RESEARCH REPORT

DECEMBER 2019

UPCOMING FUNDING OPPORTUNITIES

Click on links for more funding detail.

Queen's Research Opportunity Fund-Catalyst Grant
Notice of Intent: January 10, 2020
Full application: February 10, 2020

CIHR-Planning and Dissemination Grants
CIHR. Formal announcement will be made in January 2020. Deadline in March 2020.

Research in Clinical Assessment
MCC. February 2020

Medical Education Research Grant
RCPSC. March 2020

Fighting Blindness Canada
LOI May 2020
Full Application August 2020

Retina Foundation of Canada
Junior and Senior Investigator Clinical Research Grants
Deadline: May 2020

Physician Services Incorporated
Medical Education, Health Research
Rolling Deadline

Global Ophthalmology Awards Program (GOAP). Funding

Recent Department Publications (Sept-Dec)

Intraocular antibodies as a novel target for understanding and treating vascular diseases of the eye. Rullo J, Bae S, Far PM, Alhazimi A, Gupta V, Bal M, Hopman WM, Irrcher I, Urton T, Bona M, Campbell RJ, Gonder JT, Sharma S. Accepted in CJO.

Validation of a novel strabismus surgery 3D-printed silicone eye model for simulation training. Jagan L, Turk W, Petropolis C, Egan R, Cofie N, Wright KW, Strube YN. Accepted in J AAPOS.

A curious case of arteritis: infectious, inflammatory, or both. Rullo J, Far PM, Farmer JF, Clements-Baker M, ten Hove M. Can J Ophthalmol. Dec 2019. 54(6): e288-e292 (attached).

The Making of a Great Surgeon (Commentary). Campbell RJ. Ophthalmology. Nov 2019. 126 (11): 1490-1491, 2019 (attached).

Intraocular Calcidiol: Uncovering a role for vitamin D in the eye. Rullo J, Pennimpede T, Mehraban Far P, Strube YN, Irrcher I, Urton T, Bona M, Gonder T, Campbell RJ, Ten Hove M, Sharma S, Farmer J, Petkovich M. J Steroid Biochem Mol Biol 2019. Nov 14; 197: 105536 (attached).

Involving ophthalmology departmental stakeholders in developing workplace-based assessment tools. Braund H, Dalgarno N, McEwan L, Egan R, Reid M-A, Baxter B. Can J Ophthalmol Oct 2019 54(5): 590-600 (attached).

Papillomas in Goltz syndrome: case report, anaesthetic considerations, and review of the literature. Ruzicki J, Nair GS, Wang A, Farmer JP, Strube YN. Can J Ophthalmol. Oct 2019 54(5) e227-e230 (attached).

Inner-limiting-membrane peeling in epiretinal membrane surgery: an evolving surgical trend. Pike D, Mandelcorn ED, Sheidow T, Whelan JH. Available online September 14, 2019 (attached).

Foreign body extrusion associated with N-butyl-2-cyanoacrylate glue used with rectus muscle hang-back recession. Wright KW, Corradetti G, Strube YNJ, Mai SV. Can J Ophthalmol. 2019 Aug 20. pie S0008-4182 (19) 30473-9 (attached).

Save the Date

Ophthalmology Research Day. Wednesday May 27th, 2020. We are honoured to have Dr. Peter Kertes as the RMH Pinkerton Lecturer. Dr. Kertes is a retina specialist and Chief of Ophthalmology at Sunnybrook Hospital in Toronto, Ontario. Details to follow.

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Can J Ophthalmol 2019;54:e285–e288
0008-4182/17/$-see front matter
https://doi.org/10.1016/j.jcjo.2019.04.002

A curious case of arteritis: infectious, inflammatory, or both

Takayasu arteritis (TA) is a rare, chronic, progressive large-vessel granulomatous disease.[1,2] The specific pattern of arterial involvement in TA patients differs between geographic regions; however, the aorta and its main branches are most commonly affected in a contiguous fashion.[3,4] Ocular manifestations are also common in TA and have been reported in up to 45% of the affected patients in some reports.[5,6] Ophthalmic presentations can occur due to chronic ocular hypoperfusion due to stenosis of large vessels and less commonly the central retinal artery.[7] In addition, TA patients can present with hypertensive retinopathy and papilledema in severe cases.[5,8] In this report, we describe the ophthalmic findings of a patient with long-standing untreated TA presenting with acute visual disturbances.

Case Report

A 57-year-old female was acutely referred to the general eye clinic from the emergency department for a 3-day history of a large floater in her field of vision. The patient described the floater as central in location and without any photopsias. Past ocular history was otherwise unremarkable. She described her medical history as unremarkable aside from annual assessments for a "leaky valve." The patient denied any medication use.

On examination, Snellen visual acuity was OD 6/9 and OS 6/6. Pupils, confrontational visual fields, and cranial nerve examination were normal. Posterior segment examination OD revealed a large oblong, dense region of retinal pallor extending from the temporal disc margin to the parafoveal region with associated mild disc elevation (Fig. 1A). Posterior segment examination OS showed 2 mid-peripheral white-centered hemorrhages within the supratemporal quadrant (Fig. 1B). Vitals were measured: temperature: 37.1; pulses: right 110, left 111; blood pressure: right 156/61, left 179/77. While taking peripheral pulses, a cyanotic left hand was noted with faint radial and ulnar pulses (Fig. 1C). 10-2 Humphrey visual field revealed a dense central inferior altitudinal scotoma respecting midline (Fig. 2A). Optical coherence tomography of the macula demonstrated a region of hyperreflectivity confined to the inner layers of the retina (Fig. 2B). Urgent blood work revealed erythrocyte sedimentation rate 59, C-reactive protein 60, white blood cells 13, platelets 266. The ischemic cecocentral region along with elevated inflammatory markers was concerning for an inflammatory process.

Considering the unique presentation, additional probing into the patient's past medical history revealed a diagnosis of TA at age 27, where she was started on high-dose prednisone but self-weaned her prescribed treatment with the assistance of naturopathic remedies. She cited poor doctor–patient relationships as the primary cause of treatment failure. She has remained off treatment for 30 years without major disease flares.

After consultation with rheumatology, the patient was started on oral prednisone 1 mg/kg and instructed to follow up in 12 hours. On follow-up, the patient remained symptomatic with a generalized anxious feeling and mild diaphoresis. Physical examination was repeated and revealed a palpable subclavian thrill. She was admitted immediately to hospital for diagnostic assessment.

An urgent computed tomography with contrast was performed of the head and thorax. Focal stenosis of the right subclavian artery (Fig. 3A) was present along with tortuosity of the internal carotid artery and aortic wall thickening. Angiographic imaging of upper limb revealed an occlusion of the distal left brachial artery beyond the proximal forearm (Fig. 3B). The patient was taken for urgent surgical exploration where a thrombosed brachial artery was present with posterior wall thinning and gross purulent material. A bypass procedure was performed. Blood cultures were taken, and the patient was started on intravenous antibiotics. Histopathological assessment revealed a transmural inflammation with wall rupture (Fig. 4A) and scattered gram-positive cocci consistent with an infectious aneurysm (Fig. 4B). Drawn blood cultures were positive for streptococcus mitis. Transthoracic and transesophageal echography failed to identify any evidence of endocarditis or vegetative growths but demonstrated severe aortic valve insufficiency secondary to aortic root dilatation.

During admission, a follow-up conversation with the patient revealed a 1-month history of a recent febrile illness after a minor dental procedure. This represents the likely source of infection given streptococcus mitis is an oral microbe. In light of the diagnostic and surgical findings, the ocular manifestations were likely in keeping with a combined ischemic and infectious process: untreated vasculitis resulting in a nidus for bacterial overgrowth disseminated septic emboli after an oral surgical procedure. Her medical course improved in-hospital and at 2 months follow-up, both vision and the central visual field defect improved (Fig. 5). She is currently being managed by rheumatology, cardiology, and ophthalmology.

Discussion

The case presented highlights the ischemic complications of active TA with concurrent acute bacteremia. White-

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Footnotes and Financial Disclosures

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Author Contributions:

Conception and design: Campbell

Data collection: Campbell

Analysis and interpretation: Campbell

Obtained funding: N/A

Overall responsibility: Campbell

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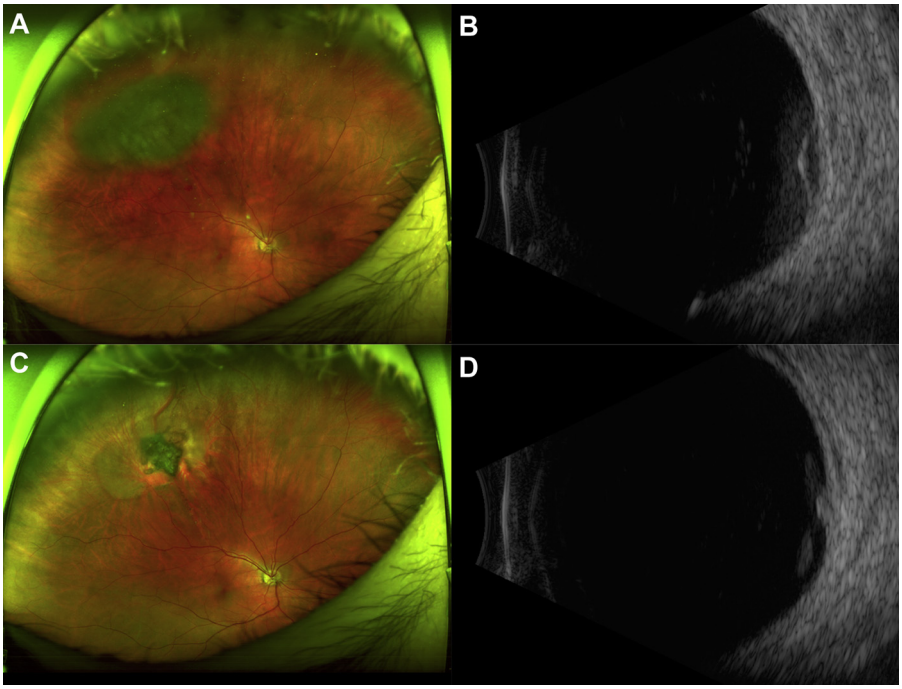
Pictures & Perspectives



Pseudomelanoma: Spontaneous Myopic Choroidal Hemorrhage

A 39-year-old man with myopia who suffered acute onset of floaters in his right eye was referred for suspected choroidal melanoma. Visual acuity, pupils, intraocular pressure, and anterior segment examination were normal, while dilated examination demonstrated a pigmented elevated lesion at the superotemporal equator, with apparent thin subretinal hemorrhage more anteriorly (Fig **A**). B-scan ultrasound showed a mass and apparent localized vitreous hemorrhage (Fig **B**). Seven months later, a well-circumscribed dark subretinal/subretinal pigment epithelial hemorrhage and resolving overlying preretinal hemorrhage was observed (Fig **C**). B-scan showed reduced size of the mass and surrounding hemorrhage (Fig **D**). Spontaneous choroidal hemorrhage may occur in myopes, which tends to resolve over time. (Magnified version of Fig **A**-**D** is available online at www.aaojournal.org).

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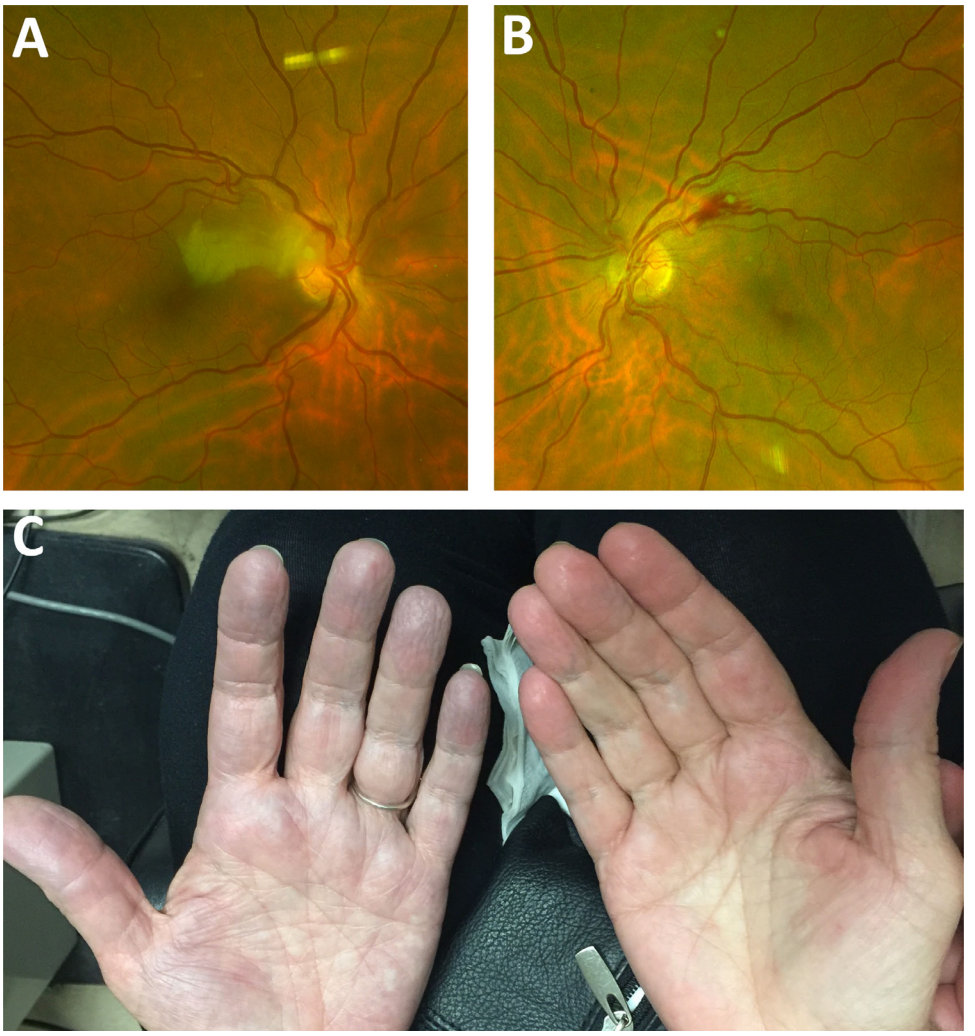

Fig. 1—Fundoscopic and physical examination findings. (A) Fundus photograph of the right eye showing a dense area of cecocentral retinal pallor. (B) Fundus photograph of the left eye illustrating 2 white-centered hemorrhages. (C) Photograph of the patient's hands illustrating cyanosis of the left hand.

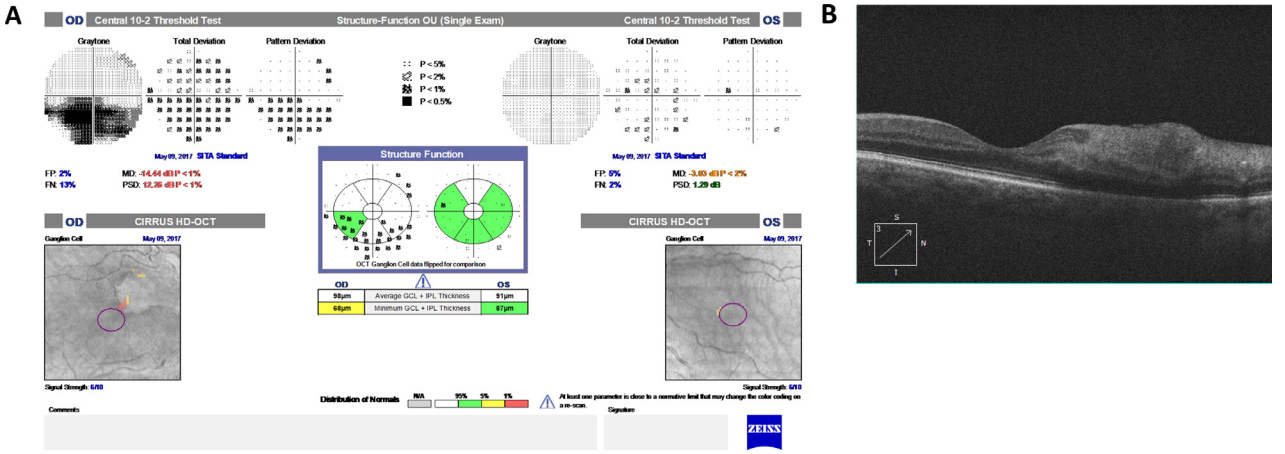

Fig. 2—Diagnostic ophthalmic assessment of the right and left eye (A) A dense central scotoma is present OD as measured by 10-2 Humphrey visual field. (B) Optical coherence tomography of the macula shows an area of hyperreflectivity localized to the inner layers of the retina consistent with an ischemic process.

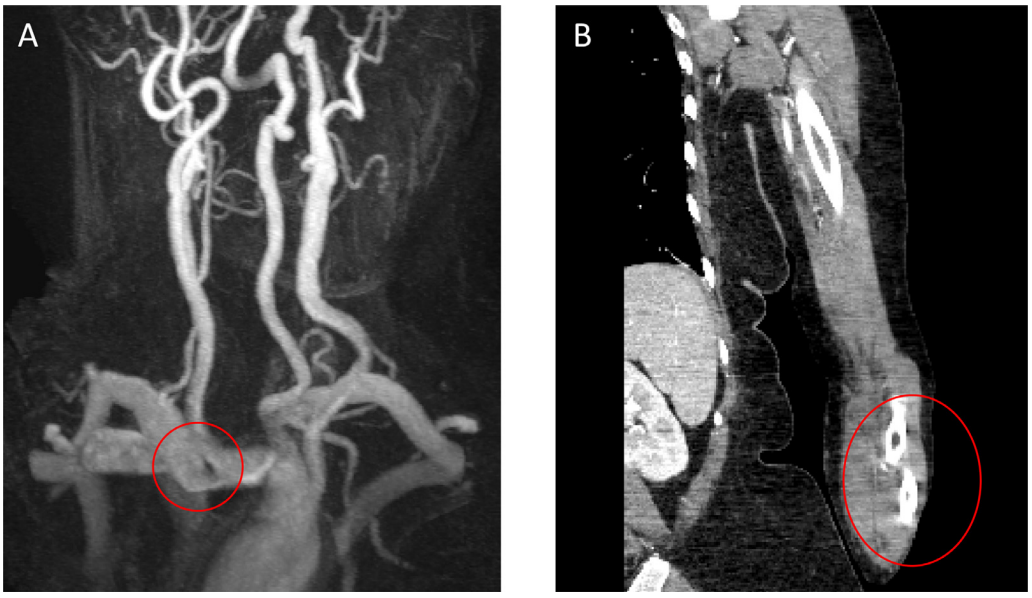

Fig. 3—Computed tomography (CT) with contrast of the thorax and left arm. (A) 3-dimensional reconstruction of the head and neck CT angiography (CTA) showing a focal area of stenosis (red circle) of the right subclavian artery. (B) CTA of the left arm showing an abrupt cessation (red circle) of contrast dye at the bifurcation of the brachial artery.

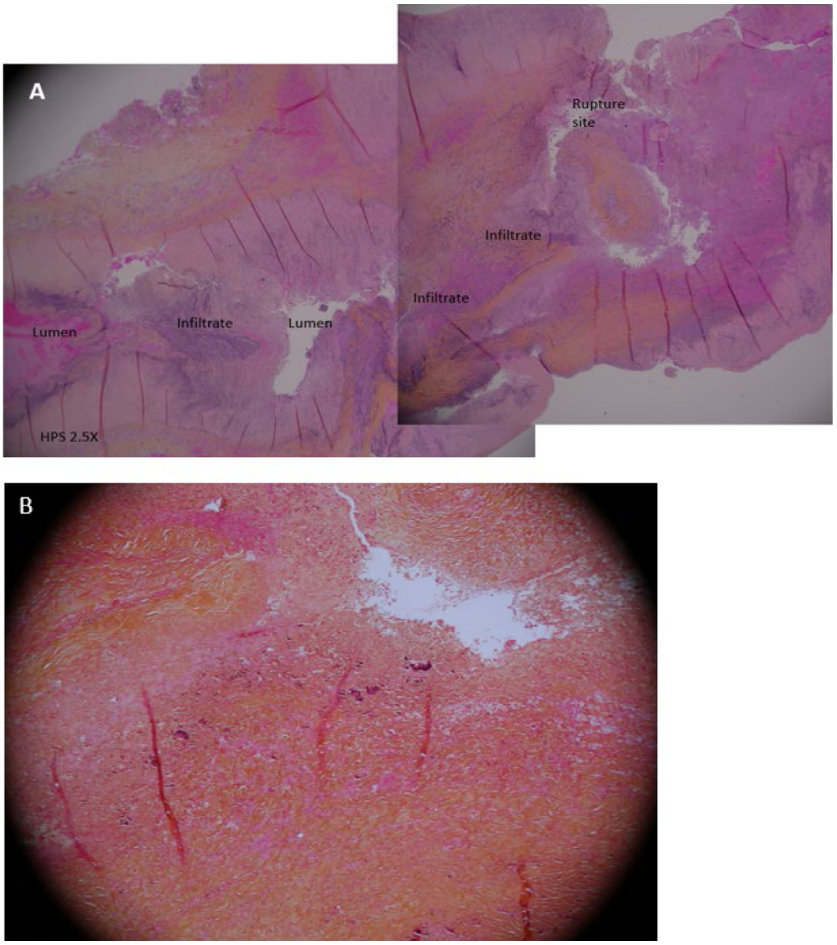

Fig. 4—Histopathological assessment of the left brachial artery. (A) Hematoxylin phloxine saffron stain of the brachial artery, 2.5 × magnification: 2 sequential images depicting the brachial artery in longitudinal section. Images show the brachial artery lumen occlusion with subsequent rupture. (B) Gram stain, 10 ×: gram-positive material within arterial inflammatory infiltrate.

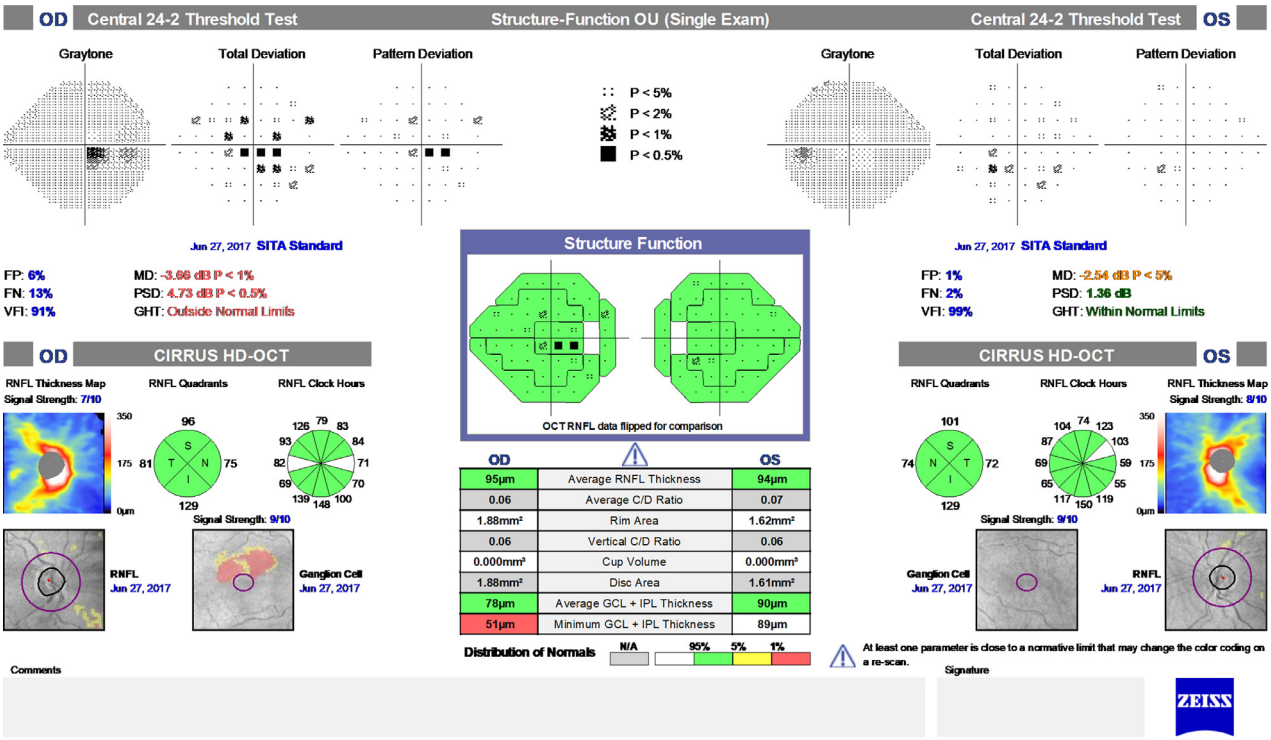

Fig. 5—Diagnostic ophthalmic assessment of the right and left eye at 2-months follow-up. 24-2 Humphrey visual field assessment demonstrating improvement in the central inferior scotoma of the right eye.

centered hemorrhages with associated ischemic infarcts should prompt a broad differential including infectious etiologies. Differentiating between an acute vasculitis and infective endocarditis as a cause for ischemic-occlusive events illustrates the necessity for timely access to medical and surgical care. Chronic vascular inflammation in the setting of TA can be a nidus for bacterial seeding.[9,10]

Although there are currently no established guidelines for antibiotic prophylaxis for dental procedures in vasculitis patients, our case demonstrated that such patients may be at high risk for infectious complication when mucosal surfaces with high microbial loads are disrupted during surgical manipulation.[11] In addition to antibacterial prophylaxis, given the broad list of clinical presentations of TA and their urgency, there is a need for an organized and collaborative approach between multiple medical disciplines for proper management of these patients.

Physicians must rely on their clinical examination to achieve positive health outcomes for their patients. The importance of a detailed and thorough history, which revealed critical information about the patient's past medical history and recent minor procedures is exemplified in this case. It is important to consider the patient's perspective and understand that a patient's agenda does not always align with the physician's, and therefore it is important to maintain an open and friendly rapport with your patient to best guide treatment. A basic physical examination can be both diagnostic and therapeutic and, in some cases, life or limb saving.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2019.02.011.

Footnotes and Disclosure:

The authors have no proprietary or commercial interest in any materials discussed in this article.

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Can J Ophthalmol 2019;54:e288–e292
0008-4182/17/$-see front matter
https://doi.org/10.1016/j.jcjo.2019.02.011

Orbital alveolar soft part sarcoma: case report and literature review

Alveolar soft part sarcoma (ASPS) is a malignant soft part tissue tumour of uncertain phenotypic expression that mainly affects young adults and children and represents less than 1% of all sarcomas.[1–4] There are only 63 cases of primary orbital ASPS reported in the PUBMED, none from Canada, with a female preponderance and a predilection for affecting the left eye.[1–3]

Herein we describe an unusual case of orbital ASPS primary of the orbit in a 31-year-old female with a previous history of breast cancer.

Case Report

A 31-year-old female presented a mild proptosis of the right eye. After magnetic resonance imaging (MRI), the preliminary diagnosis was a metastasis of her previous breast carcinoma. At age 26 years, she was diagnosed with a grade 3 invasive ductal carcinoma of the right breast, stage T2 N2. Genetic screenings were negative.

The first MRI showed a solitary lesion in the right orbit measuring 16 × 15 × 14 mm. The location was intramuscular inferior right, and the lesion was well circumscribed and reconfigured the orbit's floor. It caused swelling of the superior right portion of the optic nerve. It was iso-intense T2 and T1 with an enhanced homogeny after gadolinium injection.

Two months later, a second MRI showed an increase in size of the lesion, measuring 18 × 18 × 17 mm (Fig. 1A). Biopsy demonstrated a tumour composed of uniform polygonal epithelioid cells in a solid and alveolar architecture outlined by delicate sinusoidal vascular channels. The cells had abundant granular eosinophilic cytoplasm and vesicular nuclei with large prominent nucleoli and a very low mitotic rate with no necrosis (Fig. 1C and D). Periodic acid–Schiff with diastase stains revealed needle-shaped crystals (Fig. 1E). Immunohistochemical stains performed demonstrated tumour strong positivity for

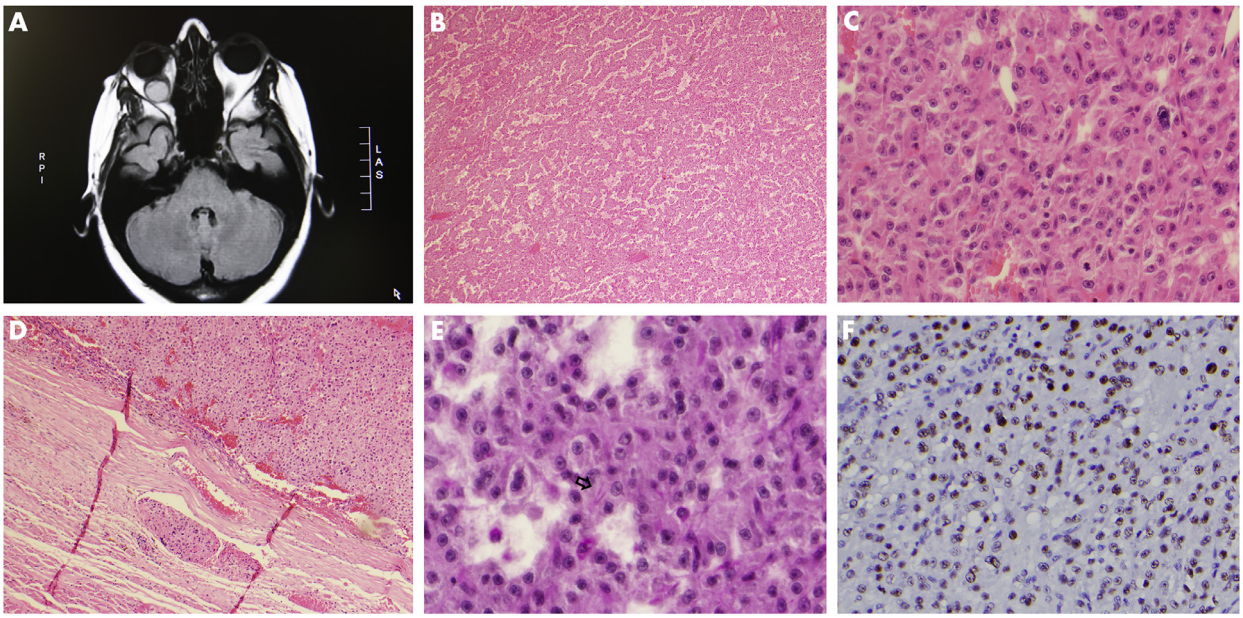

Fig. 1—A, CT scan of the orbit showed a well-circumscribed lesion in the right orbit. B, Microscopic examination shows a monotonous and uniform tumour with a sinusoidal architecture (hematoxylin-eosin [H&E], 20 ×). C, The tumour is composed of monomorphic cells with vesicular nuclei and a central nucleoli, eosinophilic and granular cytoplasm, with rare cellular pleomorphism and rare mitotic figures (H&E, 400 ×). D, Vascular invasion was identified at the periphery of the tumor (H&E, 40 ×). E, Needle-shaped crystals were identified in the cytoplasm of some of the tumoural cells by periodic acid-Schiff (PAS) with diastase stain (PAS diastase, 400 ×). F, The tumoural cells show a diffuse nuclear positivity for TFE3 by immunohistochemistry (TFE3, 100 ×).

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Commentary

The Making of a Great Surgeon

Robert J. Campbell, MD, MSc - *Ontario, Canada*

Cataract surgery is a highly technical procedure with a prolonged learning curve.[1-3] Cataract surgery is also the most common operation in many countries and is important not only for its ability to restore vision to millions of people every year but also for its impact on the health of the overall population.[4,5] Consequently, establishing the structures needed to support excellence in cataract surgery while meeting ever-growing population demand is a key objective of health care systems worldwide. While technology has moved the dial in terms of expectations and achievable outcomes, the skill and judgment of surgeons remain fundamental determinants of surgical success.

Among the important surgeon-level factors that may influence outcomes are surgical experience and surgical case volume.[1,6] In a large, single-center study of cataract surgical outcomes, Cox et al[7] (see page 1480) have added to our understanding of the interplay among surgeon case volume, experience, and outcomes. Their careful study evaluated granular data on surgeons, cataract severity, visual acuity, and surgical complications, and provides a thoughtful analysis and discussion. In particular, Cox et al[7] have provided new insight into the effect of surgeon volume on visual acuity outcomes, supporting previous research that has focused on complication rates.[1,8-11]

Although increasing surgical volume correlated with better visual acuity outcomes, Cox et al[7] were careful to point out that the observed effects were modest and that the clinical significance is important to consider. The study also showed that beyond a relatively modest number of cases (350/year), higher volumes of surgery did not lead to further improvements in visual acuity outcomes. This is a reassuring finding as it suggests that moderate surgical volumes, within a range performed by most cataract surgeons, are compatible with excellent outcomes. Notably, some previous studies have shown continued marginal improvements to higher volumes than seen in this study.[1,8-11]

Past experience, as evaluated by total career surgical volume and years of practice, was not found to be predictive of most outcomes in the study. This somewhat paradoxical finding may be the result of the correlations among these variables, notwithstanding the tolerance values reported. Alternatively, it may stem from the limited range of experience and the early-career stage of surgeons included in the study (median 3.7 years of experience).

Perhaps unsurprisingly, those surgeons who performed large numbers of cases were among those with the lowest complication rates. However, as with previous studies of this issue, the causal pathway is complex and difficult to parse. Although high volumes may lead to better outcomes, the reverse is likely also true. Indeed, for a variety of reasons, in many health care systems, some high-quality surgeons are afforded the opportunity to do large volumes while others are not. Conversely, those with poorer outcomes generally do not find themselves in high-volume practices, whether from self-selection or other forces. This results in the kind of volume-outcome distribution demonstrated by Cox et al[7] and previous investigators, with variable outcomes among surgeons with lower volume and more uniformly positive outcomes among surgeons with higher volume.[1,8,11] As with many previous studies, the authors have considered procedure-specific volume as the predictor of cataract surgical outcomes. Future studies evaluating overall surgeon practice, and in particular the impact of performing other types of surgery on cataract outcomes, would be a strong addition to our understanding.

Consistent, long-term surgeon success relies on a mix of skill, foresight, humility, and adaptability. Although surgical volume may positively affect some of these attributes, many other factors also carry significant influence. Nevertheless, when it comes to the impact of surgical volume, it would seem from the body of literature that recent volume makes a surgeon sharp, deliberate practice over years makes a surgeon skilled, and total volume over a career makes a surgeon wise. Cox et al[7] have done an admirable job of adding to our understanding of the role of these factors in cataract surgery.

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https://doi.org/10.1016/j.ophtha.2019.05.007
ISSN 0161-6420/19

Journal of Steroid Biochemistry and Molecular Biology 197 (2020) 105536

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Intraocular calcidiol: Uncovering a role for vitamin D in the eye

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ARTICLE INFO

Keywords:
Ophthalmology
Aqueous humour
Vitreous humour
Neovascularization
Vascular endothelial growth factor
Cataract surgery

ABSTRACT

Vitamin D has emerged as a potentially important molecule in ophthalmology. To date, all ophthalmic data pertaining to vitamin D has been restricted primarily to tear and serum analysis in human patients. Considering the isolated nature of the eye, we sought to determine the presence of intraocular vitamin D in ocular disease.
Methods: 25-Hydroxyvitamin D_3 ($25(OH)D_3$) concentrations were measured in the eye and blood of 120 participants undergoing ophthalmic procedures. Ocular localization of the 1,25-dihydroxyvitamin D_3-generating (CYP27B1) and deactivating (CYP24A1) hydroxylases was performed by immunohistochemistry. Gene expression of *CYP27B1*, *CYP24A1* and *VEGF-A* was measured in eyes from patients with and without disease.
Results: $25(OH)D_3$ was quantified in 112 ocular samples. In 40 cataract patient samples, the average $25(OH)D_3$ concentration was 0.057 ng/mL, compared to 72 retinal disease patient samples, average of 0.502 ng/mL ($p < 0.001$). Intraocular $25(OH)D_3$ did not correlate with serum levels of $25(OH)D_3$. There was no difference between the level of $25(OH)D_3$ measured in the aqueous and vitreous humour. The vitamin D-specific CYPs 27B1 and 24A1, strongly localized to complementary regions of the ciliary body, retinal pigment epithelium and neural retina. Gene expression analysis confirmed retinal *CYP27B1* correlated strongly with *VEGF-A* in eyes from diabetic patients ($r = 0.92$, $p < 0.001$).
Conclusions: Our data confirms that vitamin D is present in the humours of the human eye and that local synthesis/degradation is possible via the ocular CYP27B1 and CYP24A1. This argues for a functional role for local vitamin D production and signaling in the eye and suggests that vitamin D may be an important intraocular mediator in disease pathogenesis.

1. Introduction

The hormone vitamin D_3, and its active derivative calcitriol (or 1,25 dihydroxyvitamin D3 ($1,25(OH)_2D_3$) has received significant attention in the field of medicine for its pleotropic roles in preventing kidney disease, bone metabolism and immune modulation [1,2]. Calcidiol or 25-hydroxyvitamin D_3 ($25OHD_3$) is converted into the active $1,25(OH)_2D_3$ through a hydroxylation event catalyzed by the 1-α hydroxylase, or CYP27B1 [3]. In clinical practice, $25(OH)D_3$ is the standard metabolite that is measured, given its longer half-life and predominance in the circulation.

In the field of ophthalmology, interest in the so called "sunshine" vitamin has been gaining momentum for its deficiency being linked to cataracts [4], myopia [5], diabetic retinopathy [6], uveitis [7], glaucoma [8], age-related macular degeneration [9], retinopathy of prematurity [10] and optic neuritis [11]. Vitamin D has been hypothesized to play a protective role against the progression of age-related macular degeneration (AMD). Although initially not recognized as an inflammatory disease, it is now widely accepted that aberrant immune response including complement activation and the release of pro-inflammatory cytokines contributes to the pathogenesis of AMD [12]. Consistent with this, data from the third National Health and Nutrition Examination Survey showed that subjects with highest quintile of serum $25(OH)D_3$ had a lower prevalence of early AMD and drusen

Abbreviations: dAMD, dry age-related macular degeneration; NPDR, non-proliferative diabetic retinopathy; DME, diabetic macular edema; nvAMD, neovascular age-related macular degeneration; RVO, retinal vein occlusion; PDR/NVG, proliferative diabetic retinopathy/neovasular glaucoma; RD, retinal detachment; ERM, epiretinal membrane; MH, macular hole; IOP, Intraocular pressure; VEGF, vascular endothelial growth factor

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https://doi.org/10.1016/j.jsbmb.2019.105536
Received 19 June 2019; Received in revised form 30 October 2019; Accepted 6 November 2019
Available online 14 November 2019
0960-0760/

formation compared to those in the lower quartile [13]. Moreover, single nucleotide polymorphisms in enzymes involved in the metabolism of vitamin D have been shown to predispose individuals to AMD [14,15]. Given its crucial role in regulating inflammatory processes, studies have examined vitamin D signaling in the context of uveitis. Anterior acute uveitis is the most common type of uveitis and is more prevalent in patients with positive human leukocyte antigen (HLA)-B27. In a recent retrospective study, it was shown that polymorphisms in CYP27B1 are more common in HLA-B27 positive anterior uveitis patients compared to HLA-B27 positive controls without uveitis. Consequently, it is possible that dysfunctional vitamin D metabolism could create a more a pro-inflammatory environment in HLA-B27 positive individuals and further increases their risk of uveitis [16]. Vitamin D deficiency has also been linked to the presence and severity of diabetic retinopathy [17]. Further, the supplementation of 1,25-dihydroxyvitamin D to diabetic rats has been shown to be protective against glucose-mediated vascular damage via down regulation of various inflammatory pathways ultimately preventing damage to retinal vascular cells [18].

Most of the evidence for vitamin D in the eye has been derived from in-vitro assays, in-vivo animal models, and the analysis of circulating calcidiol and calcitriol in the tears and serum [19–21]. Few studies have measured vitamin D and its metabolites in the aqueous and vitreous humour of patients. Taking into account the isolated and compartmentalized nature of the eye, with its well-defined blood-ocular barriers, the utility of analyzing serum vitamin D as a parameter in eye disease remains unfounded. Despite the numerous studies examining serum vitamin D in eye disease, the exact role of vitamin D within the humours (aqueous and vitreous) of the eye remains to be defined and even the existence of a functional role remains controversial. Considering the eye's unique anatomical position and constant exposure to ultraviolet light, we hypothesized that the eye contains vitamin D within ocular fluids, and possesses the required enzymes for its tissue-specific local metabolism. We set out to define the intraocular status of vitamin D in patients with various ophthalmic disease conditions, as compared to the non-diseased state.

2. Methods

2.1. Study subjects

We conducted a cross-sectional study of patients with a series of common eye disease to assess the levels of serum and intraocular vitamin D. This cross-sectional study was approved by the institutional ethics committee (Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board) and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants. Undiluted samples of ocular fluid (aqueous and vitreous humor) and blood serum were obtained from consented study participants undergoing surgical ophthalmic procedures from December 2016 to Dec 2018. Surgical procedures included anterior chamber paracentesis, pneumatic retinopexy, cataract extraction and pars plana vitrectomy. Primary participant diagnoses included cataract, retinal detachment (rhegmatogenous and tractional), neovascular age-related macular degeneration, diabetic macular edema, retinal vein occlusion, epiretinal membrane and macular hole. Exclusion criteria included active vitreous hemorrhage and patients undergoing dialysis or chemotherapy as these can alter aqueous humor dynamics. Detailed methodology is available in the supplemental materials.

2.2. Sample collection

Patients undergoing cataract surgery, intravitreal injection or pneumatic retinopexy received an anterior chamber paracentesis using a 1 mL tuberculin syringe to remove 50–100uL of aqueous humour was removed. Vitreous humour was obtained during standard 3-port pars plana vitrectomy. Paired serum samples were obtained from participants providing aqueous or vitreous humour samples. Samples were stored until further processing.

2.3. 25-Hydroxyvitamin D detection

In order to measure 25(OH)D3, a 50–100 μL sample of aqueous, vitreous or serum was sent to the Analytical Facility for Bioactive Molecules of The Centre for the Study of Complex Childhood Diseases, The Hospital for Sick Children (Toronto, Canada) for quantification of 25-hydroxyvitamin D. Full details are available in the supplemental methods section. Briefly, A 100 u L sample was extracted via liquid-liquid extraction using a Zinc Sulfate/Methanol/n-Hexane protocol by the Analytical Facility for Bioactive Molecules of The Centre for the Study of Complex Childhood Diseases. Samples were analysed by LCMS/MS using an Aglient 1290 HPLC interfaced with an AB Sciex 5500 Q-Trap mass spectrometer. Data were collected and analyzed using Sciex Analyst v1.6.3. The lower limit of quantification for 25(OH)D_3 was 0.200 ng/mL. Quantified 25(OH)D_3 was tabulated according to group category as illustrated in the results. Samples below the limit of detection were given a value of 0.

2.4. Immuno-localization of CYP27B1 and CYP24A1

The expression of calcitriol generating (CYP 27B1) and deactivating (CYP24A1) enzymes was detected using immunohistochemistry. Twenty-five formalin-fixed paraffin embedded healthy control eye sections (4-5μm sections) were obtained from The Human Eye Biobank (Toronto, Ontario). Sections were processed using standard methods, and incubated with either anti-CYP 27B1 (Abcam, Toronto, Canada), at a dilution of 1:2000 or anti-CYP 24A1 (Abcam), 1:400 dilution. The detection system performed used alkaline phosphatase labelled anti-rabbit secondary to produce a red precipitate followed by hematoxylin counter staining (blue). A negative staining control with secondary antibody only and one with chromagen only were performed.

2.5. RNA isolation and qPCR

Fresh whole eyes were obtained following cadaveric enucleation from the Canadian Eye Bank (Toronto, Ontario). Retinal tissue was dissected and total RNA isolated from ~100 mg of retinal tissue using the PureLink™ RNA Mini Kit (ThermoFisher Scientific, Mississauga, ON) according to the manufacturer's instructions. Subsequent analysis of gene expression for *hCYP27B1, hCYP24A1, hIL-6, hCTGF, hTGF-B* and *hVEGFA* was performed by qPCR on a ViiA7 Real Time PCR system using SYBR green detection (Power Up SYBR Mastermix, ThermoFisher). Mean gene of interest expression relative to reference gene, phosphomannomutase-2 (PMM2), was reported.

2.6. Statistics

Descriptive statistics were used to evaluate frequencies and percentages for categorical data, and means, standard deviations, medians and quartiles for continuous data. Unpaired two-sided Student's *t*-test was used to compare quantitative data with a normal distribution. A p-value of 0.05 was used as the criteria for statistical significance. Statistical analysis was performed using Graphpad Prism (version 8.0).

3. Results

We obtained 86 aqueous and 34 vitreous samples from 117 participants. One hundred and twelve samples were available for analysis as three participants were excluded due to having undergone retinal dialysis or chemotherapy and two samples were of insufficient volume for mass spectrometry analysis. Fourty samples were obtained from cataract surgery patients, 31 from vitrectomy patients and 41 from

Table 1
Baseline demographic participant characteristics.

Demographics		
Number of participants		117
Number of intravitreal injection aqueous samples		43
Number of cataract aqueous samples		41
Number of vitrectomy vitreous samples		33
Number samples excluded from participants		5
Age	Mean, (SD)	74, (11)
Gender		N, (%)
	Male	63 (54)
	Female	54 (46)
Mean intraocular pressure	Mean, (SD)	15.5, (4.6)
Primary ocular disease	Category	N, (%)
Total number of analyzed samples		112
	Cataract	40 (36)
	nvAMD	27 (24)
	DME	7 (6)
	RVO	3 (3)
	PDR/NVG	3 (3)
	ERM	14 (12)
	MH	7 (6)
	RD	9 (8)

dry age-related macular degeneration (dAMD), neovascular age-related macular degeneration (nvAMD).
diabetic macular edema (DME), retinal vein occlusion (RVO), proliferative diabetic retinopathy (PDR).
neovascular glaucoma (NVG), epiretinal membrane (ERM), macular hole (MH), retinal detachment (RD).

patients undergoing intravitreal injections. Paired ocular fluid and serum samples were available in 42 cases (34 aqueous samples, 8 vitreous samples). Patient disease categories included cataract, diabetic macular edema (DME), neovascular age-related macular degeneration (nvAMD), retinal vein occlusion (RVO), proliferative diabetic retinopathy/neovasular glaucoma (PDR/NVG), retinal detachment, epiretinal membrane (ERM), and macular hole (MH). Mean age of participants was 74 years (range 34–96 years), of which 54 % of participants were male and 46 % were female. Mean intraocular pressure (IOP) was 15.5 mmHg (range 7 − 34 mmHg). There was no difference in mean age among the three sampling groups. There was no correlation with ocular or serum vitamin D and age, gender or intraocular pressure (IOP). Table 1 displays participant baseline participant characteristics.

3.1. Quantification of intraocular 25-Hydroxyvitamin D_3 in ocular disease

To determine whether vitamin D could be detected in the ocular fluid, 112 samples of aqueous or vitreous humor were analyzed by liquid chromatography- tandem mass spectrometry (LC–MS/MS) for the presence of 25(OH)D_3. Quantifiable 25(OH)D_3 in the aqueous and vitreous humour was 1–1.5 log lower compared to that in the serum (data not shown). Aqueous humour 25(OH)D_3 did not statistically differ from that of vitreous humour in all samples analyzed (Fig. 1A). There was no significant Pearson's correlation observed between ocular fluid and serum 25(OH)D_3 (Fig. 1B). 25(OH)D_3 was also compared in patients with and without active retinal disease. In 40 non-retinal disease cataract samples, the mean concentration of 25(OH)D_3 was 0.057 ± 0.121 ng/mL compared to 0.501 ± 1.06 ng/mL in 72 samples from participants with retinal disease (Fig. 1C). Samples from each disease category were collated and plotted in Fig. 1D to observe trends in 25(OH)D_3 levels. The mean concentration of 25(OH)D_3 in patients with neovascular age-related macular degeneration were 0.157 ± 0.208 ng/mL. In diabetic retinopathy patients with active diabetic macular edema the concentration of 25(OH)D_3 was 0.681 ± 0.128 ng/mL. compared to 2.91 ± 4.35 ng/mL in patients with proliferative diabetic retinopathy. Patients with retinal detachments, quantifiable 25(OH)D_3 in both the aqueous and vitreous was 0.667 ± 0.656 ng/mL. Patients requiring vitrectomy for ERM or MH had measurable 25(OH)D_3 concentrations of 0.596 ± 0.622 ng/mL and 0.411 ± 0.504 ng/mL respectively. 25(OH)D_3 in the aqueous and vitreous humour significantly correlated with a worse participant logMAR best-corrected visual acuity (BCVA) taken at the time of sample removal (Fig. 1E). There was no significant difference in the amount of 25(OH)D_3 comparing aqueous and vitreous humour of eyes with retinal disease (data not shown). The highest concentrations of 25(OH)D_3 were observed in 2 of 3 patients with active proliferative diabetic retinopathy with iris neovascularization, with individual values of 7.90 ng/mL and 3.37 ng/mL.

3.2. Serum 25-Hydroxyvitamin D and ocular disease

In all 42 patients with serum vitamin D measurements, the mean 25(OH)D_3 serum level was 34.5 ± 14.6 ng/mL (range 4.3–65.7 ng/mL) (Fig. 2A). The mean 25(OH)D_3 serum level in the cataract only group was 35.4 ± 16.9 ng/mL compared to 33.6 ± 12.8 ng/mL for all patients with retinal disease (Fig. 2B). The mean concentrations of serum 25(OH)D_3 according to disease category were as follows: DME 28.9 ng/mL, PDR 35.6 ng/mL, nvAMD 35.2 ng/mL and ERM 33.6 ng/mL. Mean levels of 25(OH)D_3 were not statistically different between groups (Fig. 2B).

3.3. CYP27B1 and CYP 24A1 enzyme expression in diabetic and control eyes

Quantitative RT-PCR was performed on fresh human retina to examine the expression of inflammatory markers and vitamin D genes-of-interest in diabetic retinopathy. Eight control eyes from 4 patients (3 males, 1 female) without type 2 diabetes mean age 62) were compared to 10 case eyes from 5 patients (4 males, 1 female) with type 2 diabetes (mean age 63.5). Vascular endothelial growth factor A (*VEGF-A*) gene expression was quantified as a marker of retinal disease. Mean *CYP27B1* and *VEGF-A* expression were two to three-fold higher in eyes from diabetic patients as compared to controls (Fig. 3A, 3B). There was a strong correlation between retinal *CYP27B1* and *VEGF-A* in cases and controls, $r = 0.90$, $p < 0.001$ (Fig. 3C). There was no correlation between *CYP27B1* and either *CYP24A1*, *IL-6*, *CTGF*, *TGF-B* or *CD14* (data not shown).

3.4. Immuno-localization of vitamin D enzymes in the eye

To determine the immuno-localization of the enzymes that convert 25(OH)D_3 into active 1,25(OH)$_2$D$_3$, and the enzymes that catabolize active 1,25(OH)$_2$D$_3$, we performed immunohistochemistry for CYP27B1 and CYP24A1 on 25 cadaveric eye samples. All sections from 25 eyes showed a consistent and strong expression of CYP27B1 and CYP24A1 in the ciliary processes, ciliary body, neural retina, and retinal pigment epithelium. (Fig. 4). CYP27B1 expression was inconsistently positive across samples in the basal layer of the corneal epithelium and endothelium (data not shown). CYP24A1 was not found to localize to any region of the cornea (data not shown). CYP27B1 was strongly expressed in both the inner non-pigmented and outer pigmented epithelial cells of the ciliary body in contrast to CYP24A1 which showed weak expression of the inner non-pigmented and strong expression of the outer pigmented epithelium (Fig. 4 A,B). Neural retina expression of CYP27B1 showed strong expression throughout all the non-nuclear layers of the retina including the proximal but not distal (beyond the cilium) photoreceptor layer (Fig. 4 C,E,G). CYP24A1 showed a weakly positive inner-, and strongly positive outer-retina staining, that being homogenous staining in the photoreceptor layer, extending into the interphotoreceptor matrix (Fig. 4 E,F,H). Expression of CYP27B1 in the retinal pigment epithelium was restricted to the basolateral surface, whereas CYP24A1 had a more apical distribution (Fig. 4 I,J).

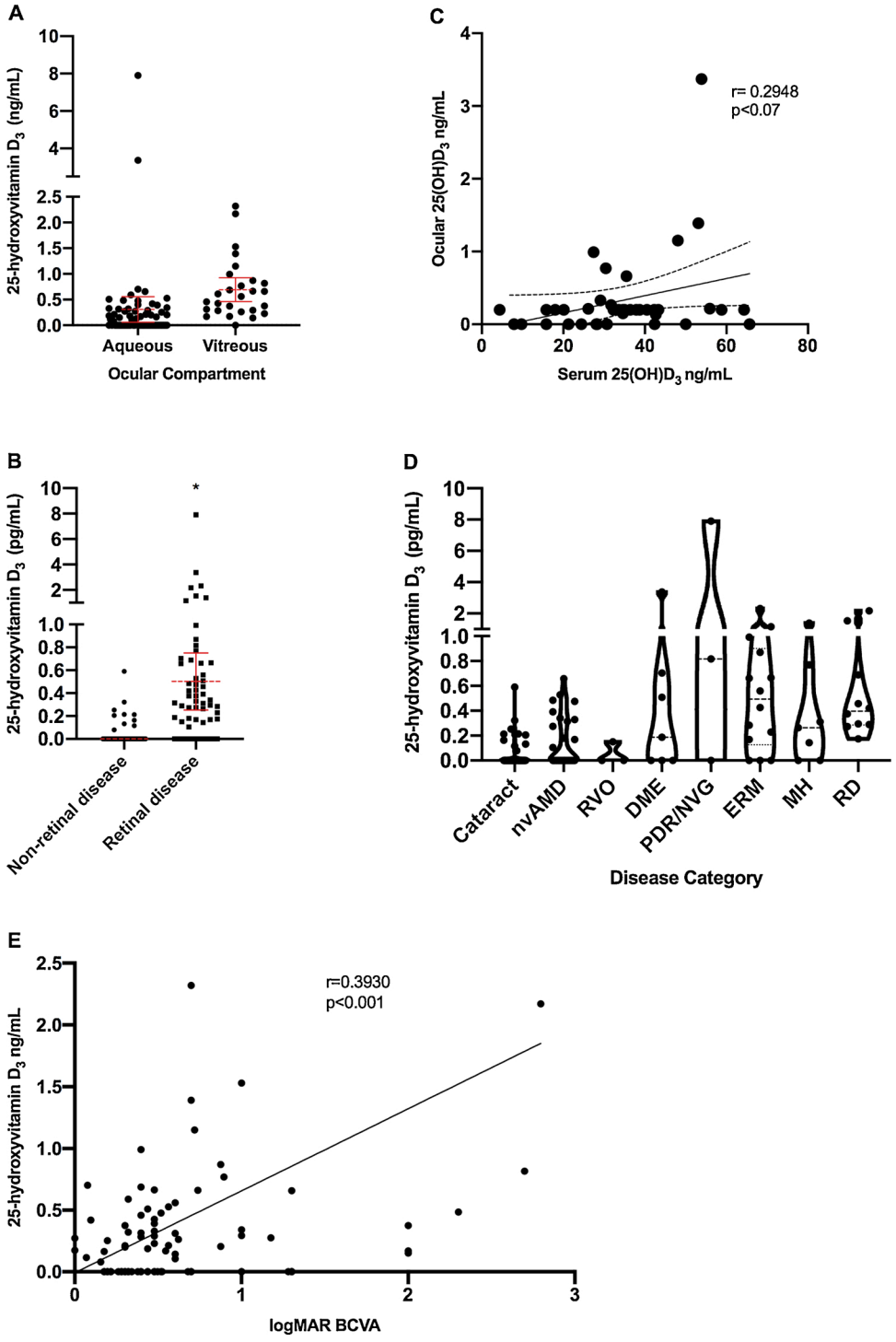

Fig. 1. Intraocular concentrations of 25(OH)D_3 in aqueous and vitreous humour from patients with several common ophthalmic diseases undergoing medical and surgical care. Panel A displays the individual participant 25(OH)D_3 concentrations separated into aqueous and vitreous samples from 112 participants. No significant difference was calculated between aqueous and vitreous samples. In Panel B, Pearson's correlation was calculated between paired ocular fluid and serum samples. There was no statistically significant relationship observed between paired ocular fluid and serum samples. C) Measured 25(OH)D_3 concentration of all aqueous and vitreous non-retinal disease samples (40 samples from cataract participants) compared to retinal disease samples (72 samples from participants undergoing treatment for retinal disease). Unpaired two tailed Student's *t*-test performed between non-retinal and retinal disease group as indicated. *-indicates $p = 0.0097$. D) Violin box-plot graphing the median, 25th and 75th percentiles of 25(OH)D_3 concentrations from patients with cataract alone (N = 40), neovascluar age-related macular degeneration (nvAMD, N = 27), diabetic macular edema (DME, N = 7), retinal vein occlusion (RVO, N = 3), retinal detachment (RD, N = 10), proliferative diabetic retinopathy/neovascular glaucoma (PDR/NVG, n = 3), epiretinal membrane (ERM, N = 14) and macular hole (MH, N = 7). Samples were not adequately powered to allow for statistical comparison. E) Pearson's correlation between ocular fluid 25(OH)D_3 concentrations and logMAR best-corrected visual acuity (BCVA) in 88 participants. Pearson's coefficient $r = 0.393$, 95 % confidence (0.200 to 0.557), $p < 0.001$.

4. Discussion

Here, we describe the quantifiable profile of intraocular 25(OH)D_3 in the aqueous and vitreous humour of patients with various common ophthalmic conditions as well as the expression pattern of vitamin D catalyzing enzymes in the eye. Active retinal neovascularization or damage to the neural retina is associated with the highest intraocular concentrations (aqueous or vitreous humour) of 25(OH)D_3, compared to low or undetectable amounts in patients with only cataracts. Gene expression and immunolocalization confirmed the presence of the vitamin D catalyzing enzymes, CYP27B1 and CYP24A1 in the eye, with a predominance for the inner and outer retina (CYP27B1) and inner retina (CYP24A1), suggesting calcitriol is produced in the retina and able to signal to and within the RPE. Taken together, our data suggest a role for vitamin D in the eye, which appears to coincide with local accumulation in eye disease.

We measured the major circulating form of vitamin D, 25(OH)D_3 in the humors of the eye and serum along with detecting expression of the CYP family enzymes required for its conversion within the neural retina and ciliary body. Our data would infer that 1,25(OH)2D3 could be locally produced within the eye. The absence of a correlation between aqueous or vitreous humour concentrations of 25(OH)D3 and those in serum further suggests a locally-driven mechanism. This was most recently confirmed by Kim KL *et al.*, measuring aqueous humour 25(OH)

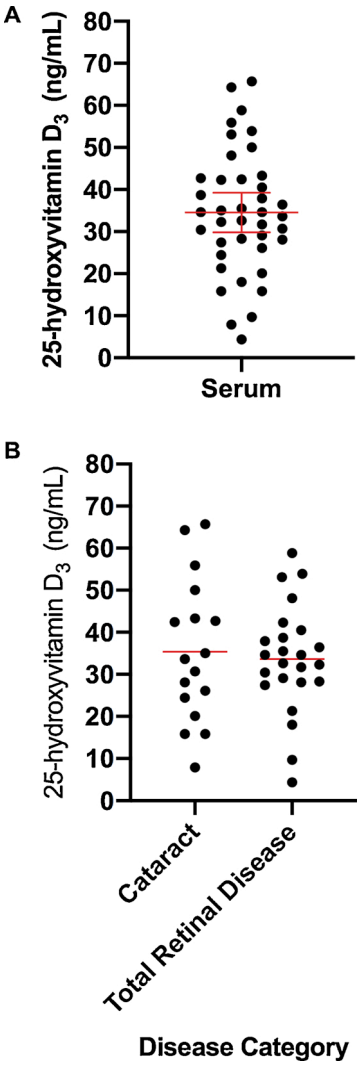

Fig. 2. Concentrations of serum 25(OH)D_3 from a medical and surgical ophthalmic population.
In Panel A, a dot plot illustration of serum 25(OH)D_3 concentration from an ophthalmic population (N = 42). Mean concentration with 95 % confidence interval plotted in red. Panel B shows a dot plot of serum 25(OH)D_3 comparing cataract patient samples from all retinal disease samples. The plot shows mean concentration (red line) of serum 25(OH)D_3 in the two subgroups (cataract, N = 17; total retinal disease, N = 24). There was no statistical difference between groups.

D3 in diabetic macular edema patients compared to controls [22]. Here, aqueous humour 25(OH)D3 concentrations was independent of the serum in both cases and controls [22]. A few additional studies have assessed the correlation between serum and ocular fluid levels of vitamin D to date. Sethu *et al.* found higher levels of 25(OH)D3 in the tear film in comparison to serum levels, however, they found the two to be positively correlated [23]. On the other hand, in a recent report by Tsun Lai *et al.*, no correlation between tear and blood levels of vitamin D was found as measured through electroluminescence [24]. The mechanism by which vitamin D circulates inside the eye compared to around may be mechanistically distinct as the tear constituents are related to a lacrimal gland functional unit where as aqueous humour is regulated by the tight junctions of the blood aqueous barrier and the functioning of the outer pigmented and inner non-pigmented epithelium of the ciliary body. Overall, there appears to be preliminary consensus in the literature, supported by our findings, that serum levels of vitamin D may not be a reliable measure of intraocular levels.

How vitamin D or its precursors enter the eye or whether it is produced locally remains experimental. In the skin, 7-dehydrocholesterol (7-DHC), in the presence of UV-B light, is converted into a pre-vitamin D, which enters the liver for conversion into 25(OH)D_3 [25]. UV-treated cell cultures of human ocular barrier cells is capable of producing active vitamin D, but only in the presence of exogenous 7-DHC [26]. Considering the choroid of the eye receives the highest blood flow per gram of tissue in the body [27], it is possible 25(OH)D_3 or its precursors, travel to the eye for conversion. However, the lack of a strong relationship between serum and ocular 25(OH)D_3 argues against this possibility. Yet, oral supplementation with vitamin D3 (cholecalciferol) in rabbits is able to increase the amount of serum and aqueous humour concentrations of 25(OH)D3 [26]. Therefore, an actively conserved mechanism remains to be defined. CYP27B1 along with other vitamin D3 catalyzing enzymes have previously been detected at the mRNA level in human ocular barrier cell cultures and are functionally capable of converting vitamin D once inside the eye into its most active form [20]. Considering the in-situ expression of CYP27B1 and CYP24A1 in the ciliary body and epithelium (Fig. 4), the site of aqueous humour generation, this would be a putative site for vitamin D precursors to enter and subsequently become converted prior to entering into the aqueous chamber. The expression of CYP27B1 within the neural retina implies 25(OH)D_3 is converted locally. The differential expression of CYP27B1 and CYP24A1 within the retina and RPE also highlights a topographical expression that may be important in normal retinal physiology. The location of CYP24A1 within the distal photoreceptor/interphotorecptor matrix/apical RPE and CYP27A1 at the basolateral surface of the RPE could suggest local currents of vitamin D activation/deactivation important in photoreceptor function or outersegment disc phagocytosis. Considering the vitamin D receptor is expressed in photoreceptors [28], the expression of these enzymes within the light-sensitive elements of the retina could suggest an unrecognized role for vitamin D in phototransduction. This remains highly speculative, but further research in the role for vitamin D in retinal neural physiology is now warranted.

Our data further supports the eye as one of the extra-renal organs with 1α-hydroxylase activity, and therefore capable of local activation of 1,25$(OH)_2D_3$. This is supported by the presence of both substrate and enzyme in the ocular fluid and tissues respectively. Our research corroborates previous in-vitro cell culture studies using primary human scleral fibroblasts, corneal endothelial cells, ciliary body epithelium and retinal pigment epithelium, all of which have been shown to produce 1,25(OH)2D3 [20] Ocular fluid 25(OH)D_3 may be analogous to 25(OH)D_3 in the serum, and therefore the ocular fluid acts as a conduit for transporting molecules important for dealing with chronic exposure to oxidative stress. Patients with cataracts contained the lowest concentrations of 25(OH)D_3. Whether this is related to consumptive effect, a complete conversion into 1,25$(OH)_2D_3$ or a reflection of a predominantly posterior eye segment phenomenon remains to be determined. Elevated concentrations of 25(OH)D_3 in the aqueous and vitreous humour could be related to an accumulation secondary to a breakdown in blood ocular barriers, especially considering the highest levels were seen in patients with proliferative diabetic retinopathy. Conversely, the elevated 25(OH)D_3 seen in patients with an ERM would argue against a breakdown in blood ocular barriers as the sole mechanism, but rather a more inflammatory or immune mediated phenomenon. Vitamin D has been shown to reduce the proliferation of CD8 T-cells, inactivate B cells and modulate the immune response towards a more T-regulatory dominant or immunosuppressive environment [29–31]. Considering the retinal predominant expression of CYP27B1, a rise in extracellular 25(OH)D_3 could reflect a backlog in substrate from the inability to convert into intracellular 1,25$(OH)_2D_3$ as a result of enzymatic damage from various retinal disease stimuli. Alternatively, elevated 25(OH)D_3 may reflect an increased demand on the system, similar to what is seen in granulomatous disease. Unregulated production of 1,25$(OH)_2D_3$ from extra-renal CYP27B1 in granulomatous macrophages is well established. Mycobacterium infection up regulates

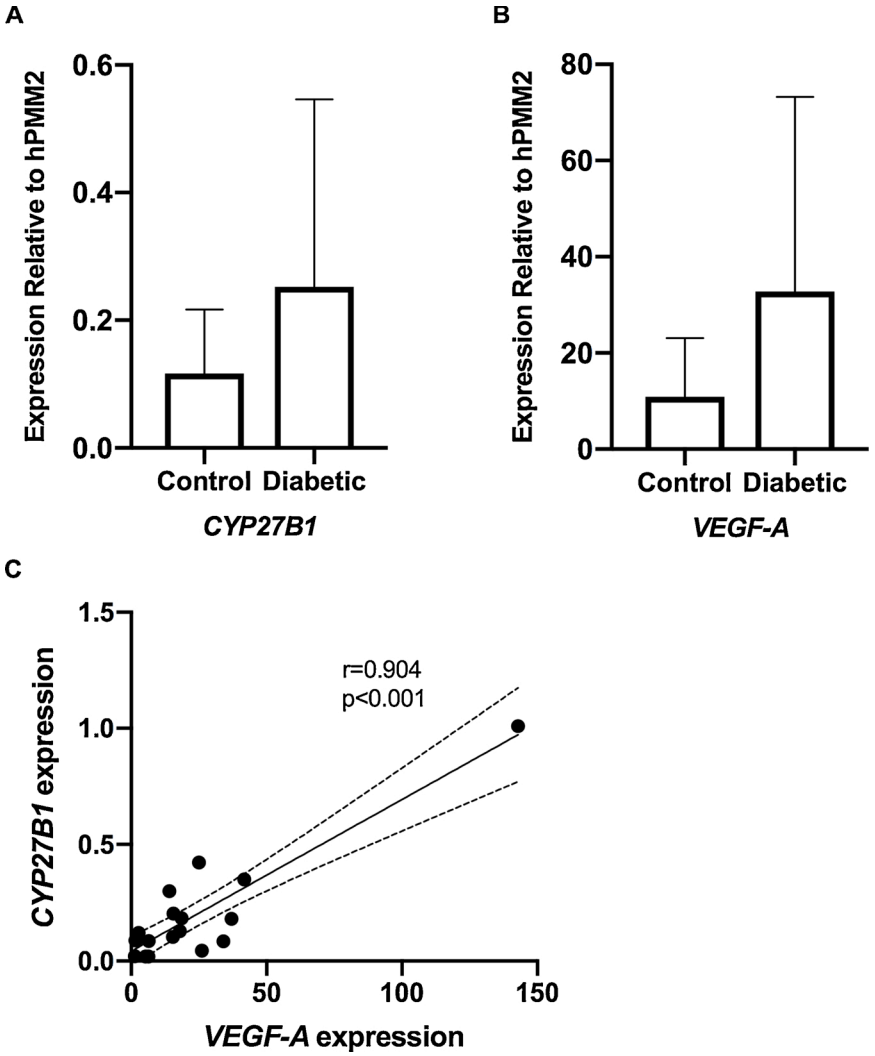

Fig. 3. mRNA expression of vitamin D activating (*CYP27B1*) gene and *VEGF-A* in control and diabetic eyes. mRNA gene expression of CYP27B1 (A) and VEGF-A (B) relative to phosphomannomutase-2 (PMM2). Control eyes, N = 8, 4 patients. Diabetic eyes denoted, N = 10, 5 patients. Mean gene of interest expression relative to PMM2 ± standard deviation B) Pearson's correlation between retinal CYP27B1 and VEGF-A expression in control and diabetic eyes. Pearson's coefficient, r = 0.904, p < 0.001, confidence interval (0.757 to 0.964).

CYP27B1 and vitamin D receptor activity, which in the presence of exogenous $1,25(OH)_2D_3$ can activate antimicrobial molecules, such as cathelicidin, which in turn kills intraceullar mycobacterium [32]. The up-regulation of CYP27B1 and production of $1,25(OH)_2D_3$ also appears to be important in wound healing [33]. Therefore, measuring elevated $25(OH)D_3$ in the ocular fluids secondary to widespread retinal injury is plausible. This may represent a new approach in understanding fundamental eye responses to disease.

In patients with retinal disease, the mean concentration of $25(OH)D_3$ was 0.502 ng/mL as compared to 0.057 ng/mL in patients with cataracts only, a 9-fold magnitude difference. The highest concentrations were found in patients with active neovascularization, diabetic macular edema, epiretinal membrane formation or retinal detachment. The relative difference of $25(OH)D_3$ in patients with retinal disease versus those without suggests vitamin D may be involved in the pathogenesis of many retinal diseases. Our data supports a growing body of research that highlights a new role for vitamin D in retinal vascular diseases. Our work also supports recent published work by Kim K.L. et al., who showed elevated 25(OH)D3 in the aqueous humour in patients with macular edema. A relationship between vitamin D signaling and VEGF-A in the context of neovascular diseases of the eye is intriguing. $1,25(OH)_2D_3$ present in smooth muscle cells is capable of driving VEGF expression through a vitamin D response element located in the VEGF promoter region [34,35]. Most recently, calcitriol engaging with the VDR in pericytes is able to increase the expression of VEGF, suggesting a pro-angiogenic capacity [36] Calcitriol has also been shown to be capable of inhibiting neovascularization and reactive oxygen species in a mouse models of ophthalmic disease [10,18,37]. Therefore, $25(OH)D_3$ measured in the humours of the eye may be elevated or driven by retinal neovascular disease activity. This is supported preliminarily by the strong correlation observed between CYP27B1 and VEGF-A in diabetic eyes as well as the highest concentrations measured in patients with VEGF-dependent disease.

Our work has a number of limitations. First, the cross-sectional nature inhibits investigators from drawing conclusions about the temporal relationship between ocular pathology and vitamin D regulation. Second, considering the sampling method for vitamin D, we are missing a critical control, namely health eyes without ophthalmic disease. The importance of this control cannot be overstated, but the ethical nature of sampling control eyes cannot be overlooked. The presence of vitamin D in the aqueous and vitreous humour in steady state conditions remains unknown. Future animal studies that recreate human retinal proliferative diseases will be essential. Third, $1,25(OH)_2D_3$ was not directly measured in this study and therefore we are not able to draw

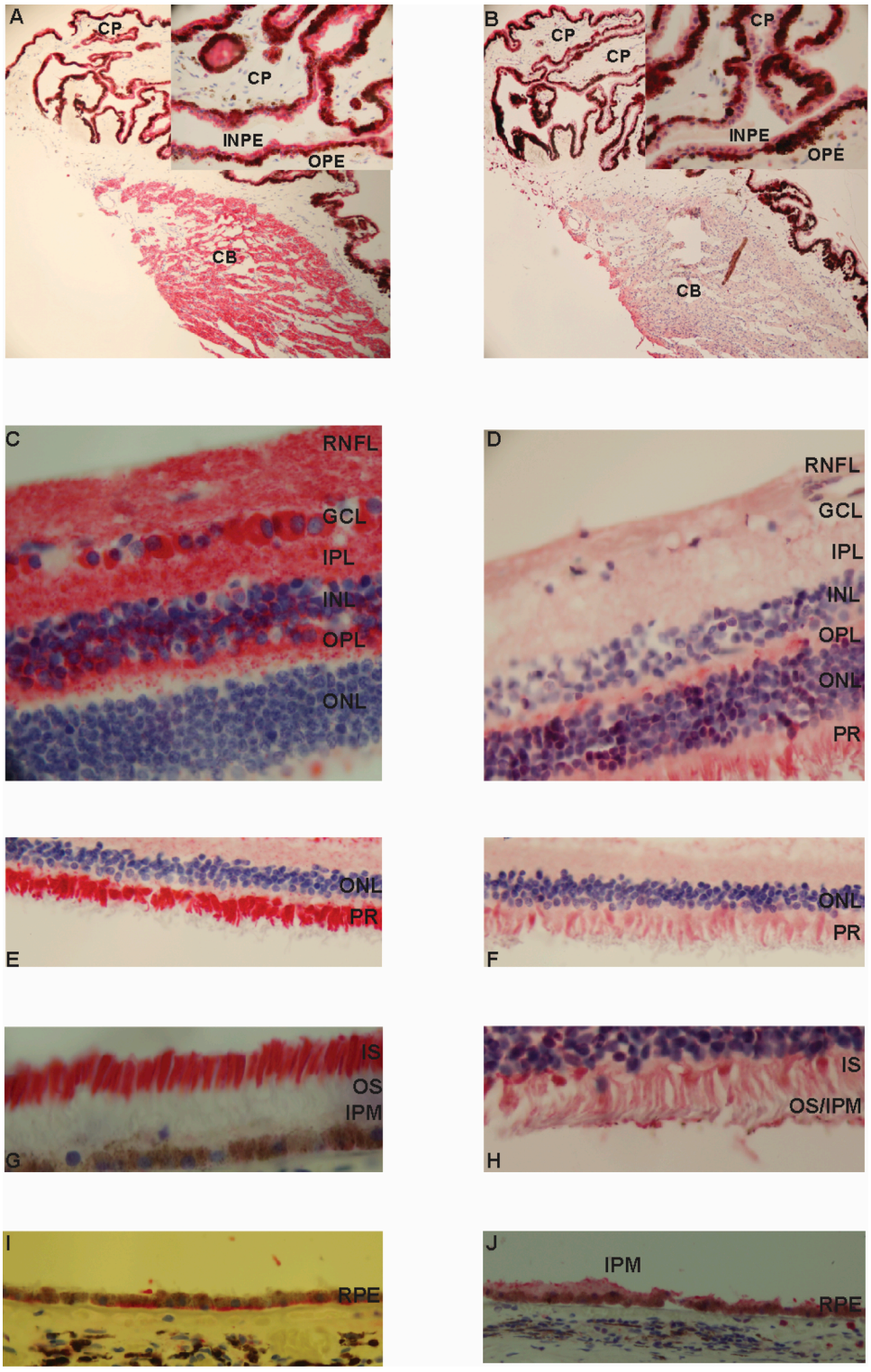

Fig. 4. Immunolocalization of vitamin D activating (CYP27B1) and deactivating (CYP24A1) P450 enzymes. Immunhistochemistry of retinal sections from cadaveric control eyes incubated with anti-CYP27B1 antibody (red), panels A, C, E, G, I or anti-CYP 24A1 antibody (red), panels B, D, F, H, J. Primary antibody localization denoted by red color. Counter-stain (blue) highlights nuclei (refer to methods for full details). A) CYP27B1 and B) CYP 24A1 localization within the ciliary body (CB) and extending ciliary processes (CP), original magnification 10×. High magnification insert (40X) illustrating the inner pigmented epithelium (INPE) and outer non-pigmented epithelium (ONP). C) CYP27B1 and D) CYP 24A1 localization of the inner and outer retina. Retinal nerve fibre layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL) and photoreceptor layer (PR) highlighted. Original magnification 40 × . E) CYP27B1 and F) CYP 24A1 localization of the outer retina only. Original magnification 20 × . G) CYP27B1 and H) CYP 24A1 localization of the outer retina/retinal pigment epithelium (RPE) region. Inner segment (IS) of the photoreceptor, outersegment (OS) and interphotorecptor matrix (IPM) highlighted. Original magnification 40 × . I) CYP27B1 and J) CYP 24A1 localization of the RPE.

direct conclusions about ocular tissue levels of active vitamin D. The instability of $1,25(OH)_2D_3$ combined with the low volume of intraocular samples collected make measurement very difficult. Lastly, we do not know if there is a specific retinal-specific stimulus that drives $25(OH)D_3$ production, the conversion into $1,25(OH)_2D_3$ or if $25(OH)D_3$ is a by-product of local tissue damage and barrier disruption.

In conclusion, the relationship of ocular $25(OH)D_3$ with retinal abnormalities of the eye implicates vitamin D as a ocular disease target. If vitamin D enzymatic activity is up-regulated in retinal disease, local application of $1,25(OH)_2D_3$ may be therapeutic. Therefore, deciphering the ocular pathway of vitamin D will prove to be critical for understanding normal physiology and the pathophysiology of ocular disease. In the future, targeting vitamin D may be a new and exciting therapeutic approach to improving or preserving vision.

Declaration of Competing Interest

Martin Petkovich is the chief scientific officer of Opko Renal, a

division of Opko Health inc., which is involved in the treatment of chronic kidney disease using forms of Vitmain D3.

Sanjay Sharma is a speaker and advisor to research trials for Novartis and Bayer.

There was no industry input with respect to the design, participant recruitment, interpretation and analysis of data for this manuscript.

No other conflicting relationship exists for any other author.

Acknowledgements

We would like to thank Lee Boudreau from Queen's University, Department of Laboratory and Molecular Pathology for his contribution in the immunohistochemistry performed in this study.

The authors wish to thank Hayley Craig-Barnes, Ashley St. Pierre and Dr. Denis Reynaud of the Analytical Facility for Bioactive Molecules, The Hospital for Sick Children (Toronto, Canada) for assistance with vitamin D detection and measurement in the eye.

The work presented in this manuscript was in part funded by the Barbera Tuck Macphee award from the Canadian National Institute for the Blind (CNIB) to JR and through the Emerging-Clinician Scientist Award from Fighting Blindness Canada to JR.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jsbmb.2019.105536.

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Involving ophthalmology departmental stakeholders in developing workplace-based assessment tools

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ABSTRACT • RÉSUMÉ

Objective: As competency-based medical education (CBME) rolls out across Canada, the assessment process is changing. Our purpose was to involve stakeholders in the selection and modification of workplace-based assessment (WBA) tools for use in an ophthalmology residency program.

Design: This is a qualitative case study conducted in one ophthalmology department at a midsized teaching hospital in eastern Ontario.

Participants: Ophthalmology faculty and residents within the Emergency Eye Clinic participated in the study.

Methods: Phase 1 consisted of faculty piloting the tools and providing written feedback. Phase 2 consisted of 2 focus groups, 1 for residents ($n = 9$) and 1 for faculty ($n = 6$), to explore their experiences with the 4 piloted adapted WBA tools.

Results: Residents and faculty discussed ongoing issues with buy-in and formalizing feedback through the new assessment process. Residents also reiterated the need for more constructive feedback delivered in a timely and sensitive manner. Generally, residents did not value numerical scales on the tools and preferred written comments. Both residents and faculty valued oral over written feedback given the interactive nature of oral feedback.

Conclusions: This study provides insight into faculty and resident perspectives about WBA tools within one ophthalmology department. These results informed the development of WBA tools within the department and highlighted the importance of shifting the assessment culture to accommodate programmatic approaches to assessment in CBME. Involving key stakeholders in the change process has been a valuable strategy. Future research should examine whether or not these perspectives change after CBME implementation.

Objectif: À mesure que se déploie la formation médicale axée sur les compétences (FMAC) dans l'ensemble du Canada, on assiste à une évolution du processus d'évaluation. Nous avions pour objectif de faire participer les intervenants dans le choix et l'ajustement des outils d'évaluation en milieu de travail (EMT) qui seront utilisés dans le cadre du programme de résidence en ophtalmologie.

Nature: Il s'agit d'une étude de cas qualitative réalisée au département d'ophtalmologie d'un hôpital universitaire de taille moyenne dans l'est de l'Ontario.

Participants: Le corps professoral et les résidents en ophtalmologie de la clinique de soins oculaires d'urgence ont pris part à l'étude.

Méthodes: Pendant la phase 1, les professeurs ont testé les outils et présenté leurs commentaires par écrit. Pendant la phase 2, 2 groupes de consultation (1 formé de résidents [$n = 9$] et 1 formé de membres du corps professoral [$n = 6$]) se sont penchés sur leur expérience quant aux 4 outils d'EMT testés.

Résultats: Les résidents et leurs professeurs ont passé en revue les problèmes liés à l'acceptation généralisée des commentaires et à l'officialisation de ces derniers dans le cadre du nouveau processus d'évaluation. Les résidents ont également insisté sur l'importance de recevoir plus de commentaires constructifs présentés en temps opportun et avec délicatesse. En règle générale, les résidents n'aimaient pas les échelles numériques associées aux outils et préféraient les commentaires écrits. De plus, tant les résidents que les professeurs avaient une préférence pour les commentaires oraux plutôt qu'écrits compte tenu de la nature interactive des commentaires oraux.

Conclusions: Cette étude met en lumière l'avis du corps professoral et des résidents sur les outils d'EMT dans un département d'ophtalmologie. Les résultats obtenus ont servi à l'élaboration des outils d'EMT au département et ont souligné l'importance d'ajuster les modalités d'évaluation pour tenir compte de l'approche programmatique dans l'évaluation de la FMAC. La participation des intervenants clés à l'étape du changement de processus s'est révélée très utile. Les projets de recherche futurs devraient vérifier si ces perspectives évoluent après l'implantation de la FMAC.

The Royal College of Physicians and Surgeons of Canada (RCPSC) is transitioning Canadian postgraduate programs to competency-based medical education (CBME) models.[1] This outcomes-based approach emphasizes resident ownership of and responsibility for learning and requires them to demonstrate competence in specific tasks termed *entrustable professional activities* (EPAs) across 4 stages of development.[2,3] EPAs are tasks performed in the clinical setting that encompass multiple competencies; they are specific to a given specialty or subspecialty and increase in complexity as residents progress through the stages of development. EPAs allow for the operationalization of required competencies and provide the opportunity for faculty to assess resident performance.[4]

Meaningfully assessing residents' competence is an ongoing challenge in CBME implementation, and requires engaging both faculty and residents.[5–7] In particular, faculty need to be prepared to complete ongoing frequent *in situ* assessments of residents' performance of EPAs, and coach residents through learning and assessment processes.[8] Further, residents need to seek out and be open to frequent and documented formative feedback relating to their performance on mandated EPAs that demonstrate progression to competence.[9]

https://doi.org/10.1016/j.jcjo.2019.01.013
ISSN 0008-4182

Queen's University was granted permission from the RCPSC to launch CBME across 29 residency programs on July 1, 2017. In preparation for this transition, the Department of Ophthalmology sought the perspectives of residents and faculty about 4 workplace-based assessment (WBA) tools. The purpose of this research was to involve stakeholders in the selection and modification of WBA tools for use in ophthalmology.[10,11]

Methods

This case study describes the experience of ophthalmology residents and faculty who piloted competency-based assessments before full CBME implementation. The WBAs included an adapted Field Note, adapted Ophthalmology Clinical Assessment Tool (OCAT),[12] adapted Ophthalmology Clinical Evaluation Exercise (OCEX),[13] and adapted Encounter Card (Appendices A–D). These WBAs were adapted from previous WBAs that have validity evidence.[12,13] The study took place in the Department of Ophthalmology Emergency Eye Clinic within a midsized teaching hospital in Ontario. Seven supervising ophthalmology faculty and 14 residents were invited to participate. Ethical clearance was received from the Health Sciences Research Ethics Board (File 6018429).

Data Collection

During phase 1 of data collection, 4 adapted WBA tools were introduced for use in the Emergency Eye Clinic over a period of 3 months. All faculty were offered the opportunity to complete all 4 forms. The forms were made available in a common area in the Emergency Eye Clinic in a paper-based format. Attending physicians were encouraged to document perceptions of and feedback about the tools. During the piloting process faculty development was provided in the form of grand rounds discussing the changes to CBME but not specifically "coaching" faculty on how to complete the tools as we wanted to establish the extent to which forms could integrate within current assessment practices. Therefore, piloting was completed before formal intervention for educating stakeholders about the forms was designed. Further, no participants indicated a need for training on how to use the assessment tools.

In phase 2, using convenience sampling, 2 focus groups were conducted, 1 for residents and 1 for faculty. One researcher external to the ophthalmology department facilitated the focus groups while a second researcher (also external to the department) took field notes commenting on preliminary themes, flagged issues with questions, and summarized key findings across focus groups for member checking. Questions focused on participants' perceptions about the usability, feasibility, and value of these WBA tools; qualities of effective feedback; strengths and challenges of the tools; and recommendations. The focus groups ranged between 66 and 87 minutes, audio-recorded, transcribed verbatim, and deidentified before analysis to ensure confidentiality.

Data Analyses

Throughout the data collection and analysis process the researcher responsible for data analysis maintained a reflexive journal to document initial findings, possible biases, and potential assumptions to help mitigate researcher bias. Transcripts were coded using Atlas.ti (v1.6.0.). To ensure interrater reliability, the transcripts and written comments were open coded independently by 2 researchers using emergent thematic design.[14,15] This process was used to look for patterns across focus groups. The final codebook contained 558 codes. A code was the smallest unit of analysis. Similar codes were grouped together into subthemes, which were then grouped into overall themes through consensus by the research team. These themes emerged directly from the data. After completion of all data analysis, data saturation had been reached as the same patterns were emerging from the data with no new patterns. In addition to the journaling process described above, the research team met frequently to talk through the themes as they emerged from the data. The analysis process was iterative with codes, themes, and selected quotations changing multiple times until the research team felt that they were most representative of the data.

Results

Phase 1

Two adapted OCATs, 2 adapted Field Notes, and 5 adapted Encounter Cards were piloted in phase 1. Despite being given the option to complete adapted OCEX forms, participants chose not to complete this form.

Phase 2

In phase 2, 9 residents attended the focus group and 6 faculty members attended their focus group. Five main themes and 15 subthemes emerged from the analyses (Table 1). Appendix E provides additional supporting quotations associated with each theme. R refers to residents and F refers to faculty members.

Table 2 to 6.

Table 1—Emergent themes and subthemes

Theme	Subthemes
Assessment process	Buy-in
	Formalizing feedback
Feedback and supervision	Greater resident initiative
	Constructive feedback
	Timeliness of feedback
	Contextual factors
Valuing narrative over numeric feedback	Devalue scales
	Valued written performance indicators
Preferred assessment tools	Promote written feedback
	Simplicity of tools
	Feasibility issues
Oral vs written feedback	Documenting oral feedback
	Interactive nature of oral feedback
	Need for more oral feedback
	Ongoing oral feedback

Table 2—Theme 1: assessment process with example quotations

Theme	Subthemes	Example Quotations
Assessment process	Buy-in	". . . there is various staff in emerge[ncy] and various residents, and no one is going out of their way to fill out the forms." (R4)
	Formalizing feedback	"There is a reason why in months [only] one has been done. No one wants to do it" (R1).
		"They don't necessarily believe that this is required to train a competent ophthalmologist. Buy-in is huge" (R8).
		"Because we didn't all really fill them out . . . the problem wasn't the form but it was that I was providing formative feedback which created a little friction. That was the challenge" (F3).
		"Generally, when you are a trainee and you are told, 'Don't worry about it, we need to do this form and I need to sit in the back.'. . . it changes the dynamic and you become more self-conscious" (F1).

Assessment Process

All participants discussed the lack of buy-in with the new assessment process. Generally, faculty and residents were resistant to completing the tools. Some residents indicated that they felt that faculty were not buying into the process. Faculty discussed the receptiveness of residents to documented formative feedback. From the faculty's perspective, the act of "formalizing" feedback changed the experience for learners, making them more self-conscious.

Feedback and Supervision

Residents expressed a desire for more feedback and supervision. The role of residents to actively seek such feedback was described as needing to increase. With regard to the nature of feedback, most residents indicated that it needed to be constructive and describe what needed to be done differently.

Table 3—Theme 2: feedback and supervision with example quotations

Theme	Subthemes	Example Quotations
Feedback and supervision	Greater resident initiative	"There are lots of people sitting here saying that they want feedback. But if you want feedback, then get the form and take some initiative" (R4).
	Constructive feedback	". . . we want to know what you want us to improve on" (R2).
	Timeliness of feedback	". . . A lot of the time we get written feedback at the end and that is not as helpful because you are done the block and you are looking at the feedback in retrospect. It may not be as good for your learning in that respect. (R6)"
	Contextual factors	"Say you are doing a procedure, having constant feedback can be more helpful in situations where you can pinpoint the actual task" (F1).
		"The timing is important because if it is done in the middle of a busy clinic I may feel pressure not to ask follow-up questions or to clarify things" (R3).

The timeliness of feedback was addressed by all participants. Residents discussed the importance of timely feedback for supporting learning and emphasized that delayed feedback was not ideal. Faculty also noted that timing affected the utility of feedback, including some instances where constant feedback is necessary (e.g., during a procedure). However, residents identified the challenge of negotiating contextual factors in relation to timely feedback since these factors can inhibit learners from fully leveraging a feedback moment.

Table 4—Valuing narrative over numeric feedback and example quotations

Theme	Subthemes	Example Quotations
Valuing narrative over numeric feedback	Devalue scales	"... the actual points to me have no meaning" (R1)
	Valued written performance indicators	"I mean if you get a '5' then I don't really understand what it means" (R4)
		". . . Residents much preferred the written comments on the assessments—advice or compliments or criticisms or whatever. What is valuable is the written word?" (R1).
		"But for the majority they feel a whole lot better if they get 'not yet' vs a 1 on a Likert [scale of] 1 to 5" (F4).

Table 5—Preferred assessment tools and example quotations

Theme	Subthemes	Example Quotations
Preferred assessment tools	Promote written feedback	"I think I personally would perceive this feedback better because the person filling it out has to actually write something down without being given preformed ideas or boxes to check" (R4).
	Simplicity of tools	"[The OCAT is] quick to fill out" (F3).
	Feasibility issues	"I filled in the Emergency Eye Clinic Encounter Card a few times and I found that it was way too busy" (F2).
		"I found it [OCAT] very helpful, however, I don't think it is realistic for it to happen like that on a normal basis. But it was very helpful" (R5).

Valuing Narrative over Numeric Feedback

Overall, residents valued narrative over numeric feedback. They expressed confusion about the meaning of numerical scales on WBA tools and indicated that the numerical scales have little to no value to them. Moreover, faculty discussed how residents were most receptive to feedback provided with written performance indicators.

Preferred Assessment Tools

Of the 4 WBA tools, residents and faculty preferred the adapted Field Note and adapted OCAT assessments.

Table 6—Oral vs written feedback and example quotations

Theme	Subthemes	Example Quotations
Oral vs written feedback	Documenting oral feedback	"Documenting it really only becomes important if you want to look at it later to review. But I don't know that many of us would choose to do that" (R4).
	Interactive nature of oral feedback	"[It is] more personalized. . .. It is so much more dynamic and interactive than written feedback" (R1)
	Need for more oral feedback	"I would agree that verbal [feedback] is the most important and we don't get enough of it" (R8).
	Ongoing oral feedback	"I do my best, but it is never as accurate as the one-on-one" (F2).

Residents appreciated the Field Note because it promoted written feedback from faculty. Faculty also appreciated the simplistic nature of the adapted Field Note and adapted OCAT, whereas the adapted Encounter Card and adapted OCEX were too complicated. The negative language use on the Encounter Card also emerged as an issue.

Despite preferring the adapted OCAT and adapted Field Note assessments, there was skepticism about the feasibility of regularly completing these tools.

Oral Versus Written Feedback

When discussing qualities of effective feedback, both groups generally valued oral over written feedback. The need to document oral feedback was not readily understood by residents. Faculty did understand the need to document feedback, especially for residents in difficulty.

Residents considered oral feedback to be more personal and fluid, and emphasized the need for additional oral feedback. Faculty also discussed the difficulty of reflecting their oral feedback in written form.

Discussion

The purpose of this research was to involve stakeholders in the selection and modification of WBA tools. By involving them, we wanted to understand what would be useful to them in an assessment tool, educate them about the changes that would be required with the implementation of CBME, as well as potentially improve their future engagement with the assessment process. Although few WBA tools were actually completed during the WBA pilot, the qualitative findings do help to inform WBA tool customization, reveal important conundrums in assessment and feedback processes, and highlight the need to actively cultivate a shift in assessment culture.

The choice of assessment tools was influenced by what was available at the time of the study. The assessment tools currently recommended by the RCPSC had not yet been released. As such, we piloted adapted WBA tools available in the literature. Going forward, assessment tools will be more reflective of specific EPAs and less detailed than some of those used in this pilot, as it is understood that not everything needs to be captured about an encounter in one assessment.

Also noteworthy is the lack of electronic assessment tools in this study. Online WBA were not available at our institution at the time of the study. With the implementation of CBME in July 2017, we have adopted an institution-wide electronic assessment platform, which has brought with it opportunities as well as challenges. It is unclear how the lack of online assessment tools may have played a role in the limited number of piloted WBA being completed.

In terms of informing the customization of WBA tools for use in ophthalmology, the findings of this study highlighted the confusion about the meaning of numerical scales on the part of residents and emphasized the high value they place on personalized commentary about their performance. In addition, faculty observed that residents seemed more accepting of behavioural anchors as performance indicators in comparison to numerical scales. The desire for simplicity was also notable. The Field Note and OCAT emerged as the preferred WBA tools, with residents preferring the personalized nature of the Field Note and faculty the OCAT for its simplicity. Leveraging these insights, hybrid CBME WBA tools have been developed at our institution that include only 4–6 items scored on a 5-point behaviourally anchored scale with a "Next steps" narrative comments section to promote coaching-style feedback from faculty.

Several important tensions in assessment and feedback processes emerged in the findings of this study. While residents wanted more feedback, they were often not receptive to feedback. Faculty discussed how the act of formalizing feedback with the use of WBA changed the teacher/learner dynamic. Resident receptivity to feedback is a well-documented phenomena and has been shown to be associated with characteristics of learners, the feedback message, and the culture in which these processes unfold.[16] A move toward promoting resident feedback-seeking behaviour and having faculty provide specific, actionable feedback in a culture that emphasizes a growth-oriented mindset[17,18] could function to optimize assessment and feedback processes. Such a culture moves away from providing high-stake judgements about competence to that of a coaching model designed to support residents' development.[18] To accomplish this shift in assessment, documenting feedback frequently as evidence of growth becomes essential.

Another contradiction that emerged in conversations with residents and faculty was the acknowledged richness of interactive feedback dialogues and the challenge of capturing the essence of those performance discussions in WBA tools contrasted with contextual factors that often impede these important activities. Time constraints associated with navigating clinical contexts as robust learning environments are well recognized in the research literature.[19,20] Although providing protected time for these activities and the role of technology to facilitate documentation have been identified as potential facilitators, the reality of service demands will require purposeful negotiation and the cultivation of a learning culture that overtly supports this kind of investment.

The findings from this study also serve to underline the challenges associated with piloting assessment tools outside the overall implementation of a change to programmatic assessment. Programmatic approaches to assessment in CBME demand frequent documentation of resident performance, which is reviewed for patterns of performance and used to inform high-stake decisions about resident progress and promotion.[20] This study was conducted in an assessment culture characterized by no formal documentation of resident performance beyond mid- and end-of-rotation In-Training Evaluation Reports (ITERs). The ITERs may have had similar elements but were less detailed than the assessments piloted in the current study. Further, the ITERs provided an overall view after 2 or 4 months on a specific rotation, whereas the piloted assessments were intended to be used after one observed patient encounter and to comment on specific elements of that encounter. So not only was there a change in the format of the assessment tools that were introduced, but there was also a required change in the timing and frequency of assessment. It is therefore not surprising that engagement of residents and faculty was low. The purpose of documenting feedback was misaligned with the dominant assessment culture at that time.

Based on preliminary assessment completion rates for ophthalmology rotations during the Transition to Discipline Stage for the July 2017 CBME resident cohort, efforts to engage residents and faculty have shown evidence of early success. CBME residents each attained 6 completed WBA tools during their first 4-week ophthalmology block and 9 during their second 4-week ophthalmology block, representing a significant improvement in completion rates as compared to the pilot period.

Limitations of the current study include a small sample size, the focus on a single centre, and the completion of a small number of forms in phase 1. Despite faculty not completing many forms, both residents and faculty were able to provide valuable feedback regarding the organization and perceived feasibility of the forms. We recognize that our results are not necessarily transferable to other programs across Canada given specific contextual factors, but our study can inform other Canadian ophthalmology programs as they transition into CBME and potentially develop their own assessment tools. Further, this study can serve as a prediction of the change in assessment culture that will be required with the transition to CBME across the country, as other ophthalmology programs start their planning. There already exists concern about faculty engagement in a system of assessment with infrequent assessment (ITERs). As such, there is genuine concern among program directors about how to manage the need for frequent WBA within CBME. This study provides some initial insight into experiences with transitioning to CBME and piloting reconceptualized WBA tools.

We hope that our findings will provide some insights and recommendations for designing assessment tools, involving stakeholders, as well as considering timing and style of feedback delivery within ophthalmology programs as they work toward CBME implementation. Based on the findings from the current study, we propose programs consider the following suggestions as they prepare for CBME implementation: i) keep assessment tools simple to avoid overwhelming users; ii) balance the use of assessment scales with opportunities to provide narrative feedback within the same tool; iii) involve residents and faculty in the process early to promote engagement ("buy-in"); iv) encourage faculty to provide constructive feedback that describes what residents need to do next so that they can improve; v) encourage the provision of timely feedback; and vi) be mindful of language used when designing assessment tools, avoiding negative language.

Conclusions

This study provides insight into faculty and resident perspectives about WBA tools within one ophthalmology department. These results informed the development of WBA tools within the department and served to highlight the importance of shifting the assessment culture to accommodate programmatic approaches to assessment within CBME. Involving stakeholders in the design of assessment tools may help to shift the culture.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jcjo.2019.01.013.

APPENDIX A.

Queen's Ophthalmology Field Note

Instructions: Can be used with an individual patient encounter, overall performance of a clinic, or general observations and/or feedback. Please choose as many CanMeds Key Competencies as apply to the feedback.

Resident Name:_____ Case:_____

Clinic:_____ Case type: Simple Complex

Stage: TD FD Frequency: Common Uncommon

EPAs

TD = Transition to Discipline **FD = Foundations of Discipline** **DD = Detailed Description**

TD1 – Perform Hx and PE, document and present findings in the ER Eye Clinic for initial and subsequent care of pts with **common and simple** acute ophthalmic presentations.

DD1 – Comprehensive Hx
DD2 – Comprehensive exam
DD3 – Basic DDx + Ix
DD4 – Focused F/U
DD5 – Collects data for mgmt.
DD6 - IDs key clinical features
DD7 – Documents and verbally presents
DD8 – Communicates effectively with patients/families

F**D1 –** Assess (perform, document and present Hx + PE) and Dx pts with **common and complex** acute ophthalmic presentations in the ER Eye Clinic setting for initial and subsequent care.

DD1 – Comprehensive Hx + PE
DD2 – Comprehensive DDx + Ix
DD3 -. Focused F/U
DD4 - Collects data for mgmt
DD5 - Documents and verbally presents
DD6 - Communicates effectively with patients/families

Feedback

Something to continue:

Something to improve:

Resident Reflection

Based on feedback, identify one learning need and your plan to address it.

Date:_____ Faculty:_____ Resident:_____ Reviewed with Resident: Y / N

FLAGGED BEHAVIOUR:

Do you have professionalism concerns about this resident's performance? **YES** **NO**

Do you have patient safety concerns related to this resident's performance? **YES** **NO**

Are there other reasons to flag this assessment? (If yes, describe on back) **YES** **NO**

GLOBAL RATING:

Would you entrust this resident to perform this activity independently next time? (other than yes, describe on back) **Not yet** **Almost** **Yes**

APPENDIX B.

Queen's Ophthalmology Clinic Assessment Tool (OCAT)

Instructions: Please complete using one half-day clinic. Complete only the pertinent portions.

1= "I had to do" – Required complete guidance, unprepared to do, had to do for them
2= "I had to talk them through" – Able to perform some tasks, but required repeated direction
3= "I had to direct them from time to time" – Demonstrated some independence, some intermittent help
4= "I needed to be available just in case" – Independence but needed help with some nuances (unable to manage all patients, still requires supervision for safe practice)
5= "I did not need to be there" – Complete independence, can safely manage clinic on own
NA= Not assessed

Resident Name:_____ Date:_____

Clinic:_____ Year /Stage: TD1 FD1

1a. Patient assessment Efficient data gathering	1	2	3	4	5	NA
1b. Patient assessment Accurate examination	1	2	3	4	5	NA
2. Case presentation Synthesis of Hx and exam, clear presentation	1	2	3	4	5	NA
3. Clinical reasoning and differential diagnosis Brings information together and prioritizes to provide a Dx and/or DDx	1	2	3	4	5	NA
4. Management plan Orders appropriate ancillary tests and develop a relevant and decisive plan	1	2	3	4	5	NA
5. Patient/family communication Effective, sensitive, and respectful communication skills (verbal + nonverbal). Able to build rapport and trust.	1	2	3	4	5	NA
6. Documentation in clinic Charting is clear and legible, prescriptions and forms properly completed.	1	2	3	4	5	NA

One thing to continue:_____

_____

One suggestion for improvement:_____

_____

Do you have professionalism concerns about this resident's performance? **YES** **NO**

Do you have patient safety concerns related to this resident's performance? **YES** **NO**

Are there other reasons to flag this assessment? (If yes, describe on back) **YES** **NO**

GLOBAL RATING: Would you entrust this resident to perform this activity independently next time? (other than yes, describe below) **Not yet** **Almost** **Yes**

_____

Date:_____ Faculty:_____ Resident:_____ Reviewed with Resident: Y / N

Adapted from Rekman J, Hamstra S, et al. A new instrument for assessing resident competence in surgical clinic: The OCAT. *J Surg Ed* 2016;73:575-82.

APPENDIX C.

Queen's Ophthalmology Clinical Evaluation eXercise (OCEX)

Instructions: Please complete using one patient encounter. Complete only the portions you observed.

1= Novice - requires complete supervision/prompting/double checking
2= Advanced beginner – requires some supervision/prompting/double checking
3= Developing – supervision/prompting/double checking on demand
4= Competent – completes task without supervision/prompting/double checking, as done by generalist
5= Expert – completes tasks efficiently/recognizes subtleties in case - as done by subspecialist
NA= Not assessed

Resident Name:_____ Case:_____

Clinic:_____ Pt type: NP RP Case type: Simple Complex

Stage/EPA: TD/1 FD/1 Frequency: Common Uncommon

Interview Skills														
1. Washed hands	1	2	3	4	5	NA		7. Oc Meds	1	2	3	4	5	NA
2. Introduced self	1	2	3	4	5	NA		8. PMedHx/PSurgHx	1	2	3	4	5	NA
3. HPI	1	2	3	4	5	NA		9. Systemic Meds	1	2	3	4	5	NA
4. Pertinent features	1	2	3	4	5	NA		10. Allergies	1	2	3	4	5	NA
5. ROS PRN	1	2	3	4	5	NA		11. Fam Hx	1	2	3	4	5	NA
6. POcHx	1	2	3	4	5	NA		12. Social Hx	1	2	3	4	5	NA
Examination Skills														
1. scVA/ccVA	1	2	3	4	5	NA		7. External exam	1	2	3	4	5	NA
2. Refraction	1	2	3	4	5	NA		8. SLE	1	2	3	4	5	NA
3. Pupils/RAPD	1	2	3	4	5	NA		9. IOP	1	2	3	4	5	NA
4. CVF	1	2	3	4	5	NA		10. Gonio	1	2	3	4	5	NA
5. Motility	1	2	3	4	5	NA		11. Macular exam	1	2	3	4	5	NA
6. Strabismus exam	1	2	3	4	5	NA		12. Peripheral retina	1	2	3	4	5	NA
Investigations and Management														
1. Investigations	1	2	3	4	5	NA		2. Management	1	2	3	4	5	NA
Case Presentation and Charting														
1. Clear & concise	1	2	3	4	5	NA		4. DDx	1	2	3	4	5	NA
2. Pertinent facts	1	2	3	4	5	NA		5. Accurate charting	1	2	3	4	5	NA
3. Prioritizes	1	2	3	4	5	NA		6. Legible charting	1	2	3	4	5	NA
Interpersonal Skills/Professionalism														
1. Gentle and caring	1	2	3	4	5	NA		5. Explained Dx/DDx	1	2	3	4	5	NA
2. Empathetic	1	2	3	4	5	NA		6. Explained plan	1	2	3	4	5	NA
3. Used lay language	1	2	3	4	5	NA		7. Answered pt ?s	1	2	3	4	5	NA
4. Explained findings	1	2	3	4	5	NA		8. Work with others	1	2	3	4	5	NA

Feedback:_____

_____

Do you have professionalism concerns about this resident's performance? **YES** **NO**
Do you have patient safety concerns related to this resident's performance? **YES** **NO**
Are there other reasons to flag this assessment? (If yes, describe on back) **YES** **NO**
GLOBAL RATING: Would you entrust this resident to perform this activity independently next time? (other than yes, describe on back) **Not yet** **Almost** **Yes**

Date:_____ Faculty:_____ Resident:_____

Adapted from Golnik KC, Goldenhar LM, GittingerJW, et al. The Ophthalmic Clinical Evaluaton Exercise (OCEX). *Ophthalmology* 2004;111:1271-4.

APPENDIX D.

OPHTHALMOLOGY EMERGENCY EYE CLINIC ENCOUNTER CARD

Instructions: Please consider one patient encounter when completing this form.

Resident Name:_____ Faculty: _____ Date: _____

Clinic:_____ Case:_____ Case type: Simple Complex

Stage/EPA: TD/1 FD/1 Pt type: NP RP Frequency: Common Uncommon

	Opportunities for growth: Close supervision		Developing: Supervision on demand		Achieving: Supervision for refinement	*	N/A
History (Medical Expert)	☐ Misses basic, relevant information OR gathers irrelevant details	☐	☐ Focused and concise	☐	☐ Identifies pertinent risk factors and acquires details, seeking corroborative info as required	☐	☐
Physical Exam *(Medical Expert)*	☐ Pupils: Incomplete exam	☐	☐ Pupils: Good exam but inaccurate interpretation of findings	☐	☐ Pupils: accurate exam & interpretation of findings	☐	☐
	☐ Ocular motility: Incomplete exam	☐	☐ Ocular motility: Good exam but inaccurate interpretation of findings	☐	☐ Ocular motility: accurate exam & interpretation of findings	☐	☐
	☐ Slit lamp: Did not identify/ recognize cornea/anterior chamber findings	☐	☐ Slit lamp: Identified **some** cornea/anterior chamber findings OR inaccurate interpretation of findings	☐	☐ Slit lamp: Identified cornea/anterior chamber & accurate interpretation of findings	☐	☐
	☐ Retina: Did not identify/ recognize findings	☐	☐ Retina: Identified **some** retinal findings OR inaccurate interpretation of findings	☐	☐ Retinal: Identified all retinal pathology & accurate interpretation of findings	☐	☐
	☐ Other: Incomplete exam OR did not identify findings	☐	☐ Other:_____ Good exam but inaccurate interpretation of findings	☐	☐ Other: Accurate exam & interpretation of findings	☐	☐
Problem formulation *(Medical Expert)*	☐ No differential	☐	☐ Limited differential	☐	☐ Useful differential including plausible rarer items	☐	☐
	☐ Did not prioritize findings	☐	☐ Prioritized findings for simple case	☐	☐ Prioritized for complex/infrequent case	☐	☐
Use/ Interpretation of tests (Medical Expert)	☐ Proposed irrelevant or incorrect investigations	☐	☐ Identified investigations, but use may be indiscriminant.	☐	☐ Strategic use of investigations (e.g., justifiable cost/benefit)	☐	☐
	☐ Misinterpreted results	☐	☐Correctly interpret results	☐	☐ Results of investigations inform management (e.g., makes sense of all info)	☐	☐
Management (Medical Expert)	☐ Proposed incorrect treatment or inadequate management plan	☐	☐ Managed simple & complex but frequently encountered diagnoses	☐	☐ Managed treatment for complex and infrequently encountered diagnoses	☐	☐
Case report (Communicator)	☐ Omitted pertinent information.	☐	☐ Presented all pertinent information.	☐	☐ Prioritized information, succinct but thorough	☐	☐
Documentation (Communicator)	☐ Documentation is inaccurate/incomplete	☐	☐ Documentation may be unclear	☐	☐ Documentation is complete, accurate, clear & concise	☐	☐
	☐ Writing is illegible	☐	☐ Writing can be difficult to read	☐	☐ Writing is legible	☐	☐
Interpersonal Skills *(Communicator)*	☐ Struggles to communicate effectively with the [patient +/- family	☐	☐ Able to communicated some of the encounter to the patient+/- family	☐	☐ Able to communicate effectively the patients diagnosis and pla	☐	☐
	☐ Awkward with patient and family, unable to achieve adequate rapport to perform adequate assessment	☐	☐ Some rapport, but patient and family not fully comfortable with the interaction	☐	☐ Establishes good rapport, patient and family are comfortable	☐	☐

Additional Feedback:_____

Do you have professionalism concerns about this resident's performance? **YES** **NO**

Do you have patient safety concerns related to this resident's performance? **YES** **NO**

Are there other reasons to flag this assessment? (If yes, describe on back) **YES** **NO**

GLOBAL RATING: Would you entrust this resident to perform this activity independently next time? (other than yes, describe on back) **Not yet** **Almost** **Yes**

Appendix E. Additional Supporting Quotations for each Theme

Theme	Selected Quotes
1. Assessment Process	"It is a systemic issue inherent with numeral feedback. No one wants a '1' even though it is perfectly normal on your very first day as a PGY2 in emerge to get 1′s and 2′s down the left-hand side. That is what it is saying to give but no one wants to give that. And no one wants to receive that." (R1)
	"I have gone to a couple of the CBME talks and you have to change the culture at the foundation where this is just second nature. . .but because it is so ingrained in our OCD type A personalities that we cannot receive something lower than a '4' and anything else is a failure then that is a hard paradigm shift to achieve." (F3)
	"I would say that you need to be open to feedback and not take it upfront as criticism but more as a stepping stone to get better. If you are open to that and you show your supervisors that then you will get more feedback. Versus shutting them off, moving on and not delving too much into it." (R5)
	"I don't think just the existence of the form changes the culture of getting feedback." (R2)
2. Feedback and supervision	"We want the feedback on the technical skills that we need to know. Having the cameras and having someone watch your interaction with patients is not going to be nearly as helpful as, 'this is a skill you will do for the rest of your career'. But no one has ever watched you do it." (R2)
	"We are really lacking in feedback in general so anything at this point would be a welcome change that we would be willing to try." (R1)
	"I think it would be helpful to have someone at least give feedback on basic skills that we are supposed to know through emerge[ncy] up front or after a certain time period." (R2)
	"Just creating these forms without addressing the issue about having the timing and the right setting and all these things will not actually make a difference to our development." (R2)
	"I think feedback should be done in an appropriate time and fashion." (R1)
	"When it is done informally even in front of a patient or if it is really egregious I will do it outside the room and say, this is what you should have done." (F2)
3. Valuing Narrative over Numeric Feedback	"I mean if you get a '5' then I don't really understand what it means. Does that mean that your performed it well enough that you could be an attending staff and do this or does it mean that you performed it well enough for your expected level? The numbers to me don't have a good meaning other than people are generally happy with what you are doing." (R4)
	"There are 5 or 6 categories and a whole breakdown. But I don't read them and don't care what they say. I just care that I am not lacking in anything and then I look at the comments. So those are as a learner what is valuable because it is tailored to me as a person—advice or compliments or criticisms. That is what is valuable is the written word and then knowing if I have any major deficiencies to work on. Otherwise the scoring system is just north of useless." (R1)
4. Preferred Assessment Tools	"With the field note I imagine it could be applied to anything. . .. It [field note] is much more adaptable to any scenario because of that. . .. They are not predetermined statements that you are choosing to agree with to a certain degree. So, it is more meaningful and personalized." (R4)
	"They [OCAT] actually map out nicely to the different milestones for your transition to discipline and foundations." (F3)
	"It [OCAT] would reflect more than the other ones for my philosophy of the intermediate informal feedback with no confrontation associated with it. That is why I like it." (F2)
5. Oral vs. Written Feedback	"You are more likely to retain [feedback] because it is an important conversation that you have had more so than the generic forms that you get at the end." (R4)
	"You can communicate quicker and more efficiently verbally than in written form." (R1)
	"I think if we're to first get verbal feedback and they talk to us, and then to spend time to put all that you have discussed into a form that reflects what was discussed... that would be difficult and redundant." (R6)

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Footnotes and Disclosure:

We would like to thank the Southeastern Ontario Academic Medical Organization Endowed Scholarship and Education Fund for their support, and the faculty and residents who participated in this research.

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Originally received Aug. 17, 2018. Final revision Jan. 27, 2019. Accepted Jan. 30, 2019.

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CORRESPONDENCE

Inner-limiting-membrane peeling in epiretinal membrane surgery: an evolving surgical trend

An epiretinal membrane (ERM) forms in the posterior pole from cellular proliferation on the inner limiting membrane (also known as the internal limiting membrane, ILM). ERMs are most commonly idiopathic and develop after posterior vitreous detachment but can occur secondary to ocular or systemic diseases or retinal injuries such as tears and detachments. Most patients who develop ERMs remain asymptomatic; however, metamorphopsia and progressive decline in visual acuity can occur over time with epiretinal contraction. Surgery with pars plana vitrectomy is indicated in patients with symptomatic ERMs. In recent years there has been a surgical trend among vitreoretinal surgeons to combine ILM peeling in procedures for ERM removal. The reason for the increasing popularity of these combined surgeries is multifold; though, the role of an ILM peel in these cases is not entirely clear and has been debated. Here, our objective is to provide a brief overview of the literature and opinions on ILM peeling during ERM surgery.

As the ILM is relatively transparent, its surgical removal was largely regarded as technically challenging until the advent of retinal staining techniques began to be reported in the early 2000s. Initial reports showed that stripping of all epiretinal tissue, including the ERM and ILM, could be expedited and facilitated using indocyanine green (ICG) dye.[1] The benefit for vitreoretinal surgeons in doing this was that ICG showed a distinct contrast between the ILM and deeper retinal tissue, leading to reduced intraoperative complexity whereby there was no need to start and restart the peeling or worry about peeling tissue from the underlying retina. Shortly thereafter it was noted that retinal toxicity may result from ICG staining, and another vital dye, brilliant blue G, could also be useful in staining the epiretina with potentially low retinal toxicity.[2,3] Eventually, many well-executed studies provided evidence establishing that both ICG and brilliant blue G were safe for use in vitreoretinal surgeries.[4] The advent of surgical dyes led to a trend to concomitantly peel the ILM during ERM removal surgery. Subsequently, as reported in the American Society of Retina Specialists "preferences and trends survey," from 2008 to 2010, the number of vitreoretinal surgeons doing ILM peeling for ERM surgery increased from 25% to 44%.[5]

It has been well established that there is equal improvement in postoperative best corrected visual acuity (BCVA) with or without ILM peeling during ERM surgeries. Many cross-sectional and retrospective studies have provided data to support this concept over the past decade. More recently, several longitudinal studies have investigated the long-term outcomes of ERM surgeries up to 3 years,[6,7] and in the spring of 2018, the first data evaluating 5-year outcomes of ERM surgeries were published.[8] The longitudinal data show that, up to 5 years postoperatively, there are no significant differences between the improvement in BCVA in patients who underwent a combined ERM and ILM peeling procedure versus those who only had the ERM removed. These longitudinal studies reinforce the notion that BCVA outcomes are similar whether the ILM is peeled or not. At the same time, these studies have provided valuable insight into other clinically relevant endpoints for ophthalmologists such as ERM recurrence and postoperative anatomical changes in retinal thickness. By peeling the ILM, vitreoretinal surgeons can be assured that an ERM is completely removed. Therefore, in the absence of surgical complications, the possibility of leaving a "persistent" ERM postoperatively from an incomplete peel is extremely low with a combined ILM and ERM peeling procedure. In keeping with this, the cross-sectional and longitudinal literature has established that there is in fact lower ERM recurrence postoperatively in these combined surgeries.[6–11] Similarly, postoperative anatomical changes such as central retinal and macular thickness have also been investigated. However, the results from these studies are not as straightforward to interpret.[7] A cross-sectional study reported that ILM peeling during ERM surgeries is associated with an increase in macular thickness postoperatively.[12] Yet, longitudinal data suggest that there is a progressive decline in retinal thickness postoperatively, and after 5 years there is not a significant difference in retinal thickness for combined ERM and ILM peeling versus non-ILM peeling.[8] These findings likely reflect the progressive resolution of cystoid macular edema that occurs postoperatively, but it is important to note that fluctuations in central retinal thickness are common within the first postoperative year.

Opponents against a combined procedure for ILM removal during ERM surgery highlight that with no difference in visual outcomes, peeling the ILM subjects patients to unnecessary risks and complications that would otherwise not come into play. Common complications associated with ILM peeling in ERM surgeries related to either surgical technique or intraoperative complications include macular holes, visual field defects, retinal toxicity from surgical dyes, and photoreceptor dysfunction.[2,3,11,13,14] These adverse events have been well described and must always be considered to have an effect on the overall surgical outcomes.

In conclusion, there has been an evolving trend among vitreoretinal surgeons to perform ILM peeling during ERM surgery. However, given current data, the role of ILM peeling in these cases is controversial and the role of a combined surgery remains unclear. With emerging longitudinal postoperative data we are developing a better understanding of visual outcomes, ERM recurrence, and anatomical changes after ERM surgeries. At this point, it appears that ILM peeling during ERM surgery does not result in a significantly greater improvement in BCVA compared with ERM peeling alone. However, combining ILM peeling does appear to be associated with a lower rate of ERM recurrence at least up until 5 years. A larger body of longitudinal evidence is needed to better understand which patients will have the best long-term

to prevent sudden pressure fluctuations while removing viscoelastic, an important detail to prevent SCH recurrence. This case outlines factors to consider when deciding upon the timing of surgery for nonhemorrhagic complications of SCH, particularly IOL placement. We illustrate the possibility of achieving excellent postoperative visual acuity using a conservative approach.

This article includes online-only material. Video 1 can be found on the CJO web site at http://pubs.nrc-cnrc.gc.ca/cjo/cjo.html. It is linked to this article in the online contents of the xxx 20xx issue.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2019.02.015.

Footnotes and Disclosure: Chris J. Rudnisky - Novartis (consultant) Kelsey A. Roelofs and Jingyi Ma — None

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Can J Ophthalmol 2018;54:e225–e227
0008-4182/17/$-see front matter
https://doi.org/10.1016/j.jcjo.2019.02.015

Papillomas in Goltz syndrome: case report, anaesthetic considerations, and review of the literature

A 10-year-old Caucasian female with Goltz syndrome (GS) was referred for management of ocular papillomas (Fig. 1A). She was born full-term with multiple congenital dysmorphisms, including syndactyly (Fig. 1B), ear anomalies, hearing loss, generalized vesicular rash, atrial septal defect, and developmental delay. GS was diagnosed clinically and confirmed genetically; parental genetic testing was negative. Surgical history included bilateral myringotomies, tonsillectomy and adenoidectomy for obstructive sleep apnea (OSA), right toe amputation, and multiple papilloma excisions (axilla, ears, and lips).

Our patient received eye care since infancy elsewhere, including dacryocystorhinostomy for nasolacrimal duct obstruction; medically controlled congenital glaucoma with drops stopped at age 4, with family reporting no longer necessary; bilateral ectopia lentis, sclerocornea, optic nerve, and macular chorioretinal colobomas; and left eye retinal detachment.

On examination visual acuity was light perception right eye and no light perception left eye. Both eyes had large conjunctival papillomas causing irritation, and she complained that the right papilloma obstructed her vision, and requested removal.

Papilloma excision and examination under anaesthesia was planned. Pre-operative anaesthesia consultation was requested due to pre-existing oropharyngeal papilloma enlarging after airway instrumentation for tonsillectomy. Anaesthesiology determined that the patient's airway was reassuring except for a large partially occluding papilloma (Fig. 1C) and multiple small oropharyngeal papillomas; avoidance of endotracheal intubation and airway management with intermittent bag-mask ventilation to minimize further papilloma irritation was recommended. Inhalation induction of general anaesthesia with sevoflurane, maintenance of spontaneous ventilation, and avoidance of airway instrumentation proceeded as planned. With absence of a definite airway, anaesthesia was maintained intravenously with propofol and remifentanil, and intermittent bag-mask ventilation support to provide the surgical access. Paper tape and padding were used to prevent injury to her fragile skin.

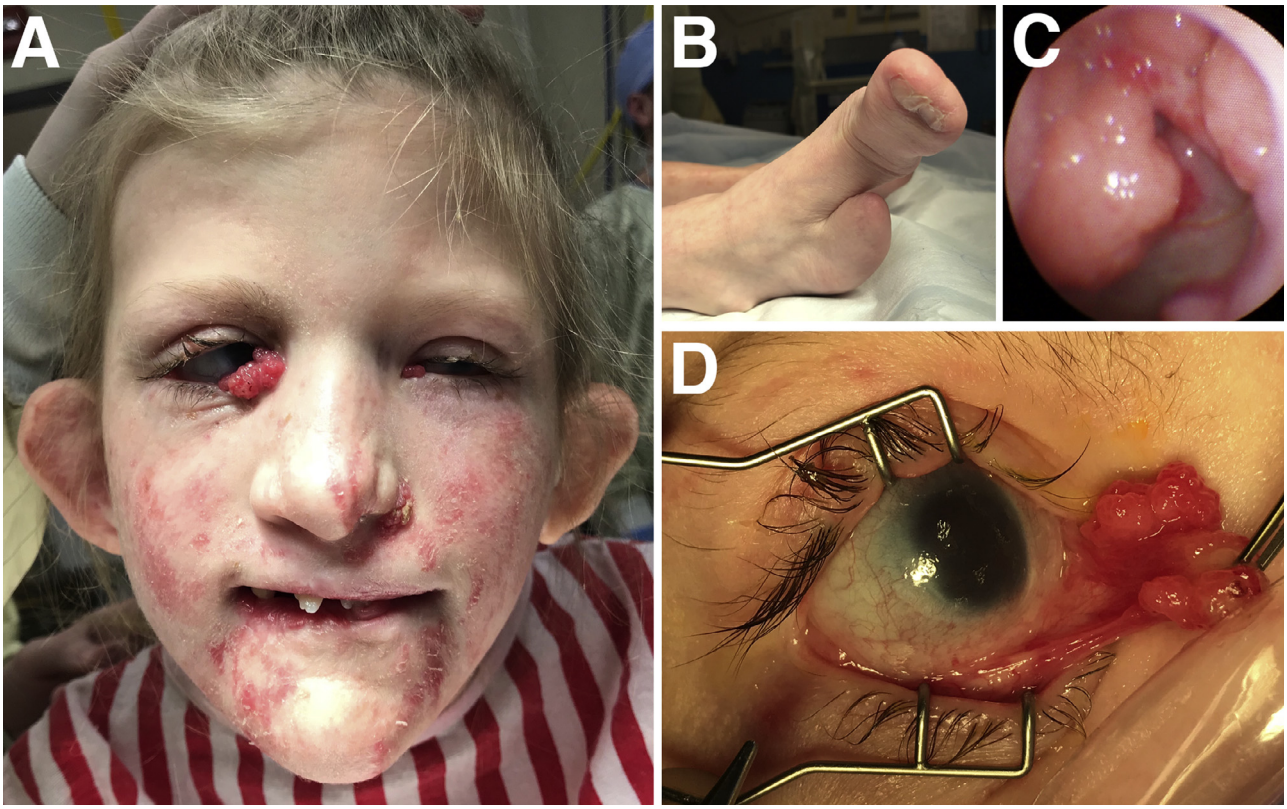

Fig. 1—Manifestations of Goltz syndrome in our patient. (A) Craniofacial features and dysmorphology demonstrating triangle-shaped facies, atrophic linear skin lesions, low set ears, small pinnae, peg-shaped teeth, left microphthalmos, and medial bulbar conjunctival papillomas with the right significantly larger than left. (B) Right foot syndactyly with lobster claw deformity. (C) Fiber-optic bronchoscopy demonstrating a large papillomatous mass on the right side of her oropharynx, which had increased in size to 3 cm since her last surgery in 2009. (D) Right eye aniridia and palpebral conjunctival papilloma.

Ocular examination revealed bilateral aniridia and microcornea, with diffuse corneal haze and thick corneas: 616 and 766 microns right and left eyes. Intraocular pressure was 30 and 15 mm Hg right and left eyes (Perkins tonometry). The right lens had posterior subscapular opacities and was dislocated inferonasally with visible zonules superotemporally. The left lens was completely dislocated in the posterior segment. Fundus examination of the right eye showed a chorioretinal coloboma inferiorly and inferonasally; due to corneal haze, cataract, and dislocated lens, retina and optic nerve visualization was difficult. No posterior structures were clearly delineated in the left eye. B-scan ultrasonography confirmed dislocated lenses bilaterally, a right eye chorioretinal coloboma, and left eye chronic retinal detachment. Axial lengths measured 24.33 mm right eye and 13.30 mm left eye.

The right eye had a large palpebral conjunctival papilloma inferonasally abutting the caruncle, obscuring the visual axis (Fig. 1D). The left eye had a small caruncular papilloma. The papillomas were excised with no complications. Pathological

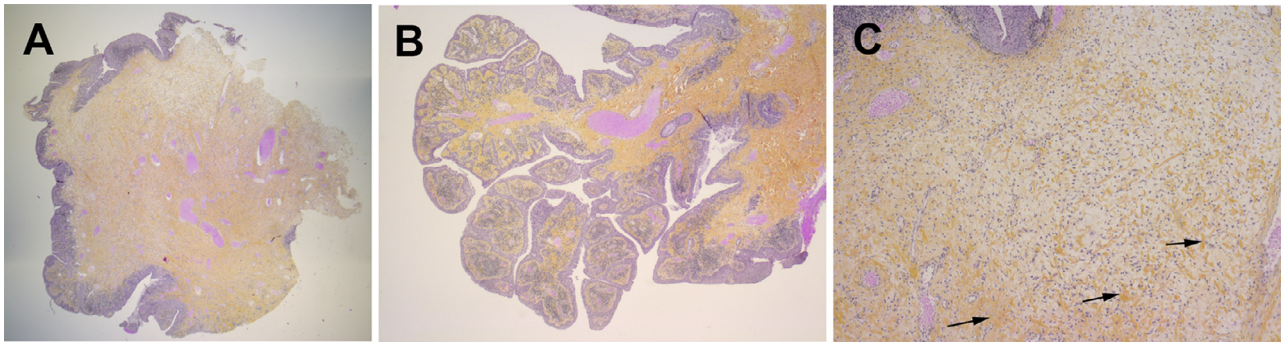

Fig. 2—Conjunctival papilloma histopathology slides. (A) Microscopic examination at 12.5 × magnification (hematoxylin, phyloxine, and saffron stain) showing a polypoid lesion with mildly hyperplastic conjunctival epithelium and significant stromal overgrowth. (B) Focal stumpy papillary cores at 25 × magnification. (C) High-power view of an area of stromal overgrowth, containing proliferating bland spindle-shaped stromal cells and increased collagen deposition (arrows).

Table 1—Ophthalmic findings in Goltz Syndrome.

Anophthalmia
Microphthalmia
Microcornea
Corneal clouding
Blue sclera
Aniridia
Heterochromia
Irregularity of the pupils
Cataract
Lens subluxation
Anterior persistent hyperplastic primary vitreous
Vitreous debris
Optic atrophy
Ocular colobomas (retina, choroid, optic nerve)
Retinal pigment changes
Retinal neovascularization
Ectropion
Ptosis
Hyperteleorism
Strabismus
Nystagmus
Papillomas of conjunctiva and eyelid
Blocked lacrimal drainage

assessment confirmed conjunctival papillomas with marked subepithelial stroma expansion, proliferating stromal cells, and collagen deposition. Unlike typical conjunctival papillomas, the epithelial lining thickness was mildly hyperplastic. No viral cytopathic effects were identified (Fig. 2). The ocular papillomas have not recurred 1 year postexcision, and the elevated intraocular pressure is managed medically. She subsequently received the HPV-9 vaccine.

Goltz syndrome (also known as focal dermal hypoplasia or Goltz-Gorlin syndrome) is a rare multisystem disorder characterized by anomalies of skin (atrophy, linear pigmentation and fat herniation, papillomas, ridged dysplastic nails), skeletal system (limb hypoplasia, syndactyly, polydactyly, oligodactyly), teeth (hypoplastic teeth), and face (facial asymmetry, pointed chin, small underfolded pinnae) due to dysplasia of ectodermal and mesenchymal derived tissues.[1,2] It is an X-linked dominant disorder caused by *PORCN* gene mutations (171 different mutations registered in the online *PORCN* mutation database), with approximately 90% being female and 95% of all cases being de novo mutations; heterozygous nonmosaic male *PORCN* mutations are presumed lethal.[3–5] Our case had a de novo c.1021C>T (p.H341Y) mutation, previously reported in only one other patient.[4,6] Approximately 400 GS cases are reported worldwide; prevalence estimates are unavailable.[7]

Ocular manifestations have been reported with varying incidence between 40% and 77% (Table 1), most commonly ocular colobomas, strabismus, and microphthalmia.[1,8,9]

The least commonly reported ocular finding in GS is conjunctival and eyelid papillomas (5% in the largest case series).[1] Conjunctival papilloma is a benign epithelial tumour with prominent intrinsic vascularity; they frequently show exophytic growth pattern but can exhibit mixed or rarely an inverted growth pattern, the latter having a greater tendency for malignant transformation into transitional cell, squamous cell, or mucoepidermoid carcinoma.[10] A causal relationship between human papillomavirus (HPV) and conjunctival papilloma has been documented in 5%–45% of cases.[10] Conjunctival papillomas are most commonly associated with low-risk HPV strains 6 and 11, especially in children, and rarely with high-risk HPV strains.[10] Treatment options include observation; however if lesions are irritating, cosmetically unacceptable or obscuring vision, they can be excised, with or without use of cryotherapy. Recurrence rate after removal ranges between 3% and 27%, possibly more common in children and limited by adjuvant oral cimetidine and/or topical interferon alfa-2b.[10] HPV-9 vaccine, which includes the serotypes associated with conjunctival papillomas, may reduce papilloma recurrences,[11] with anecdotal reduced recurrences in GS.

There is limited information in the literature concerning anaesthesia in GS.[12–14] Papillomas in the airway and hypertrophy of the gums and buccal mucosa[10] can complicate airway management. Irritation of papillomas or tissues in the upper airway can trigger rapid growth of papillomas, making airway instrumentation a concern, as in our patient.[12,13] Most previous reports describe unanticipated difficult airway due to unexpected papillomas. Anaesthetic management of these patients may require preoperative awake fiberoptic airway assessment. Maintenance of spontaneous ventilation and avoidance of airway instrumentation can minimize airway trauma, thus preventing new papilloma formation. Children with GS are prone to OSA. A case series of 18 GS patients demonstrated that 93% reported OSA symptoms, with 87% requiring tonsillectomy, similar to our case.[3] Presence of fragile skin with chronic scarring in GS requires careful tissue handling and intravenous line placement.

In summary, we describe conjunctival papillomas, a less commonly recognized ophthalmic finding in GS. Our case report emphasizes the anaesthetic risks an ophthalmologist may otherwise unknowingly encounter in bringing a patient with GS to the operating room. We recommend a mandatory pre-operative anaesthetic consultation for all GS patients to limit possible anaesthetic complications in this population who often require multiple surgeries.

Footnotes and Disclosure: The authors have no proprietary or commercial interest in any materials discussed in this article.

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Can J Ophthalmol 2018;54:e227–e230
0008-4182/17/$-see front matter
https://doi.org/10.1016/j.jcjo.2018.12.007

Vertical asymmetric mitochondrial ophthalmoplegia

A 53-year-old female presented with a 2-year history of left upper eyelid blepharoptosis that began acutely. She had attributed the ptosis to contact lens usage and did not seek medical evaluation immediately. After several weeks of persistent ptosis, she was seen by an outside provider who performed levator resection surgery. Several weeks postoperatively, she began to notice vertical diplopia and difficulty elevating her left eye. Her surgeon believed that myasthenia gravis was a possible etiology. Review of symptoms was negative for any other neurologic symptoms, and she denied exposure to any myotoxic medications. She therefore started pyridostigmine 60 mg 4 times a day and prednisone up to 40 mg daily for over 4 months, but her symptoms did not resolve or improve. Serology for acetylcholine receptor antibodies and anti-muscle-specific kinase antibodies revealed to be negative. She also underwent 2 single-fibre electromyograms of the frontalis muscle, both of which were reportedly normal. However, given clinical concern for possibility of seronegative myasthenia gravis and persistence of ptosis and diplopia, she underwent plasmapheresis (6 sessions), which did not improve her symptoms. Due to the lack of improvement with treatments for myasthenia gravis, she underwent magnetic resonance imaging of the brain and orbits, which was unremarkable.

She was then referred to our institution, where her examination (Fig. 1) revealed a right hypertropia of 30 prism diopters (PD), increasing in upgaze and decreasing in downgaze. She had markedly limited elevation of the left eye, especially in adduction and mildly limited elevation of the right eye. Forced duction testing was negative. The patient returned 3 months later and her examination was stable, and so the decision was made to perform strabismus surgery. With a large chin-up position, the patient could fuse and was orthotropic; she therefore underwent left superior rectus muscle plication (5.5 mm), right superior rectus muscle recession (5 mm), and right lateral rectus central plication (2 mm). Postoperatively, the patient was orthotropic in all directions of gaze, and her diplopia resolved. She was diplopia-free until 4 months later, when she noted a return of her diplopia. At this point, her examination revealed a left hypertropia (40 PD) increasing in upgaze and decreasing in downgaze. She had no horizontal strabismus. Her ductions revealed severe limitation to elevation of the right eye, especially in adduction (Fig. 2).

At this point, the diagnosis of myasthenia gravis was re-entertained. She underwent an additional single-fibre electromyogram, a congenital myasthenic panel, and a paraneoplastic panel, all of which were negative. Her alignment stayed stable for 6 months, and so additional strabismus surgery was performed. At the time of surgery, her right superior rectus was found and determined to be in proper position from the previous surgery (5 mm from the original insertion, 12.5 mm from the limbus) and free of any stretched scar. The muscle was resected 7 mm and advanced to the original insertion 7.5 mm from the limbus. The resected specimen was sent to pathology for evaluation. Postoperatively, the patient's ductions were markedly improved—she was orthotropic in all positions of gaze except for upgaze in which she demonstrated a small left hypertropia (8 PD). Her

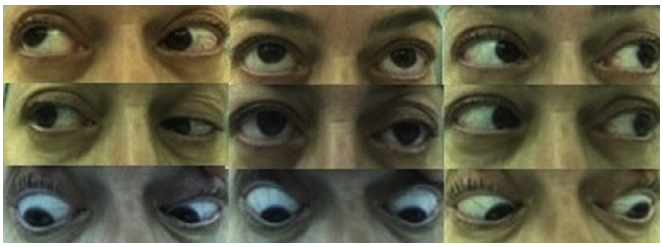

Fig. 1—Baseline photographs demonstrate left hypotropia associated to severe limitation to elevation of the left eye in all gazes.

CORRESPONDENCE

Inner-limiting-membrane peeling in epiretinal membrane surgery: an evolving surgical trend

An epiretinal membrane (ERM) forms in the posterior pole from cellular proliferation on the inner limiting membrane (also known as the internal limiting membrane, ILM). ERMs are most commonly idiopathic and develop after posterior vitreous detachment but can occur secondary to ocular or systemic diseases or retinal injuries such as tears and detachments. Most patients who develop ERMs remain asymptomatic; however, metamorphopsia and progressive decline in visual acuity can occur over time with epiretinal contraction. Surgery with pars plana vitrectomy is indicated in patients with symptomatic ERMs. In recent years there has been a surgical trend among vitreoretinal surgeons to combine ILM peeling in procedures for ERM removal. The reason for the increasing popularity of these combined surgeries is multifold; though, the role of an ILM peel in these cases is not entirely clear and has been debated. Here, our objective is to provide a brief overview of the literature and opinions on ILM peeling during ERM surgery.

As the ILM is relatively transparent, its surgical removal was largely regarded as technically challenging until the advent of retinal staining techniques began to be reported in the early 2000s. Initial reports showed that stripping of all epiretinal tissue, including the ERM and ILM, could be expedited and facilitated using indocyanine green (ICG) dye.[1] The benefit for vitreoretinal surgeons in doing this was that ICG showed a distinct contrast between the ILM and deeper retinal tissue, leading to reduced intraoperative complexity whereby there was no need to start and restart the peeling or worry about peeling tissue from the underlying retina. Shortly thereafter it was noted that retinal toxicity may result from ICG staining, and another vital dye, brilliant blue G, could also be useful in staining the epiretina with potentially low retinal toxicity.[2,3] Eventually, many well-executed studies provided evidence establishing that both ICG and brilliant blue G were safe for use in vitreoretinal surgeries.[4] The advent of surgical dyes led to a trend to concomitantly peel the ILM during ERM removal surgery. Subsequently, as reported in the American Society of Retina Specialists "preferences and trends survey," from 2008 to 2010, the number of vitreoretinal surgeons doing ILM peeling for ERM surgery increased from 25% to 44%.[5]

It has been well established that there is equal improvement in postoperative best corrected visual acuity (BCVA) with or without ILM peeling during ERM surgeries. Many cross-sectional and retrospective studies have provided data to support this concept over the past decade. More recently, several longitudinal studies have investigated the long-term outcomes of ERM surgeries up to 3 years,[6,7] and in the spring of 2018, the first data evaluating 5-year outcomes of ERM surgeries were published.[8] The longitudinal data show that, up to 5 years postoperatively, there are no significant differences between the improvement in BCVA in patients who underwent a combined ERM and ILM peeling procedure versus those who only had the ERM removed. These longitudinal studies reinforce the notion that BCVA outcomes are similar whether the ILM is peeled or not. At the same time, these studies have provided valuable insight into other clinically relevant endpoints for ophthalmologists such as ERM recurrence and postoperative anatomical changes in retinal thickness. By peeling the ILM, vitreoretinal surgeons can be assured that an ERM is completely removed. Therefore, in the absence of surgical complications, the possibility of leaving a "persistent" ERM postoperatively from an incomplete peel is extremely low with a combined ILM and ERM peeling procedure. In keeping with this, the cross-sectional and longitudinal literature has established that there is in fact lower ERM recurrence postoperatively in these combined surgeries.[6–11] Similarly, postoperative anatomical changes such as central retinal and macular thickness have also been investigated. However, the results from these studies are not as straightforward to interpret.[7] A cross-sectional study reported that ILM peeling during ERM surgeries is associated with an increase in macular thickness postoperatively.[12] Yet, longitudinal data suggest that there is a progressive decline in retinal thickness postoperatively, and after 5 years there is not a significant difference in retinal thickness for combined ERM and ILM peeling versus non-ILM peeling.[8] These findings likely reflect the progressive resolution of cystoid macular edema that occurs postoperatively, but it is important to note that fluctuations in central retinal thickness are common within the first postoperative year.

Opponents against a combined procedure for ILM removal during ERM surgery highlight that with no difference in visual outcomes, peeling the ILM subjects patients to unnecessary risks and complications that would otherwise not come into play. Common complications associated with ILM peeling in ERM surgeries related to either surgical technique or intraoperative complications include macular holes, visual field defects, retinal toxicity from surgical dyes, and photoreceptor dysfunction.[2,3,11,13,14] These adverse events have been well described and must always be considered to have an effect on the overall surgical outcomes.

In conclusion, there has been an evolving trend among vitreoretinal surgeons to perform ILM peeling during ERM surgery. However, given current data, the role of ILM peeling in these cases is controversial and the role of a combined surgery remains unclear. With emerging longitudinal postoperative data we are developing a better understanding of visual outcomes, ERM recurrence, and anatomical changes after ERM surgeries. At this point, it appears that ILM peeling during ERM surgery does not result in a significantly greater improvement in BCVA compared with ERM peeling alone. However, combining ILM peeling does appear to be associated with a lower rate of ERM recurrence at least up until 5 years. A larger body of longitudinal evidence is needed to better understand which patients will have the best long-term

outcomes from ERM surgery with ILM peeling. For now, vitreoretinal surgeons should continue to take patient-centred approach to planning ERM surgery while considering the operative risks in combination with the growing body of evidence of postoperative outcomes.

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Originally received Jul. 21, 2019. Final revision Jul. 30, 2019. Accepted Jul. 31, 2019.

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Can J Ophthalmol 2019;■:1–2
0008-4182/17/$-see front matter
https://doi.org/10.1016/j.jcjo.2019.07.016

Foreign body extrusion associated with *N*-butyl-2-cyanoacrylate glue used with rectus muscle hang-back recession

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ABSTRACT •

Objective: Standard rectus muscle recessions require suturing muscle to sclera posterior to the insertion, which is dangerous as the sclera is thin. Extraocular muscle hang-back recession can avoid the posterior scleral needle pass but has been reported to be unstable. The purpose of this study is to assess the use of *N*-butyl-2-cyanoacrylate to aid reattachment of rectus muscle to sclera during hang-back recession.

Design: 2 Phase Study: Phase 1 was a wet lab animal study; Phase 2 was a small case series.

Participants: Phase 1, 14 frozen bank rabbit heads; Phase 2, 4 human adult patients with myopia and large exotropia.

Methods: Phase 1: Frozen bank rabbit heads were used to simulate human hang-back rectus muscle recession. Fourteen rectus muscles were recessed by hang-back and glued to sclera with either cyanoacrylate glue alone (group 1) or glue over prolene mesh for greater stability (group 2). Primary outcome was muscle detachment force measured at 20, 30, and 40 seconds. Phase 2: Four patients with myopia and large exotropia who underwent bilateral hang-back lateral rectus recessions with cyanoacrylate glue were retrospectively studied.

Results: Phase 1: Group 1 mean detachment force measured at 30 seconds was 172.07 g versus 376.5 g in group 2 ($p < 0.01$). Phase 2: All patients had excellent postoperative alignment within 5 PD of orthophoria and no overcorrections. Two patients had unilateral glue extrusion at 1 month requiring in-office removal under topical anaesthesia.

Conclusions: Cyanoacrylate glue with or without mesh resulted in adequate muscle-to-sclera adhesion with a detachment force at least 2 times the force of a normal rectus muscle contraction. Patients undergoing hang-back lateral rectus recession with cyanoacrylate glue had excellent stable postoperative alignment; however, half had the complication of late extrusion of glue foreign body.

The most delicate and dangerous aspect of standard rectus muscle recession is the posterior scleral needle pass, as the sclera posterior to the muscle insertion is thin at approximately 0.3 mm. Inadvertent posterior scleral perforation can result in a retinal tear, retinal detachment, or even endophthalmitis.[1] The incidence of scleral perforation has been reported to be approximately 1% to 5%.[2–4]

Hang-back rectus muscle recession with the scleral needle pass anterior to the muscle insertion eliminates the complication of retinal perforation as the sclera anterior to the muscle insertion is thick and the underlying tissue is pars plana, not retina. A concern regarding the hang-back procedure has been instability of the new insertion. Anterior muscle creep, especially with large recessions greater than 5 mm, and late posterior muscle slippage has been reported.[5,6] This report studies the use of medical-grade *N*-butyl-2-cyanoacrylate adhesive (Histoacryl Blue; B Braun; Hessen, Germany) to aid in the reattachment of extraocular muscles to sclera when using the hang-back recession technique.

Materials and Methods

This study was conducted at the Wright Foundation for Pediatric Ophthalmology and Strabismus, Los Angeles, CA. There were 2 phases to this study. Phase 1 measured the adhesive strength of medical-grade cyanoacrylate glue to reattach extraocular muscle to sclera. Phase 2 studied the use of cyanoacrylate glue to reattach extraocular muscle to sclera in hang-back rectus muscle recessions in highly myopic patients with clinically determined thin sclera.

Phase 1

Frozen bank rabbit heads were used to test the adhesive strength of medical-grade *N*-butyl-2-cyanoacrylate glue (Histoacryl Blue) to reattach rectus muscle to sclera. Once received, the frozen bank rabbit heads were stored in a refrigerator at 4°C. Before each experimental procedure, the rabbit heads were anchored to a platform on the surgical table, the residual fascia was removed, and the eyes were kept moist using a couple drops of balanced salt solution. Surgical procedures were performed on 14 recti muscles. In each procedure the rectus muscle was exposed through a limbal incision and secured using 5.0 Mersilene suture (Ethicon, Somerville, NJ), suturing over the Wright Grooved Hook (Titan Surgical, Kazan, Russia). (Mersilene 5-0 suture is used by the authors in situations where the surgeon is trying to prevent stretched scar, and therefore was selected as the suture of choice for this

https://doi.org/10.1016/j.jcjo.2019.07.003
ISSN 0008-4182

study.) Muscles were detached from the globe using Westcott scissors and repositioned with a hang-back suture to 5 mm posterior from the original muscle scleral insertion (rectus recession). Two techniques were used to glue the muscle to sclera. In technique 1 (group 1) the muscle was reattached by directly gluing the Mersilene suture and muscle to sclera with *N*-butyl-2-cyanoacrylate (Histoacryl Blue). In technique 2 (group 2) the muscle was reattached to sclera by gluing a 4 mm × 6 mm prolene mesh patch (VentrioTM Hernia Patch, Bard, NJ) over the Mersilene suture and muscle. This technique was studied with the hypothesis that the additional mesh may add additional strength and a larger required detachment force. The idea to incorporate a mesh scaffold was based on previous studies, including a study that used a polyglactin mesh with suture and cyanoacrylate glue in a laboratory study as a possible alternative to scleral suturing.[7] The amount of glue used in each procedure was approximately 1−2 drops applied using a tuberculin syringe. After 30 seconds to allow polymerization, the detachment force was measured using a tension strain gauge (PCE-FM50, Jupiter, FL). The peak detachment force was defined as the force at the point of bond failure between muscle and sclera. The primary outcome was detachment force required to detach the muscle from the sclera. We compared peak detachment force for technique 1 glue alone and technique 2 glue plus mesh at 30 seconds. Detachment force of group 2 was also measured at 20 and 40 seconds, in order to assess the least amount of surgical waiting time required to obtain an effective polymerization. Statistical analysis was performed using a *t* test.

Phase 2

Four patients with large-angle exotropia associated with high myopia who underwent bilateral lateral rectus recessions using hang-back suture technique plus medical-grade *N*-butyl-2-cyanoacrylate glue (Histoacryl Blue) were retrospectively studied. This study was approved by the local Institutional Review Board and conformed to the requirements of the US Health Insurance Portability and Accountability Act of 1996. All patients had large-angle exotropia >40 PD and high myopia >6 D. Use of a hang-back suture plus glue was indicated to avoid a posterior scleral needle pass that appeared dangerous because of thin sclera seen at the time of surgery. Before surgery, all patients signed an informed consent for the possible off-label use of *N*-butyl-2-cyanoacrylate glue (Histoacryl Blue) to reattach muscles if the eye wall appeared thin. All patients were followed-up at 1 day, 1 month, and 6 months postoperatively. Two patients had the 6-month follow-up through a phone call and evaluation of photographs. The lateral rectus recession technique used a hang-back modification that secures the muscle to sclera with a single 5-mm horizontal needle pass 1 mm anterior and parallel to the insertion. The modification ties the suture knot posterior to the scleral muscle insertion, closer to the rectus muscle recession point. This is in contrast to the usual hang-back, where there are 2 needle passes directed anteriorly and perpendicular to the insertion, and so the knot is tied anterior to the scleral insertion. Posterior knot placement avoids the complication of suture erosion through the anterior conjunctiva and minimizes the risk of a conjunctival cyst and corneal dellen in the paralimbal area. The muscle was then glued to sclera posteriorly with *N*-butyl-2-cyanoacrylate glue (Histoacryl Blue) (Fig. 1). One to 2 drops of glue were applied directly to the cut muscle edge with a syringe and the surgeon waited 40 seconds to ensure polymerization. The lateral recti recessions were large averaging 8.5 mm (standard deviation [SD] ± 0.5). All procedures were performed by the same surgeon (KWW).

Results

Phase 1

The primary outcome was peak detachment force for both groups 1 and 2 at 30 seconds. Detachment force measured at 30 seconds was 172.07 g (SD ± 30.25) in group 1 glue alone and 376.5 g (SD ± 41.30) in group 2 glue and mesh ($p < 0.01$). These results showed that using mesh increased the peak detachment force, and the difference was statistically significant. The secondary outcome evaluated was the minimal surgical waiting time required to achieve sufficient polymerization. The minimal surgical waiting time was evaluated in group 2 only. Therefore, in group 2 the peak detachment force was measured at 20, 30, and 40 seconds. Mean detachment force of *N*-butyl-2-cyanoacrylate (Histoacryl Blue) over mesh measured 117.64 g (SD ± 15.09) at 20 seconds versus 376.5 g (SD ± 41.30) at 30 seconds ($p < 0.01$). There was no significant difference between detachment force measured either at 30 (376.5 g ± SD 41.30) and 40 s (388 g ± SD 10.43) in group 2 ($p > 0.01$). These results demonstrate that polymerization time and peak detachment force are directly

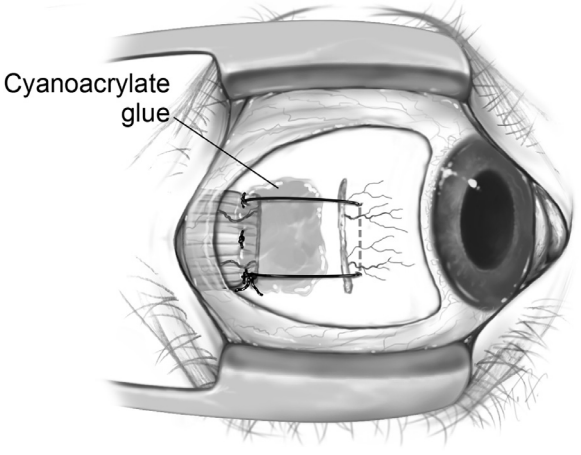

Fig. 1—Hang-back technique lateral rectus muscle recession + glue (phase 1). Patients underwent muscle rectus recession by hang-back suture plus *N*-butyl-2-cyanoacrylate glue over the muscle-suture junction. Note in the figure that the knot is placed posterior to the insertion close to the muscle. Posterior knot placement avoids the complication of suture erosion through the anterior conjunctiva and minimizes the risk of a conjunctival cyst and corneal dellen in the paralimbal area. The gray oval represents cyanoacrylate glue.

Table 1—Peak detachment force (in grams) over time for group 1 (*N*-butyl-2-cyanoacrylate glue alone) and group 2 (*N*-butyl-2-cyanoacrylate glue with prolene mesh)

Polymerization Time (seconds)	Group 1 (Glue Alone), Peak Detachment Force (g) ± SD	Group 2 (Glue + Mesh), Peak Detachment Force (g) ± SD
20	NA	117.64 ± 15.09
30	172.07 ± 30.25†	376.5 ± 41.30†
40	NA	388.67 ± 10.43

NA, not applicable; SD, standard deviation.
N-butyl-2-cyanoacrylate glue with or without prolene mesh resulted in an adequate muscleto-sclera adhesion at 30 seconds, reaching a peak detachment force being at least 2 times the force of a muscle contraction. The usage of a prolene mesh resulted in a significantly better muscle-to-sclera adhesion than glue alone.
†Statistically significant, $p < 0.01$.

related: an increase in bond strength is achieved with increasing polymerization time, but the effect plateaus (Table 1).

Phase 2

Postoperative alignment was within 5 prism diopters of orthophoria for all 4 patients undergoing rectus muscle recession with suture hang-back plus glue at the last follow-up visit. There were no overcorrections and no slipped muscles or stretched scars. None of the 4 patients experienced diplopia during the postoperative period. At 1 month postoperatively, 2 patients (25% of the muscles operated) developed unilateral conjunctival hyperemia and foreign body sensation over the operated site. In both cases, crystalized glue had eroded through the conjunctiva and was exposed. The exposed glue was removed with forceps in the office under topical anaesthesia. The ocular alignment remained excellent and did not change after removal of the extruded glue. No other complications occurred and there were no further sequelae. All patients were satisfied and happy with the surgical outcome. Because of the high incidence of foreign body extrusion (25%), use of cyanoacrylate glue with hang-back recession was suspended (Fig. 2).

Discussion

Use of tissue adhesives to reattach the muscle to sclera has the potential to eliminate the complication of retinal tear from a needle pass scleral perforation. Tissue adhesives have been studied for use in strabismus surgery.[8–14] One of the first applications of adhesive tissue in ophthalmic surgery was reported in 1963 by Straatsma et al[12] and by Ellis and Levine[15] regarding its use in retinal detachment surgery. In general, biological adhesives such as fibrin glue demonstrate lower bonding strength than the synthetic glues such as *N*-butyl-2-cyanoacrylate glue (Histoacryl Blue).[16] Spierer et al described the inadequate bond formed to reattach muscles to sclera using fibrin glue in rabbit models.[8] Cyanoacrylate glues are synthetic adhesives that polymerizes on contact with water and are useful for moist tissues. They are U.S. Food and Drug Administration-approved for skin closure and more recently have been U.S. Food and Drug Administration-approved for vein closure in patients with varicose veins.[9,17] We used medical-grade *N*-butyl-2-cyanoacrylate (Histoacryl Blue) because of its bond strength, degradation time of approximately 2 months, and relatively short polymerization time around 30 seconds.[10,11] Recti muscles normally generate a maximum contractile force of 75 g.[7,18] Results of our phase 1 study showed that hang-back recession with cyanoacrylate glue alone and hang-back recession with cyanoacrylate glue with mesh both provided adequate adhesive force being at least 2 times the maximum contractile force of a rectus muscle. The mesh with glue provided a stronger bond; however, adding mesh resulted in a

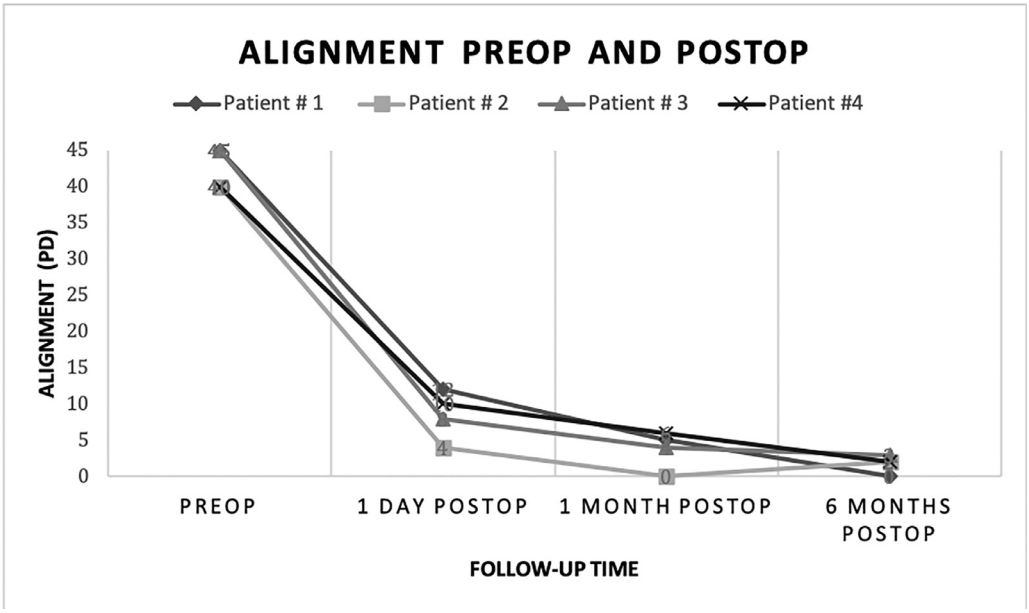

Fig. 2—Alignment preop and postop (phase 2). Preop and postop alignment of patients with large-angle exotropia undergoing hang-back technique lateral rectus muscle recessions with glue. PD, prism diopters; all alignment data >0 are referring to exotropia/exophoria; 0, orthotropia state.

large foreign body mass compared with glue alone. We noted that peak detachment force is directly related to the surgical waiting time. At 20 seconds we reported an inadequate detachment force, whereas the most effective bond was achieved at 30−40 seconds. We conclude that the minimal surgical waiting time to achieve a sufficient polymerization is 30 seconds.

The second phase retrospectively studied the use of Histoacryl Blue glue with hang-back lateral rectus recessions in patients with high myopia and thin sclera. The scleral needle pass was performed anterior to the rectus muscle insertion to avoid the danger of posterior retinal perforation in these highly myopic patients with thin sclera. Glue was added to the hang-backed muscle to help secure the muscle to sclera. Anterior muscle creep and late posterior muscle slippage have been reported with the hang-back recession technique, both in animal studies and in human subjects.[5,6,19−23] It is the authors' experience with hang-back adjustable sutures for lateral rectus recessions >5 mm that the muscle often will not retract posteriorly and the location of the new muscle insertion is anterior to the desired recession point. The hang-back plus glue technique showed excellent and stable postoperative results, with all patients achieving alignment within 5 PD of orthophoria and no patient had an overcorrection. At 1 month postoperatively, however, 2 of the 4 patients (25% of muscles) had extrusion of glue. The glue foreign body was removed in office without complication and good alignment remained without further sequelae. Because of the high incidence of crystalized glue extrusion, use of cyanoacrylate glue was suspended.

The most difficult step in our reported procedure was administrating the glue. We used a 1-cc tuberculin syringe, but it was difficult to control the amount of glue delivered. Cyanoacrylate glue crystalizes rapidly and excess glue is very difficult to remove. Our early experience tells us that "less is more" when applying the cyanoacrylate glue, and the challenge is to deliver a consistent small microdrop of glue.

In conclusion, the hang-back suture technique with an anterior scleral needle pass used in conjunction with tissue glue can eliminate the complication of retinal perforation associated with posterior scleral needle passes while providing a secure and stable rectus muscle recession. The benefits of using glue with a hang-back suture to prevent a possible scleral perforation greatly outweigh possible negatives of using the glue, which would include slightly increased cost and slightly increased time of procedure with use of the glue. Although in the animal model we demonstrated that the glue and mesh provided a stronger bond, the mesh created a large foreign body mass that would likely be undesirable in a human patient. *N*-butyl-2-cyanoacrylate glue appears to provide adequate muscle to scleral adherence; however, it was difficult to control glue delivery, and late extrusion of crystalized glue foreign body was a significant problem. Topiwala et al also reported localized granuloma formation requiring surgical removal in 2 out of 19 eyes operated on using cyanoacrylate glue and reported significant inflammation and chemosis associated with cyanoacrylate glue.[13] We, the authors, do not recommend using cyanoacrylate at this time. Fibrin glue may be a suitable alternative to cyanoacrylate glue to avoid the crystalized glue foreign body.[13] A combination of hang-back recession combined with fibrin glue has been investigated in the rabbit model with success,[23] and may be a solution to this problem. The use of fibrin glue combined with hang-back recessions is currently being investigated by our authors.

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Footnotes and Disclosure:

The authors have no proprietary or commercial interest in any materials discussed in this article.

This study was supported by grant funding from the Wright Foundation for Pediatric Ophthalmology and Strabismus, a not-for-profit 501(c)(3) foundation in Los Angeles.

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Originally received Apr. 29, 2019. Final revision Jun. 27, 2019. Accepted Jul. 5, 2019.

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