVR classification includes:

- Stage A (minimal PVR): characterized by pigment clumps and inflammatory cells in the vitreous, associated with vitreous haze but without clinical evidence of retinal traction or membranes – reflecting early, mild inflammation.
- Stage B (moderate PVR): defined by partial-thickness folds on the inner retinal surface and/or wrinkling of retinal break margins. The retina often appears stiffer with localized vessel tortuosity, indicating the beginning of tangential traction.
- Stage C (severe PVR): marked by fixed, full-thickness retinal folds and the presence of epiretinal or subretinal contractile membranes. This stage is anatomically subdivided into anterior (C-A), posterior (C-P), or combined (C A/P) based on the location of the membranes relative to the equator. The extent of retinal involvement is graded as C1 (≤ 1 quadrant), C2 (≤ 2 quadrants), C3 (≤ 3 quadrants), or C4 (total retinal involvement). This stage is anatomically subdivided approximately at the level of the ocular equator into anterior PVR (C-A), posterior PVR (C-P), or combined (C A/P). On the basis of the extent of retinal involvement, grade C PVR is further classified as:
  - C1: up to one quadrant (3 clock hours).
  - C2: up to two quadrants (4 to 6 clock hours).
  - C3: up to three quadrants (7 to 9 clock hours).
  - C4: involvement of all four quadrants.

Table 3. Classification of proliferative vitreoretinopathy according to severity grade, anatomical location and extent of vitreoretinal alterations

Grade	Characteristics	Location	Extent
A	Vitreous cells	—	—
B	Retinal wrinkling, fixed folds	—	—
C-P	Tractional membranes	Posterior retina	1 to 4 quadrants
C-A	Tractional membranes	Anterior retina	1 to 4 quadrants

Stage D (massive PVR), previously described as full thickness fixed retinal folds involving all four quadrants,[1] was ultimately removed from the classification system. Despite significant efforts toward standardization, current classification schemes continue to show limited and inconsistent application in clinical practice. Studies have demonstrated a low rate of comprehensive use of these criteria, particularly concerning the detailed anatomical and severity-based description of grade C PVR.[22] Updating the existing clinical classification of PVR may provide clinicians with a more precise framework for subclassifying cases, enabling earlier recognition and treatment and ultimately improving patient outcomes.[23]

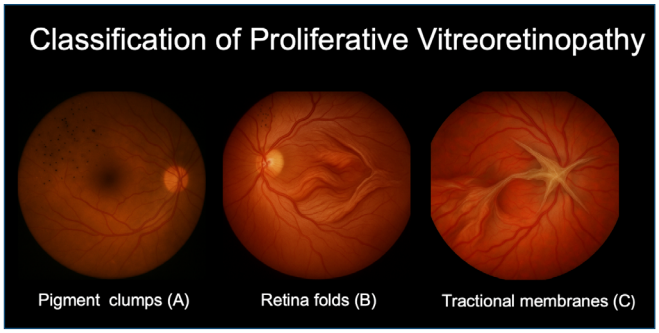


Figure 3. Simplified schematic representation of proliferative vitreoretinopathy classification. Illustration generated with de assistance of an artificial intelligence tool (Chat GPT, Open AI), subsequently adapted and validated by the authors.

Classification of contraction patterns in grade C proliferative vitreoretinopathy [21,22]

Posterior proliferative vitreoretinopathy (C-P)

Type 1: focal

Focal posterior contractions or localized traction with retinal folds confined to specific areas. Single starfold or multiple single isolated starfolds.

Type 2: diffuse

Presence of multiple retinal folds involving more extensive regions of the retina.

Type 3: subretinal

Formation of subretinal membranes, as illustrated in Figure 4, including:

- Starfolds posterior to the vitreous base.
- Confluent folds potentially obscuring the optic disc.
- Subretinal proliferation with annular or linear membranes.

Anterior proliferative vitreoretinopathy (C-A)

Type 4: circumferential contraction

Circumferential contraction exerting traction on the retina at the posterior margin of the vitreous base, pulling the peripheral retina centripetally, leading to distortion and potential shortening of the retina. These configurations may pose significant challenges to surgical reattachment due to the rigidity and fixed nature of the folds.

Type 5

Anterior displacement: anterior traction of the retina at the vitreous base, potentially leading to anterior displacement of the retina. This pattern pulls the peripheral retina forward, toward the vitreous base, ciliary body or even the posterior surface of the iris. The anterior traction causes the retina to fold or buckle anteriorly, often resulting in shortening of the peripheral retina. Such displacement may create a rigid trough-like configuration, making retinal reattachment more challenging and increasing the risk of retinal incarceration during surgery.

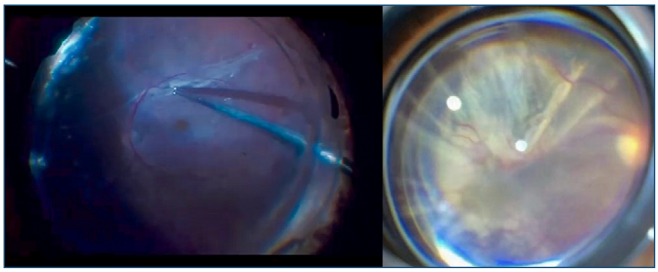


Figure 4. Examples of grade C-P proliferative vitreoretinopathy with subretinal membranes.

TREATMENT OF PROLIFERATIVE VITREORETINOPATHY

During the preoperative evaluation of patients with rhegmatogenous retinal detachment, it is important to consider:[18]

- The extent and duration of the detachment: the more extensive and prolonged the retinal detachment, the more pronounced the exposure of RPE cells and the release of pro-inflammatory cytokines is.
- The presence of grade B or C PVR at initial diagnosis: the presence of PVR at the time of diagnosis increases the risk of progression, even after complete surgical removal.
- Vitreous hemorrhage: the presence of blood cells in the vitreous cavity promotes cell migration and proliferation.

- Ocular trauma or history of previous intraocular surgery: disruption of the blood-retinal barrier facilitates the migration of inflammatory cells.
- Intraocular inflammation: eyes with uveitis represent an increased risk of developing PVR.
- Several of these risk factors are depicted in Figure 5.

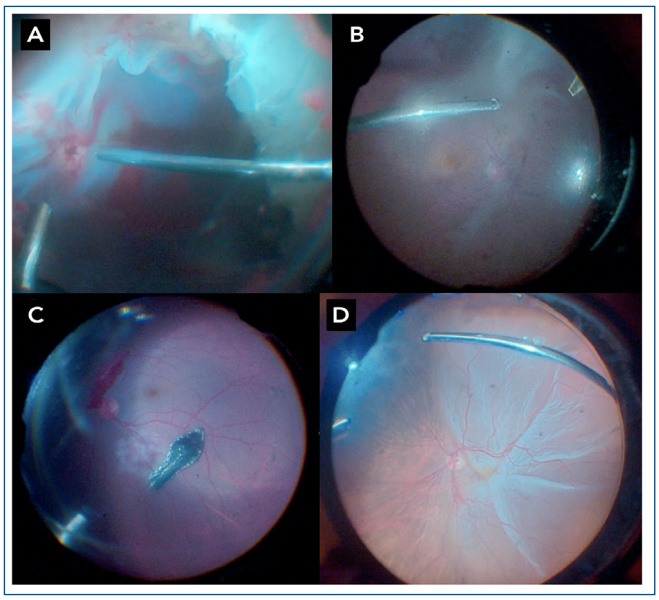


Figure 5. Preoperative risk factors for proliferative vitreoretinopathy development. (A) Retinal detachment following penetrating trauma with giant retinal tear and vitreous hemorrhage; (B) endophthalmitis; (C) trauma with metallic intraocular foreign body; (D) macula-off rhegmatogenous retinal detachment with grade B proliferative vitreoretinopathy.

The main intraoperative risk factors include:[24] iatrogenic retinal breaks; intraoperative hemorrhages; prolonged surgical time with excessive tissue manipulation; choroidal detachment; and excessive laser application and cryotherapy.

Surgical management of PVR involves complete removal of the residual vitreous, posterior hyaloid, and both epiretinal and subretinal membranes responsible for retinal traction. The PVR formation cycle is known to extend over approximately 90 days. However, in cases of recurrent retinal detachment due to early membrane formation, it may be advisable to delay reoperation until membrane maturation to facilitate dissection and reduce the risk of exacerbating the inflammatory response associated with early surgical intervention. Moreover, mature membranes are typically easier to identify and remove. In contrast, if the redetachment involves the macula, immediate reintervention is imperative to preserve the patient's visual prognosis.[26]

Small-gauge vitrectomy systems (23, 25 or 27 G) have significantly advanced the surgical management of PVR by enabling a less invasive approach, characterized by smaller incisions, reduced ocular trauma, and faster postoperative recovery. These platforms provide superior fluidic control and enhanced intraocular stability, which are critical for the effective removal of both epiretinal and subretinal membranes. Furthermore, the use of chandelier illumination and bimanual techniques – facilitated by small-gauge systems – improves visualization and enhances safety during complete vitreous and tractional membrane dissection. These factors contribute to higher rates of anatomical success, reduced postoperative inflammation and subsequently lower recurrence rates of PVR.[(27)]

In the context of membrane identification, chromovitrectomy has emerged as an essential tool in the surgical management of PVR. Brilliant blue dye plays a particularly important role in the visualization and effective removal of the ILM, which may serve as a scaffold for the recurrence of epiretinal membranes. Brilliant blue provides excellent staining of the ILM, facilitating membrane peeling even in peripheral regions or in areas with structural alterations secondary to PVR. The dye can be applied following fluid-air exchange to achieve a higher concentration over the retinal surface, enhancing visualization of preretinal membranes through a negative staining effect (Figure 6). Moreover, brilliant blue stands out for its superior safety profile when compared to other dyes, such as indocyanine green, demonstrating lower retinal toxicity at clinically used concentrations.[28] Consequently, its use may reduce the risk of PVR recurrence and contribute to improved anatomical and functional postoperative outcomes.

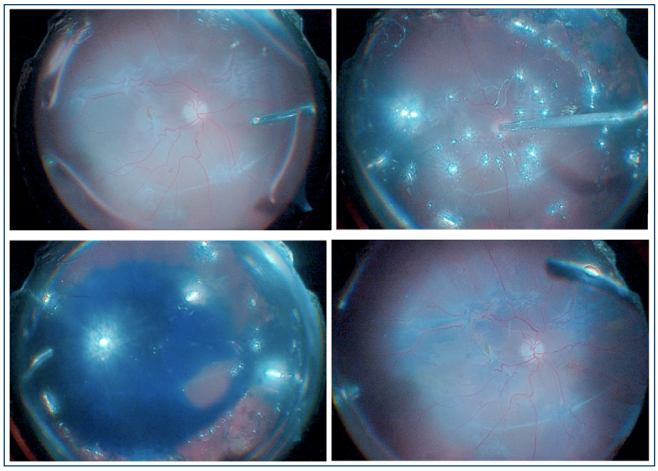


Figure 6. The phenomenon of negative staining is observed, in which a fluid-air exchange is performed followed by injection of brilliant blue dye under air. Upon BSS infusion, areas of proliferative vitreoretinopathy become highlighted adjacent to the internal limiting membrane stained by the brilliant blue dye.

The surgical technique for the removal of PVR requires meticulous maneuvers, in which the use of retinal forceps plays a central role. High-precision forceps are employed to peel both epiretinal and subretinal membranes. A critical initial step is the identification of the most accessible adhesion point of the membrane, often revealed following staining with brilliant blue dye. Using delicate forceps, such as the Eckardt type, the surgeon initiates a pinch-and-peel maneuver, gently lifting the membrane to separate it from the retinal surface. Frequently, the posterior pole – particularly the macular region – is the preferred site for initiating membrane dissection. In advanced PVR cases, membranes are often densely adherent or interdigitated with the retina, requiring adjunctive techniques such as delamination or bimanual dissection. In this approach, one hand manipulates the forceps while the other uses a pick or spatula to dissect the interface between the membrane and the retina. Accessory chandelier illumination is essential in this context, allowing bimanual manipulation and enhancing stereoscopic visualization. Perfluorocarbon liquid is widely used to stabilize the retina during these maneuvers by flattening detached areas and providing counter-traction, thus facilitating membrane removal with reduced iatrogenic risk (Figure 7). Additionally, PFCL may serve as a temporary tamponade during retinectomies or aid in the exclusion of active subretinal traction (Figure 8).[29,31] The precise combination of appropriate surgical instruments and intraocular adjuvants such as PFCL is essential for optimizing visualization, minimizing trauma and improving surgical success rates in complex cases of PVR.

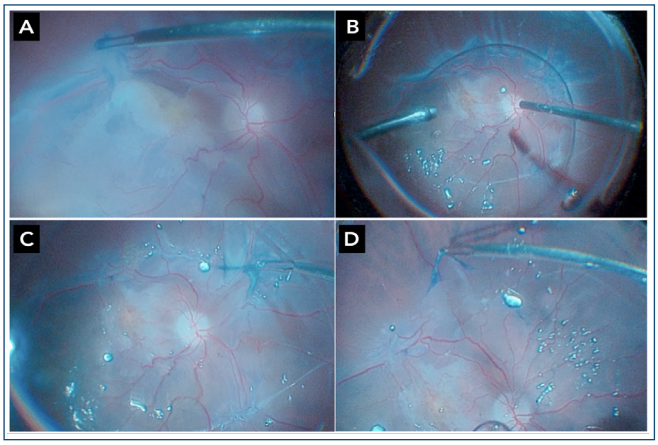


Figure 7. (A) Membrane dissection is initiated at the macular region; (B) perfluorocarbon liquid is applied to stabilize the posterior pole; (C and D) removal of preretinal membranes under perfluorocarbon using forceps.

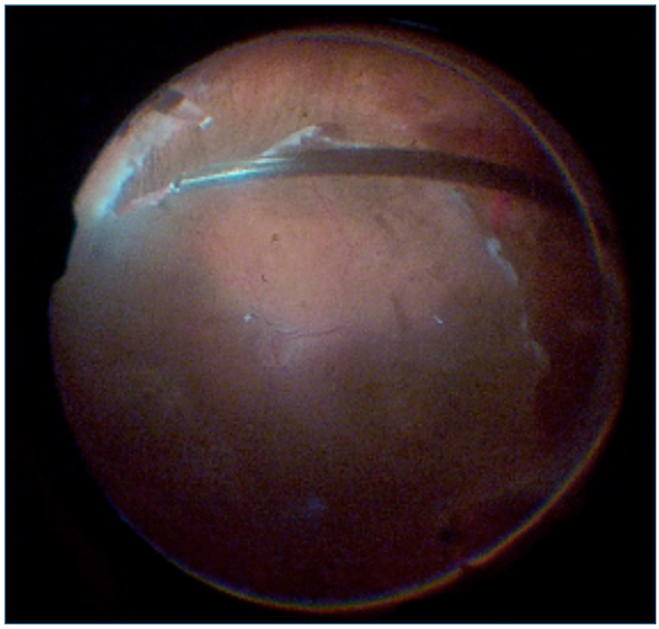


Figure 8. Advanced case of recurrent retinal detachment due to proliferative vitreoretinopathy, in which an inferior retinectomy was performed with the aid of perfluorocarbon liquid to stabilize the posterior pole.

SURGICAL STRATEGIES TO MAXIMIZE RETINAL ATTACHMENT SUCCESS

Combination pars plana vitrectomy and scleral buckle

Some studies have shown that single surgery attachment success (SSAS) is higher in eyes predisposed to PVR, most likely because the buckle mitigates residual circumferential and antero-posterior traction at the vitreous base. In a series of 389 eyes, SSAS was 80.8% with PPV-SB *versus* 67% with PPV alone.[6]

The combination of these techniques provides additional mechanical support to the retina. Retrospective analysis has demonstrated a significantly higher rate of anatomical success compared to PPV alone, particularly in cases involving inferior retinal breaks and advanced PVR.[32] Moreover, scleral buckling may be especially beneficial in pseudophakic eyes, where vitrectomy alone may be insufficient to manage peripheral traction.[33] Therefore, the combined approach should be considered in cases of recurrent retinal detachment due to PVR, with the aim of optimizing both anatomical and functional outcomes.

Extended internal limiting membrane peeling

Removing the ILM beyond the vascular arcades could help eliminate a potential scaffold for cell proliferation.

Two retrospective series showed the benefit of "arcade to arcade" ILM peeling in improving anatomic success and reducing PVR-related redetachments.[34,35] Prospective, randomized trials are still lacking; nevertheless, converging observational evidence supports incorporating extended ILM peeling to maximize anatomic and visual outcomes.

Vitreous-base management

Vitreous-cortex remnants appear to be an important intraoperative contributor to PVR, and complete removal of these scaffolds at the vitreous base is recommended during vitrectomy in high-risk eyes.[7] Triamcinolone acetonide staining markedly improves visualization of the posterior hyaloid and vitreous remnants, permitting more thorough excision and lowering the likelihood of residual scaffold. In a prospective series of eyes undergoing rhegmatogenous retinal detachment repair complicated by early PVR, triamcinolone-assisted vitrectomy achieved higher hyaloid removal and lower membrane recurrence rate.[36]

Amniotic membrane patching

Human amniotic membrane patches placed over large retinal breaks or retinectomy edges could also work as both a physical barrier and a biologically active TGF-β-suppressive matrix.[37] Although this therapy is not widely available and is rarely used, it may nevertheless serve as a valuable adjuvant in eyes with complex PVR.

Tamponade selection

Tamponade selection influences both the mechanical stability of the retina and the biological environment in which PVR evolves. Silicone oil is the vitreous substitute of choice in cases of retinal detachment associated with PVR, particularly in complex scenarios involving multiple retinal breaks, subretinal traction and peripheral retinectomies.[38] However, the Silicone Oil Study,[39,40] multicenter prospective randomized trial, and the European Vitreoretinal Society Retinal Detachment Study found no significant difference in anatomical success between perfluoropropane gas and silicone oil.[41] Collectively, these data support the use of either C_3F_8 or standard-viscosity (1,000 or 5,000 cSt) silicone oil in eyes with established or high-risk PVR, while discouraging the use of short-acting gases. When extensive and complex inferior pathology is present, heavy silicone oils or short-term perfluoro-octane tamponade may still confer additional mechanical benefit.[38] It is always important to consider potential complications associated with prolonged use of silicone oil, such as ocular hypertension, cataract formation in phakic patients and silicone oil emulsification.

PHARMACOLOGIC APPROACH

Methotrexate

Folate antagonism offers dual anti-proliferative and anti-inflammatory effects – both of which target key pathways in the development of PVR. Methotrexate has emerged as the most promising pharmacologic agent in this context. In phase 3 GUARD trial, 13 intravitreal injections of methotrexate 0.8% (ADX-2191) administered over four months reduced the rate of redetachment within six months from 39% in historical controls to 24% in treated eyes, achieving statistical significance and meeting the trial's primary endpoint.[42] Other series have reported similar findings with alternative low-dose methotrexate regimens; however, some studies, including multicenter trial, have shown no significant difference in overall rates of PVR formation.[43] These mixed outcomes suggest that while methotrexate appears to be a feasible pharmacologic adjuvant in selected cases, further well-designed prospective studies are still necessary to confirm its efficacy, define optimal dosing strategies and fully establish its safety profile.[43-45]

Corticosteroids

One of the first classes of agents studied to prevent PVR were systemic corticosteroids. However, systemic corticosteroid therapy has yielded conflicting results in this context.[(46,47] Intravitreal triamcinolone acetonide, although commonly employed for its anti-inflammatory properties, has not shown consistent efficacy in preventing recurrent retinal detachment or improving anatomical outcomes in eyes with PVR. Sustained-release corticosteroid delivery systems have also been investigated, but results have been similarly inconsistent.[48] Nevertheless, it remains a valuable adjunct in managing postoperative cystoid macular edema.[49]

Antimetabolites and alkylating agents

5-fluorouracil (5-FU) combined with heparin has shown inconsistent outcomes; large, randomized trials found no anatomical benefit.[50,51]

Melphalan, widely used in the treatment of intraocular retinoblastoma, is currently undergoing a first-in-human safety assessment clinical trial led by a Brazilian group at the *Escola Paulista de Medicina*. Its rationale is based on its potent nucleic acid alkylating mechanism

and a potentially favorable low-dose ocular safety profile,[52,53] and it may offer a promising new therapeutic alternative for managing PVR in the coming years.

Infliximab

Infliximab is a chimeric monoclonal antibody that targets tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine involved in the pathophysiology of several ocular and systemic inflammatory diseases. Its prior success in treating autoimmune and ocular inflammatory conditions supports its potential utility in modulating the inflammatory cascade that drives PVR progression.[54,55] The FIXER trial evaluated a single 1 mg intravitreal injection of infliximab into the air-filled globe prior to silicone oil placement during vitrectomy for grade C PVR. The study reported modest improvements in final visual acuity but no significant difference in anatomical outcomes.[56]

PERSPECTIVE

Several ongoing clinical trials are exploring novel pharmacological strategies for the prevention and treatment of PVR. Among the most promising are Rho-kinase (ROCK) inhibitors, such as topical netarsudil, and intravitreal melphalan, an alkylating agent currently undergoing first-in-human evaluation. While many of these agents remain investigational, methotrexate continues to be the only therapy supported by phase 3 evidence demonstrating reduction in redetachment rates in high-risk eyes.

Looking ahead, combination therapies that sequentially target both the inflammatory and proliferative phases of PVR are a rational next step. In parallel, the integration of artificial intelligence tools – integrating clinical data, ultra-widefield imaging and genetic risk markers – may enable individualized risk stratification and optimize prophylactic strategies. These advances have the potential of shifting PVR management from reactive treatment to proactive prevention.

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