Ocular Disease: Part I *Presented by MBKU | SCCO*

Live CE Webinar | Day One | AM Session

Saturday | March 20, 2021 | 8:00 a.m. - 11:50 a.m.

Marshall B. KETCHUM UNIVERSITY
Southern California College of Optometry

Department of Continuing Education

ketchum.edu /ce | ce@ketchum.edu

Department of Continuing Education

OCULAR DISEASE PART I

Marshall B. KETCHUM UNIVERSITY
Southern California College of Optometry

SATURDAY, MARCH 20

Pacific Time Zone | Live Webinar | Pending COPE approval

8:00 - 8:55 A.M.
Protecting Against Retinal Disease by Reducing Oxidative Stress with Targeted Nutrition
presented by John Nolan, PhD

8:55 - 9:50 A.M.
Retinal Grand Rounds
presented by Julie Rodman, OD, MSc

10:00 - 10:55 A.M.
Diseases of the Vitreomacular Interface
presented by Julie Rodman, OD, MSc

10:55 - 11:50 A.M.
Retinal Vascular Occlusive Disease
presented by Julie Rodman, OD, MSc

11:50 A.M. - 12:10 P.M.
Lunch

12:10 - 1:05 P.M.
Demystifying Periorbital Edema
presented by Shora Ansari, OD

1:05 - 2:00 P.M.
Ocular Surface Preservation for the Glaucoma Patient
presented by Vin Dang, OD

2:10 - 3:05 P.M.
When the SPK won't go away. Detection and Management of Early Neurotrophic Keratitis
presented by Vin Dang, OD

3:05 - 4:00 P.M.
Cannabis: Medical and Recreational Use and Abuse
presented by Ed Fisher, PhD, RPh

SUNDAY, MARCH 21

Pacific Time Zone | Live Webinar | Pending COPE approval

8:00 - 9:50 A.M.
Corneal Dystrophies and Degenerations and *ODs Guide*
presented by Marc Bloomenstein, OD

10:00 - 10:55 A.M.
Review of Pathological Myopia and Prevention of Myopic Pathology
presented by Jessica Sun, OD and Katherine Zhang, OD

10:55 - 11:50 A.M.
Vaping: Is it Healthier?
presented by Ray Chu, OD, MS

11:50 A.M. - 12:10 P.M.
Lunch

12:10 - 1:05 P.M.
Hereditary Fundus Dystrophies in a Low Vision Practice
presented by Patrick Yoshinaga, OD, MPH

1:05 - 2:00 P.M.
Updates in Genetic Testing and Gene Therapy for Inherited Retinal Dystrophies
presented by Rachelle Lin, OD, MS

2:10 - 3:05 P.M.
AMD: Current Care Optometric Management
presented by Carl Jacobsen, OD

3:05 - 4:00 P.M.
Substance Abuse: Opioids - How to Best Use Them and Stay Out of Trouble
presented by Kayvan Moussavi, PharmD, BCCCP

This activity is supported by an unrestricted educational grant from the following education partner. We sincerely thank them for their support!

MacuHealth and Dompe

Ocular Disease: Part I

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Ocular Disease: Part I

Day One | Saturday | March 20, 2021

Marshall B. KETCHUM UNIVERSITY
Southern California College of Optometry
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Instructor Biographies

John Nolan, PhD

Director of the Nutrition Research Center Ireland
Principal Investigator Macular Pigment Research Group, Waterford Institute of Technology

Professor John Nolan is the Principal Investigator of the Macular Pigment Research Group at the Waterford Institute of Technology in Ireland. He specializes in the role of eye nutrition for vision and prevention of blindness, and the link between nutrition and brain health and function. He won the prestigious European Research Council Starting Grant where he conducted the Central Retinal Enrichment Supplementation Trials (CREST). This work essentially confirms the scientific discovery that the use of meso-zeaxanthin, in conjunction with lutein and zeaxanthin (the three nutritional pigments that are found at the back of the eye), can enhance vision in healthy subjects and in patients with early age-related macular degeneration (the leading cause of blindness in the western world). His current research interests include the study of key nutrients for cognitive function and brain health with a major goal of identifying ways to reduce risk of Alzheimer's disease.

Julie Rodman, OD

Chief, The Eye Care Institute
Professor of Optometry, Nova Southeastern University College of Optometry

Dr. Julie Rodman graduated from Brandeis University in 1994 with a B.A. in Neuroscience. She received her optometry degree from the New England College of Optometry in 1998. Dr. Rodman went on to complete a residency in hospital-based optometry at the VAMC Brockton/West Roxbury, MA. Since completing her residency, Dr. Rodman has worked in various settings, including an ophthalmology private practice and an HMO-based practice. Dr. Rodman joined the Nova Southeastern College of Optometry as a part-time faculty member in May 2000. In 2014, Dr. Rodman received her Masters of Science in Clinical Vision Research from Nova Southeastern University. In February 2008, Dr. Rodman joined the Nova Southeastern faculty on a full-time basis as an Assistant Professor of Optometry and now holds the rank of Professor of Optometry. Dr. Rodman has taught in the Optometry Theory and Methods Laboratory and currently serves as the Chief of the Broward Eye Care Institute in downtown Fort Lauderdale. She has been the recipient of numerous teaching awards, including the Golden Apple Award for Excellence in Clinical Precepting, and Preceptor of the Year. She has been recognized as Primary Care Optometry's "Top 300 Innovators in Optometry". Dr. Rodman has served as Residency Education Coordinator where she was responsible for arranging the didactic assignments for the Resident Conference Series as well as interdisciplinary presentations. Dr. Rodman is a residency supervisor and mentors and guides the residents with Grand Rounds Presentations, posters, and publications. Dr. Rodman is actively involved in the residency program and has served on the Residency Advisory Committee as well as the ASCO Residency Affairs Committee.

Shora Ansari, OD

Adjunct Faculty, MBKU | SCCO

Dr. Shora Ansari is a graduate of the Southern California College of Optometry, where she was the Valedictorian of her graduating class. Dr. Ansari also earned a BS and MS in pharmacological chemistry from UC San Diego. Prior to attending optomåetry school, she worked for several years in the pharmaceutical research industry focusing her research efforts on oncology, immunology, and HIV and HBV/HCV antiviral therapy. She currently serves as adjunct faculty for SCCO at MBKU in the Cornea and Contact Lens Clinic. She also works in a private optometric practice in Orange County and manages patients with ocular surface disease, glaucoma, diabetes and specialty contact lens fitting.

Ocular Disease: Part I

Day One | Saturday | March 20, 2021

Marshall B. KETCHUM UNIVERSITY
Southern California College of Optometry
Department of Continuing Education

Instructor Biographies

Ed Fisher, PhD, RPh

Dean & Professsor, MBKU | COP

Dr. Fisher serves as Dean of the College of Pharmacy at Ketchum University. He received his BA in Biology and PhD in Pharmaceutical Sciences from Temple University, Philadelphia, Pennsylvania. He received his BS in Pharmacy at Temple University College of Pharmacy. Dr. Fisher has been employed in academia for more than 25 years at three colleges of pharmacy: Southwestern Oklahoma State University College of Pharmacy; Midwestern-Glendale as the first Chair of the Department of Pharmaceutical Sciences; and Daniel K. Inouye College of Pharmacy, University of Hawaii at Hilo, as inaugural associate dean. At the University of Hawaii at Hilo, he also served as the director of the MS in Clinical Psychopharmacology program. Currently licensed as a pharmacist in Arizona and Pennsylvania, he has practiced in an array of clinical settings. Dr. Fisher has devised and presented more than 100 continuing education seminars and innovative NSF-sponsored short courses. As former National Secretary of Rho Chi, the only pharmacy honor society, and a recipient of the National Rho Chi Advisor of the Year award, he has been integral to initiating two new Rho Chi chapters. Dr. Fisher has also taught and consulted in his areas of expertise: substances of abuse and addiction, nutrition, and pharmacotherapy of mental disorders.

Vin Dang, OD

Primary Care Optometrist, Empire Eye & Laser Center
Adjunct Faculty, MBKU | SCCO

Born in Paris, France, Dr. Dang grew up in the suburbs of Paris. He moved to the United States at the age of 16. Dr. Dang earned a B.S. in Biochemistry from University of California San Diego, and went on to receive his Doctorate in Optometry at the Southern California College of Optometry. He received his Fellowship in the American Academy of Optometry in the fall of 2016. As our Primary Care Optometrist, Dr. Dang is fully capable and certified to handle everything from comprehensive eye examinations to the diagnosis and treatment of medical eye conditions such as glaucoma, macular degeneration or diabetic eye exams. Dr. Dang is also the Director of our Dry Eye Center of Excellence. Click here to learn more about Dr. Dang's personal experience and treatment for dry eyes. He currently focuses on the complex treatment of dry eye disease, allergies and blepharitis. Empire Eye and Laser Center recently acquired a new piece of technology for dry eye treatment called Lipiflow®, which treats the oil layer of the tear film. Dr. Dang is a member of the American Optometric Association (AOA), California Optometric Association, and current president-elect of the Kern County Optometric Society. Dr. Dang is also a Clinical Assistant Professor for the College of Optometry, an auxiliary faculty position where he supervises Western University and Southern CA College of Optometry students participating in clinical education experiences/internships. Dr. Dang speaks fluent French and Cantonese.

Ocular Disease: Part I

Presented by MBKU | SCCO

Protecting Against Retinal Disease by Reducing Oxidative Stress with Targeted Nutrition

Presented by John Nolan, PhD

Live CE Webinar | Day One | AM Session

Saturday | March 20, 2021 | 8:00 a.m. - 8:55 a.m.

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UNDERSTANDING THE YELLOW SPOT

Protecting against retinal disease by reducing oxidative stress with targeted nutrition

NRCI Nutrition Research Centre Ireland

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About John Nolan

Director of Nutrition Research Centre Ireland

Disclosures

Provide educational lectures and consultancy advisory work for the following companies:

1. Stauber Nutrition
2. IOSA
3. MacuHealth
4. MacuLearn
5. Heidelberg Engineering
6. BASF
7. Howard Foundation
8. EPAX

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Our Agenda

Part I: THE IMPORTANCE OF TARGETED NUTRITION

- AMD
- Carotenoids & Omegas
  - Structure and functions
- Food sources and devolution

Part II: EVIDENCE-BASED RESEARCH AND FINDINGS

- NRCI and our research standards
- Key peer-reviewed studies
- Implication of findings

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PART I

The Importance of Carotenoids

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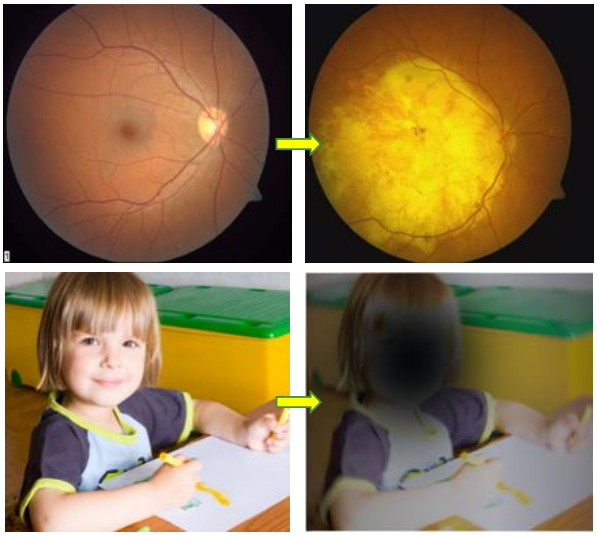
PART I: AGE-RELATED MACULAR DEGENERATION

Age-Related Macular Degeneration



11 MILLION

in the United States have some form AMD.

BY 2050,

This number is expected to double to nearly **22 million.**

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PART I: AGE-RELATED MACULAR DEGENERATION

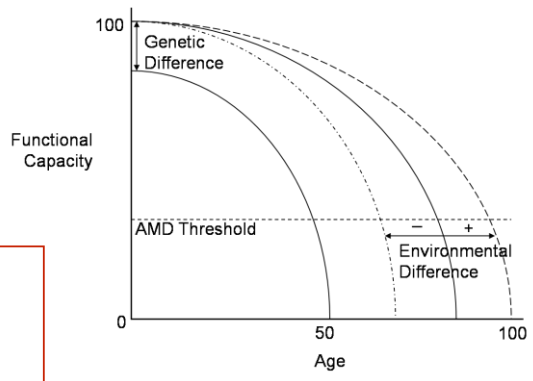
Age-Related Macular Degeneration Risk Factors

Risk Factors

Established
- Age
- Smoking
- Family history
- Nutrition

Putative
- Light
- Obesity
- Cardiovascular disease
- Diabetes
- Low macular pigment levels

Genetic and Environmental Basis of AMD



Ref: Adapted from Cai et al., 2000.

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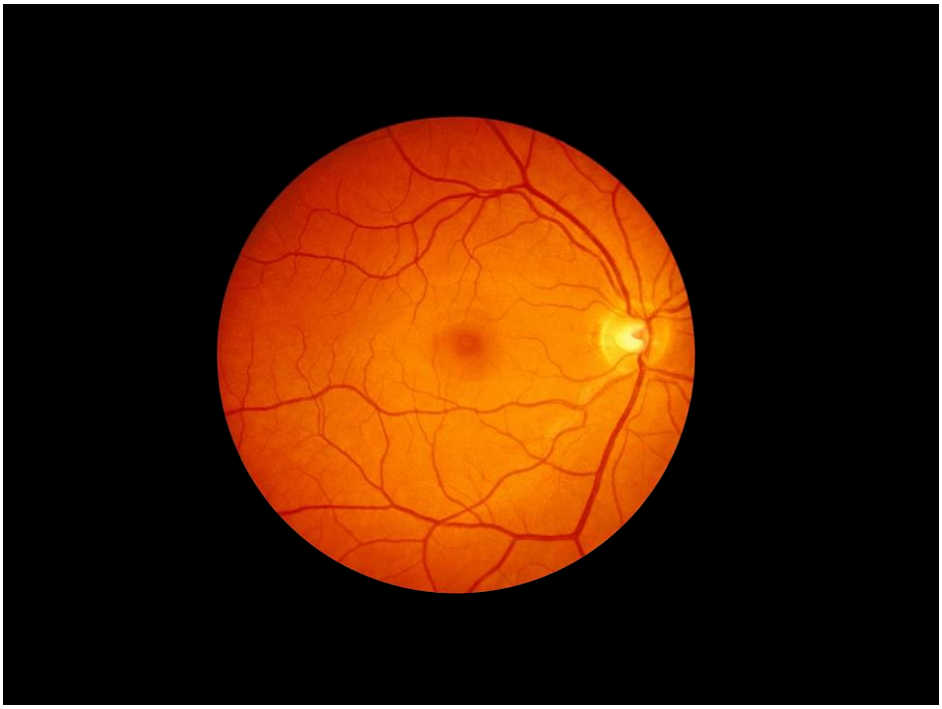

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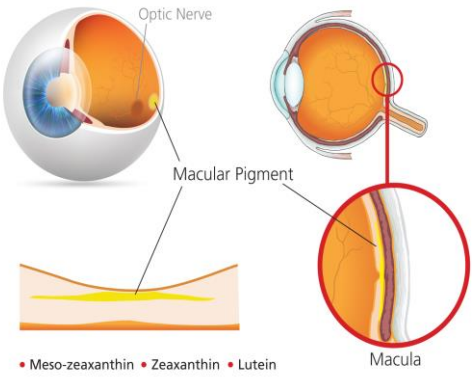
PART I: BACKGROUND OF CAROTENOIDS

Carotenoids in the Eye

Macular Pigment (MP) and biological sensitivity



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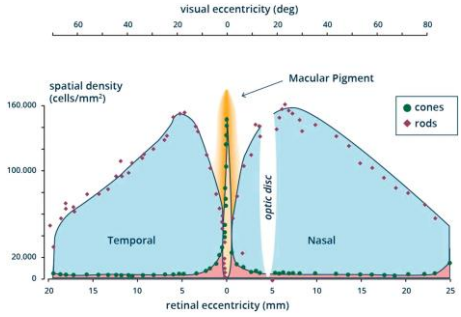
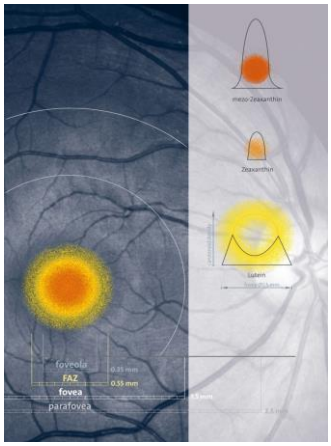
PART I: BACKGROUND OF CAROTENOIDS

Distribution of Carotenoids in the Macula

Macular Pigment is concentrated at the very center of the retina and forms a mountain shape profile





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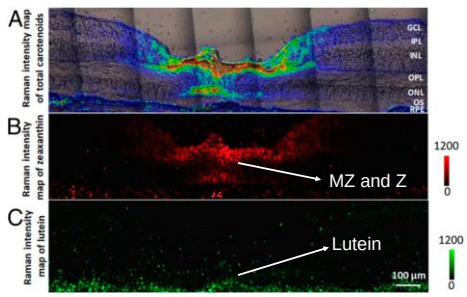
PART I: BACKGROUND OF CAROTENOIDS

Distribution of Carotenoids in the Macula

Recent findings illuminate the importance of zeaxanthin and meso-zeaxanthin over lutein

Imaging lutein and zeaxanthin in the human retina with confocal resonance Raman microscopy



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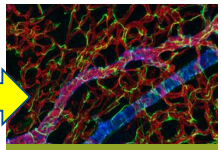
PART I: BACKGROUND OF CAROTENOIDS

Carotenoids Found

~700 in nature

~50 in nature



~20 in serum

Only lutein, zeaxanthin, and meso-zeaxanthin found in the eye (concentration over 1000X serum)

FUNNEL EFFECT

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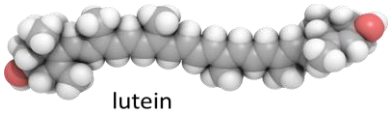
PART I: BACKGROUND OF CAROTENOIDS

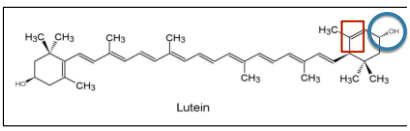
Molecular Structure of Carotenoids $C_{40}H_{56}O_2$

BROTHERS AND SISTERS

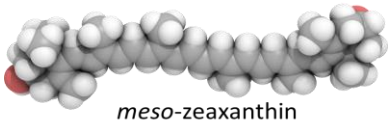
Lutein, Zeaxanthin, *AND* Meso-Zeaxanthin are very close in structure



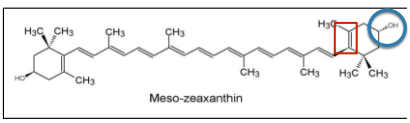
lutein



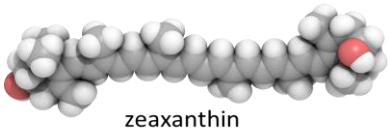
Lutein



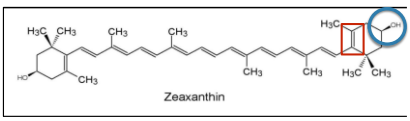
meso-zeaxanthin



Meso-zeaxanthin



zeaxanthin



Zeaxanthin

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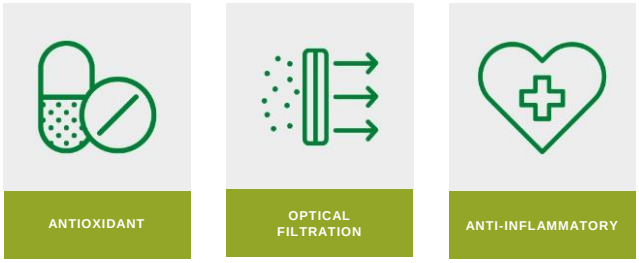
PART I: FUNCTIONS OF CAROTENOIDS

Functions of Carotenoids



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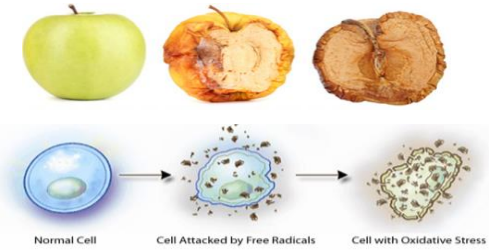
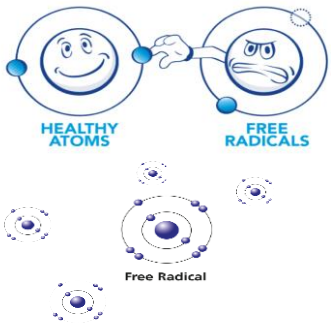
PART I: FUNCTIONS OF CAROTENOIDS

Problem: Oxidative Stress and the Retina

Cell damage caused by unstable molecules



What is a free radical?



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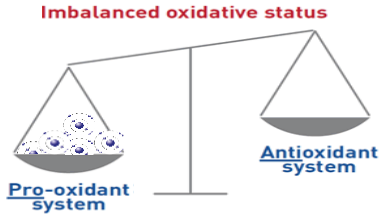
PART I: FUNCTIONS OF CAROTENOIDS

Problem: Oxidative Stress and the Retina

The trigger that leads to AMD



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Cell Damage

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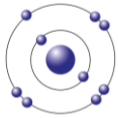
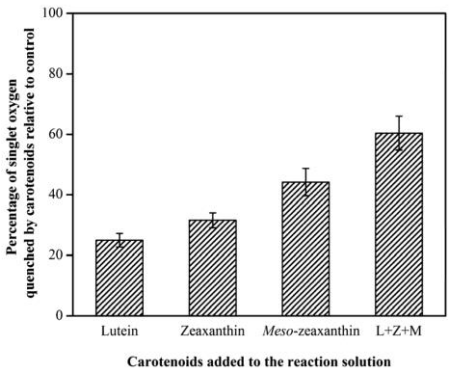
PART I: FUNCTIONS OF CAROTENOIDS

Solution: Antioxidant



Free Radical



NIH Public Access
Author Manuscript

Studies on the Singlet Oxygen Scavenging Mechanism of Human Macular Pigment

Binxing Li, Faisal Ahmed, and Paul S. Bernstein*
Department of Ophthalmology and Visual Sciences, Moran Eye Center, University of Utah School of Medicine, Salt Lake City, UT 84132

Abstract

Keywords

1. Introduction

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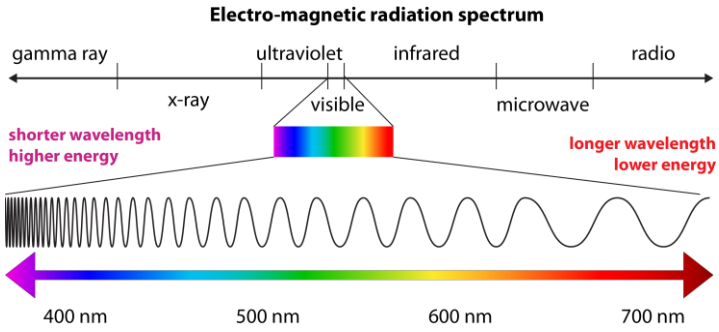
PART I: FUNCTIONS OF CAROTENOIDS

Problem: Blue Light



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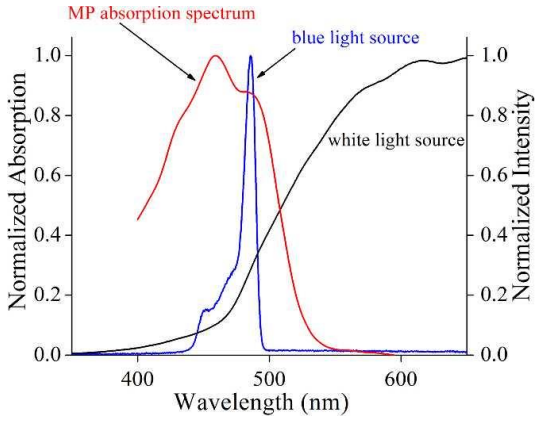
PART I: FUNCTIONS OF CAROTENOIDS

Solution: Optical Filtration

Reducing intensity or time = reduces the probability of damage



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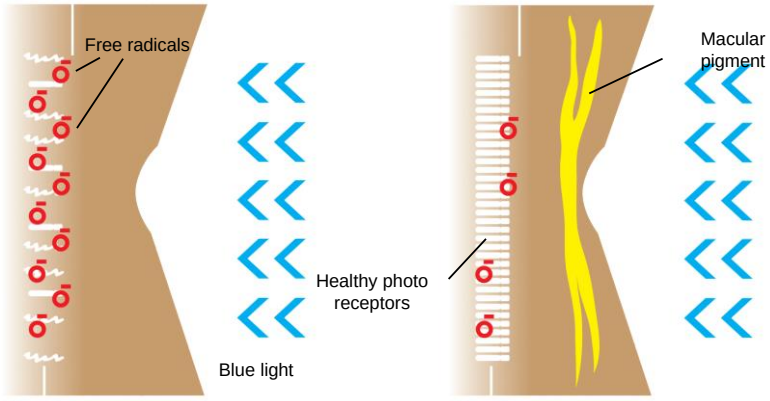
PART I: FUNCTIONS OF CAROTENOIDS

Solution:



Macula without macular pigment

Macula with macular pigment

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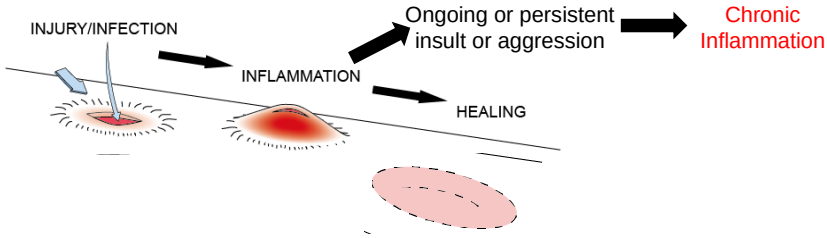
PART I: FUNCTIONS OF CAROTENOIDS

Problem: Inflammation



Chronic Inflammation = More tissue damage

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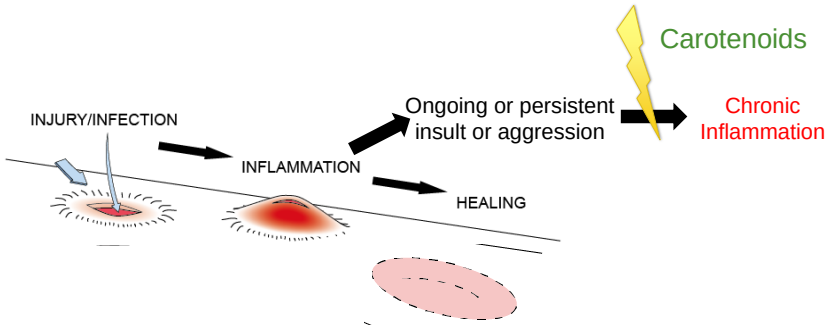
PART I: FUNCTIONS OF CAROTENOIDS

Solution: Anti-inflammatory



Lutein, zeaxanthin, and meso-zeaxanthin break the cycle of chronic inflammation and help in the resolution

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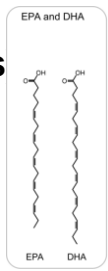
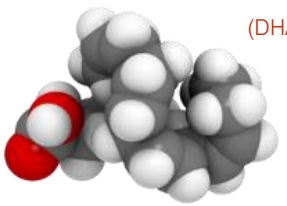
PART I: POLYUNSATURATED FATTU ACIDS

Polyunsaturated Fatty Acids (n-3 PUFAs

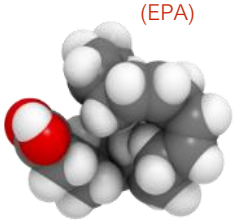


- Long chain polyunsaturated fatty acids (n-3 PUFA)
  - Eicosapentaenoic acid (EPA, 20:5n-3)
  - Docosahexaenoic acid (DHA, 22:6n-3)
- Other PUFAs n-6 family:
  - Linoleic acid
  - Sunflower oil

DocosahexaenoicAcid (DHA)



Eicosapentaenoic Acid (EPA)



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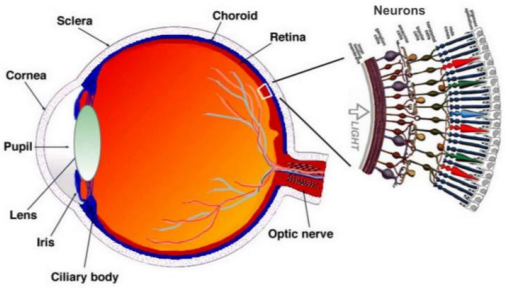
PART I: POLYUNSATURATED FATTU ACIDS

Polyunsaturated Fatty Acids (n-3 PUFAs)



Docosahexaenoic acid (DHA) constitutes half of the mass of the retinal neuronal membrane.

DHA constitutes over 90% of omega-3 fatty acids in the brain and 10-20% of its total lipid content (Weiser et al., 2016).

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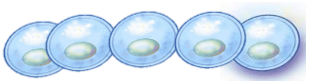
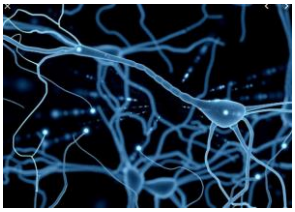
PART I: POLYUNSATURATED FATTU ACIDS FUNCTIONS

Polyunsaturated Fatty Acids (n-3 PUFAs)



Maintain cell structure and function



Enhance neuronal health e.g. increasing the expression of myelin-related proteins that can facilitate axonal transmission and thus better neuronal signaling.

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PART I: FUNCTIONS OF CAROTENOIDS

Sources of Carotenoids

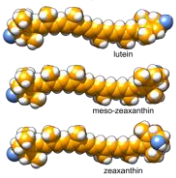
In the Western World, the typical dietary intake is *only* 1.5mg per day of lutein and Zeaxanthin combined.


Dark leafy


Colored fruits


Yellow Corn


Eggs



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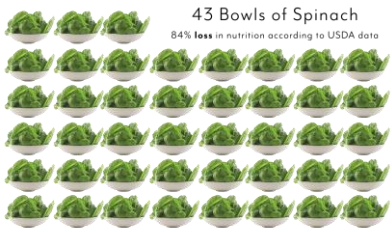
PART I: FUNCTIONS OF CAROTENOIDS

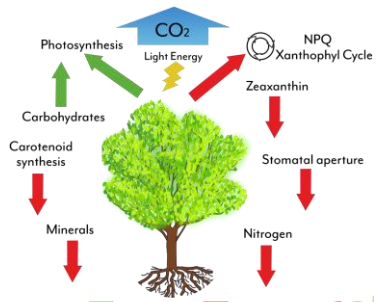
Problem: Devolution

We live in an era of nutrient-deficient foods

1953
1 Bowl of Spinach
has the same nutrional content as...




REVIEW
Rising Atmospheric CO_2 Lowers Concentrations of Plant Carotenoids Essential to Human Health: A Meta-Analysis



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PART I: FUNCTIONS OF CAROTENOIDS

Solution : Supplementation

NUTRI-MZ Natural Carotenoid Formulations

IOSA INDUSTRIAL ORGÁNICA

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PART I: HYPOTHESIS

Diet vs Supplements

VS

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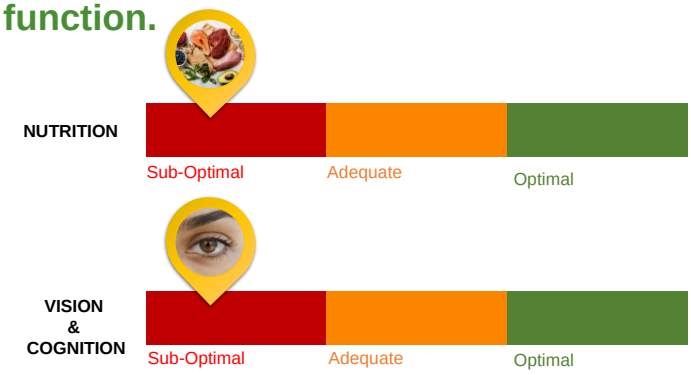
PART I: HYPOTHESIS

Hypothesis

Enriching nutrition with carotenoids and omegas, will enhance visual & cognition function.



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PART II

Evidence-based Research and Findings

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PART II: NRI AND OUR RESEARCH STANDARDS

Nutrition Research Centre Ireland (NRCI)

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PART II: NRI AND OUR RESEARCH STANDARDS

NRCI: State-Of-The-Art Research Facility

CLINICAL TRIALS

MP MEASUREMENT

VISUAL PERFORMANCE EVALUATION

COGNITIVE FUNCTION TESTING

ANALYTICAL LAB FOR SERUM CAROTENOIDS

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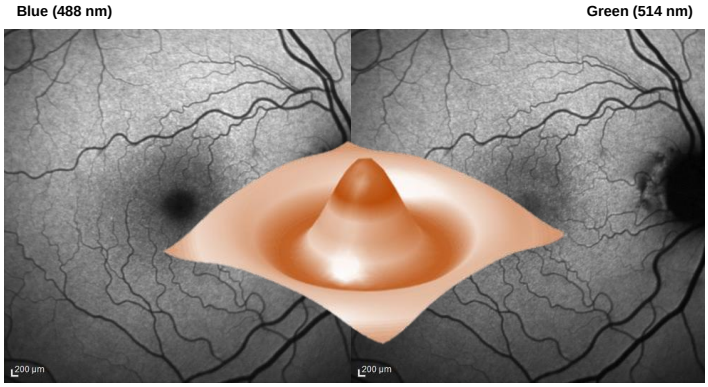
PART II: NRI AND OUR RESEARCH STANDARDS

Macular Pigment

Dual-wavelength fundus autofluorescence (AF) Technique

In the fovea, excitation light within the absorbance range of MP is partially absorbed by the carotenoids, resulting in an area of reduced fluorescence.



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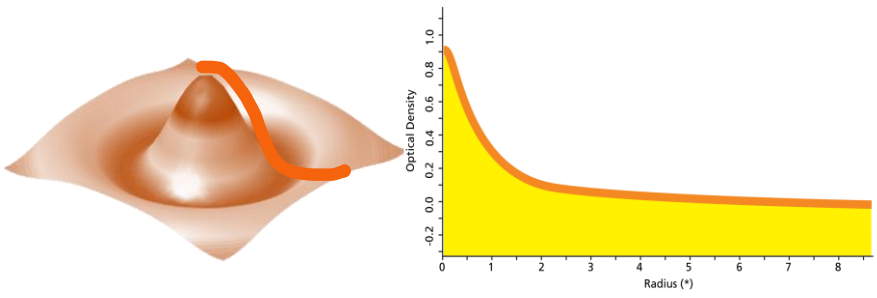
PART II: NRI AND OUR RESEARCH STANDARDS

Macular Pigment

Dual-wavelength fundus autofluorescence (AF) Technique

In the fovea, excitation light within the absorbance range of MP is partially absorbed by the carotenoids, resulting in an area of reduced fluorescence.



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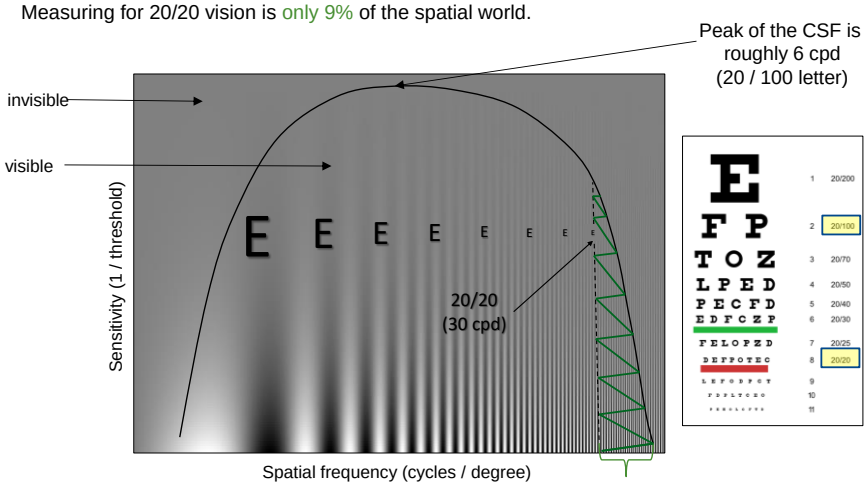
PART II: KEY PEER-REVIEWED STUDIES

The Contrast Sensitivity Function

Measuring for 20/20 vision is only 9% of the spatial world.



From Campbell & Robson, 1968

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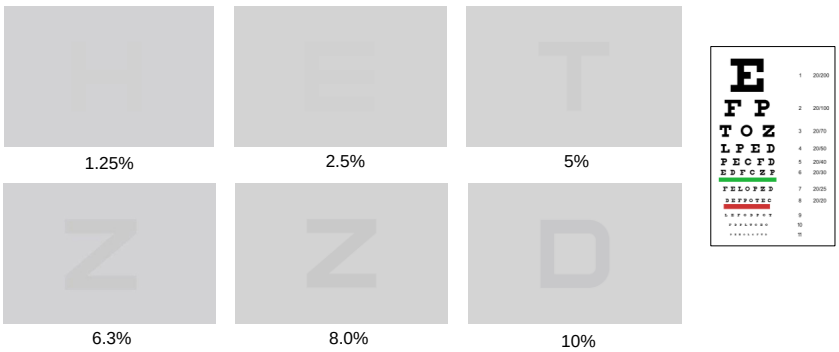
PART II: KEY PEER-REVIEWED STUDIES

Contrast Sensitivity vs. Visual Acuity

One may read 20/20, but may exhibit a wide range of CS



Courtesy Mark Roark, OD

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Key Peer-Reviewed Studies

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PART II: EVIDENCE-BASED RESEARCH

Carotenoids Stability and Efficacy

nutrients

MDPI

Article

Stability of Commercially Available Macular Carotenoid Supplements in Oil and Powder Formulations

David Phelan *, Alfonso Prado-Cabrero and John M. Nolan

Nutrition Research Centre Ireland, School of Health Science, Carrigtwohill Road, Waterford Institute of Technology, West Campus, Waterford X91 K236, Ireland; AFRADO-CABRERO@wit.ie (A.P.-C.); JohnM@wit.ie (J.M.N.)

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Received: 8 September 2017; Accepted: 13 October 2017; Published: 17 October 2017

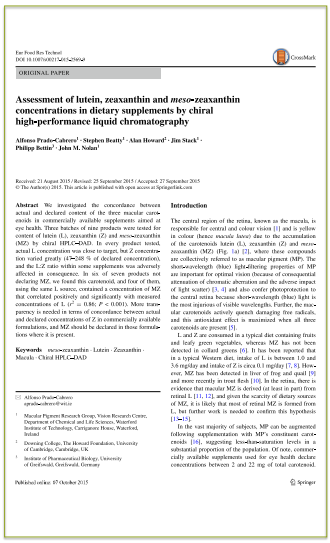
Abstract: We previously identified that the concentration of zeaxanthin in some commercially available carotenoid supplements did not agree with the product's label claim. The conclusion of this previous work was that more quality assurance was needed to guarantee concordance between actual and declared concentrations of these nutrients i.e., lutein (L) zeaxanthin (Z) and *meso*-zeaxanthin (MZ) in commercially available supplements. Since this publication, we performed further analyses using different commercially available macular carotenoid supplements. Three capsules from one batch of eight products were analysed at two different time points. The results have been alarming. All of the powder filled products (n = 3) analysed failed to comply with their label claim (L: 19–74%; Z: 52–73%; MZ: 63–87%); however, the oil filled soft gel products (n = 5) met or were above their label claim (L: 98–122%; Z: 117–162%; MZ: 97–119%). We also identified that the carotenoid content of the oil filled capsules were stable over time (e.g., L average percentage change: −1.7%), but the powder filled supplements degraded over time (e.g., L average percentage change: −17.2%). These data are consistent with our previous work, and emphasize the importance of using carotenoid interventions in oil based formulas rather than powder filled formulas.

Keywords: macular carotenoid supplementation; lutein; zeaxanthin; *meso*-zeaxanthin; macular pigment

1. Introduction

Three macular carotenoids, lutein (L), zeaxanthin (Z) and *meso*-zeaxanthin (MZ) accumulate in the central retina (macula), where they are collectively known as macular pigment (MP) or the macular carotenoids [1] (See Figure 1).

The macula is the area of the retina which has the highest visual performance in terms of visual acuity i.e., motion detection, colour perception and contrast sensitivity [2]. MP has a distinctive yellow colour due to the presence of the macular carotenoids. MP has short-wavelength (blue) light filtering, antioxidant, and anti-inflammatory properties [3–6]. The filtration of blue light at the macula is believed to enhance visual performance, due to the attenuation of chromatic aberration; veiling luminescence and blue haze [3–6]. Furthermore, MP actively quenches free radicals, and this antioxidant capacity is optimised when all three macular carotenoids are present [6]. L and Z are consumed in a typical diet from sources such as fruits and leafy green vegetables [10,11]. MZ is not present in a typical diet, although it has been detected in shrimp, fish and turtle [12], and also in the liver of frog and quail [13]. More recently MZ has been identified in trout skin and trout flesh [14,15], thereby confirming the presence of this carotenoid in the human food chain [16].



Eur Food Res Technol
DOI 10.1007/s00217-015-2569-0

CrossMark

ORIGINAL PAPER

Assessment of lutein, zeaxanthin and *meso*-zeaxanthin concentrations in dietary supplements by chiral high-performance liquid chromatography

Alfonso Prado-Cabrero · Stephen Beatty · Alan Howard · Jim Stack · Philipp Bettin · John M. Nolan

Received: 21 August 2015 / Revised: 25 September 2015 / Accepted: 27 September 2015

Abstract We investigated the concordance between actual and declared content of the three macular carotenoids in commercially available supplements aimed at eye health. Three batches of nine products were tested for content of lutein (L), zeaxanthin (Z) and *meso*-zeaxanthin (MZ) by chiral HPLC–DAD. In every product tested, actual L concentration was close to target, but Z concentration varied greatly (45–248 % of declared concentration), and the L:Z ratio within some supplements was adversely affected in consequence. In six of seven products not declaring MZ, we found this carotenoid, and four of them, using the same L source, contained a concentration of MZ that correlated positively and significantly with measured concentrations of L ($r^2 = 0.86$; $P < 0.001$). More transparency is needed in terms of concordance between actual and declared concentrations of Z in commercially available formulations, and MZ should be declared in those formulations where it is present.

Keywords *meso*-zeaxanthin · Lutein · Zeaxanthin · Macula · Chiral HPLC–DAD

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2 Downing College, The Howard Foundation, University of Cambridge, Cambridge, UK

3 Institute of Pharmaceutical Biology, University of Greifswald, Greifswald, Germany

Published online: 07 October 2015

Springer

Introduction

The central region of the retina, known as the macula, is responsible for central and colour vision [1] and is yellow in colour (hence macular lutea) due to the accumulation of the carotenoids lutein (L), zeaxanthin (Z) and *meso*-zeaxanthin (MZ) (Fig. 1a) [2], where these compounds are collectively referred to as macular pigment (MP). The short-wavelength (blue) light-filtering properties of MP are important for optimal vision (because of consequential attenuation of chromatic aberration and the adverse impact of light scatter) [3, 4] and also confer photoprotection to the central retina because short-wavelength (blue) light is the most injurious of visible wavelengths. Further, the macular carotenoids actively quench damaging free radicals, and this antioxidant effect is maximised when all three carotenoids are present [5].

L and Z are consumed in a typical diet containing fruits and leafy green vegetables, whereas MZ has not been detected in collard greens [6]. It has been reported that in a typical Western diet, intake of L is between 1.6 and 3.6 mg/day and intake of Z is circa 0.1 mg/day [7, 8]. However, MZ has been detected in liver of frog and quail [9] and more recently in trout flesh [10]. In the retina, there is evidence that macular MZ is derived (at least in part) from retinal L [11, 12], and given the scarcity of dietary sources of MZ, it is likely that most of retinal MZ is formed from L, but further work is needed to confirm this hypothesis [13–15].

In the vast majority of subjects, MP can be augmented following supplementation with MP's constituent carotenoids [16], suggesting less-than-maximum levels in a substantial proportion of the population. Of note, commercially available supplements used for eye health declare concentrations between 2 and 22 mg of total carotenoid,

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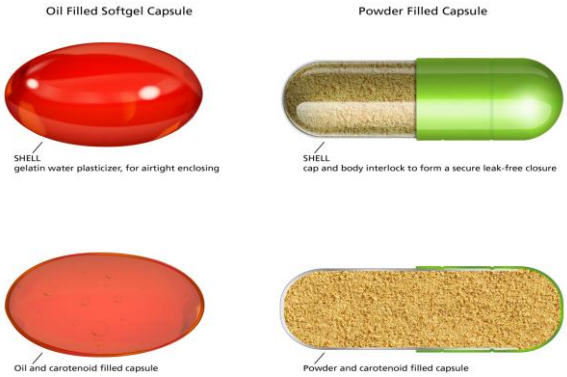
PART II: EVIDENCE-BASED RESEARCH

Capsule Types

Oil-filled softgels protect carotenoids from degradation



Graphical representation of an oil-filled soft gel capsule and a two-part powder filled capsule

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PART II: EVIDENCE-BASED RESEARCH

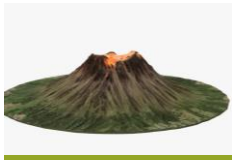
Atypical Central Dips in MP

Retina

A Central Dip in the Macular Pigment Spatial Profile Is Associated with Age and Smoking

Mark L. Kirby, Stephen Beatty, Eduard Loane, Mukunda C. Akkali, Eithne E. Connolly, Jim Stack, and John M. Nolan

The mountain and volcano analogy



VOLCANO

Atypical macular pigment

The MZ (middle-top) section is missing

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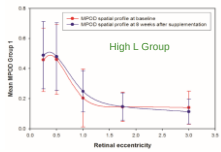
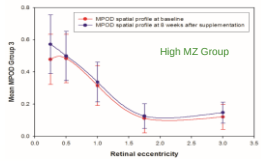
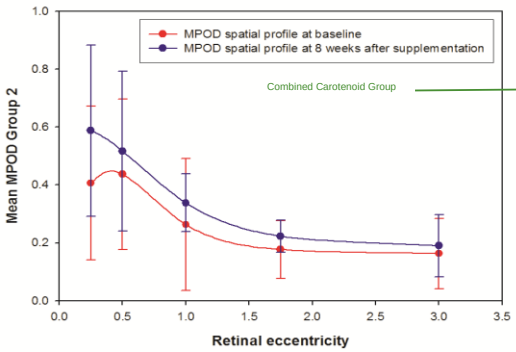
PART II: KEY PEER-REVIEWED STUDIES

MPOD Spatial Profile Results from Supplementation

The results of 3 groups







A discovery for all three carotenoids

A Triple-Carotenoid Formula was the only supplement that was able to increase MPOD spatial profile.

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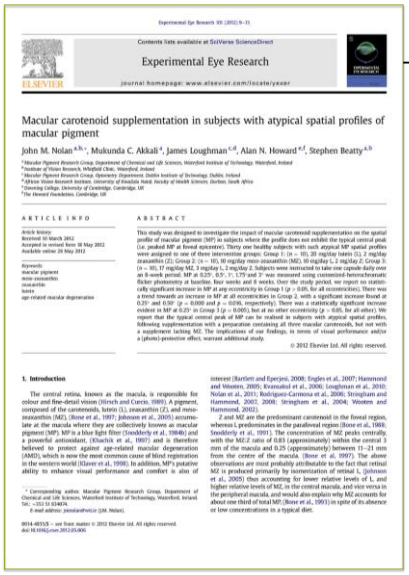
PART II: EVIDENCE-BASED RESEARCH

Atypical Central Dips in MP

The mountain and volcano analogy



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Macular carotenoid supplementation in subjects with atypical spatial profiles of macular pigment

John M. Nolan, Mukunda C. Akkali, James Loughman, Alan N. Howard, Stephen Beatty

ARTICLE INFO

ABSTRACT

This study was designed to investigate the impact of macular carotenoid supplementation on the spatial profile of macular pigment (MP) in subjects where the profile does not exhibit the typical central peak (i.e. peaked MP at foveal epicentre). Thirty one healthy subjects with such atypical MP spatial profiles were assigned to one of three intervention groups: Group 1: (n = 10), 20 mg/day lutein (L); 2 mg/day zeaxanthin (Z); Group 2: (n = 10), 10 mg/day meso-zeaxanthin (MZ), 10 mg/day L, 2 mg/day Z; Group 3: (n = 10), 17 mg/day MZ, 3 mg/day L, 2 mg/day Z. Subjects were instructed to take one capsule daily over an 8-week period. MP at 0.25°, 0.5°, 1°, 1.75° and 3° was measured using customized heterochromatic flicker photometry at baseline, four weeks and 8 weeks. Over the study period, we report no statistically significant increase in MP at any eccentricity in Group 1 ($p > 0.05$, for all eccentricities). There was a trend towards an increase in MP at all eccentricities in Group 2, with a significant increase found at 0.25° and 0.50° ($p = 0.030$ and $p = 0.016$, respectively). There was a statistically significant increase evident in MP at 0.25° in Group 3 ($p = 0.005$), but at no other eccentricity ($p > 0.05$, for all other). We report that the typical central peak of MP can be realised in subjects with atypical spatial profiles. Following supplementation with a preparation containing all three macular carotenoids, but not with a supplement lacking MZ. The implications of our findings, in terms of visual performance and/or a (photo)-protective effect, warrant additional study.

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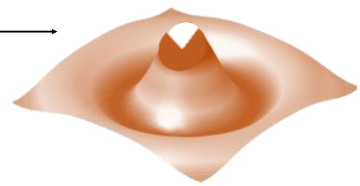
1. Introduction

The central retina, known as the macula, is responsible for colour and fine-detail vision (Hirsch and Curcio, 1989). A pigment, composed of the carotenoids, lutein (L), zeaxanthin (Z), and meso-zeaxanthin (MZ), (Bone et al., 1997; Johnson et al., 2005) accumulate at the macula where they are collectively known as macular pigment (MP). MP is a blue light filter (Snodderly et al., 1984b) and a powerful antioxidant. (Khachik et al., 1997) and is therefore believed to protect against age-related macular degeneration (AMD), which is now the most common cause of blind registration in the western world (Klaver et al., 1998). In addition, MP's putative ability to enhance visual performance and comfort is also of interest (Bartlett and Eperjesi, 2008; Engles et al., 2007; Hammond and Wooten, 2005; Kvansakul et al., 2006; Loughman et al., 2010; Nolan et al., 2011; Rodriguez-Carmona et al., 2006; Stringham and Hammond, 2007, 2008; Stringham et al., 2004; Wooten and Hammond, 2002).

Z and MZ are the predominant carotenoid in the foveal region, whereas L predominates in the parafoveal region (Bone et al., 1988; Snodderly et al., 1991). The concentration of MZ peaks centrally, with the MZ:Z ratio of 0.83 (approximately) within the central 3 mm of the macula and 0.25 (approximately) between 11–21 mm from the centre of the macula. (Bone et al., 1997). The above observations are most probably attributable to the fact that retinal MZ is produced primarily by isomerization of retinal L, (Johnson et al., 2005) thus accounting for lower relative levels of L and higher relative levels of MZ, in the central macula, and vice versa in the peripheral macula, and would also explain why MZ accounts for about one third of total MP, (Bone et al., 1992) in spite of its absence or low concentrations in a typical diet.



Supplementation with Triple-Carotenoid Formula

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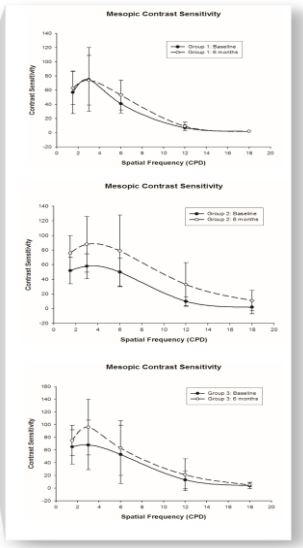
PART II: KEY PEER-REVIEWED STUDIES

MZ Ocular Supplementation Trial (M.O.S.T.)

VISUAL PERFORMANCE: Supplementation with all three macular carotenoids offered advantages over preparations lacking MZ to improve visual performance

SAFETY AND VISUAL PERFORMANCE IN AMD: Enhancements in contrast sensitivity were best achieved after supplementation with a formulation containing high doses of MZ in combination with L and Z (in a MZ:L:Z [mg] ratio of 10:10:2).

The safety of consumption of this formulation was confirmed following extensive clinical pathology analysis.



2012

2014

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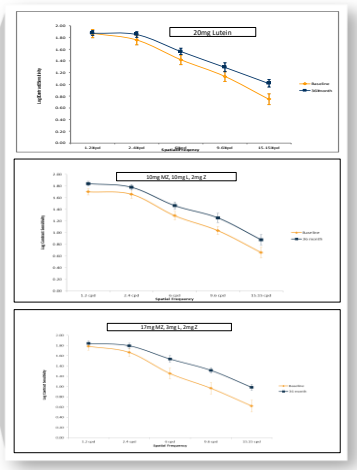
PART II: KEY PEER-REVIEWED STUDIES

M.O.S.T. Continued

This final report from M.O.S.T found that the inclusion of MZ in a supplement formulation confers benefits in terms of MP augmentation and in terms of enhanced contrast sensitivity in subjects with early AMD.



2015

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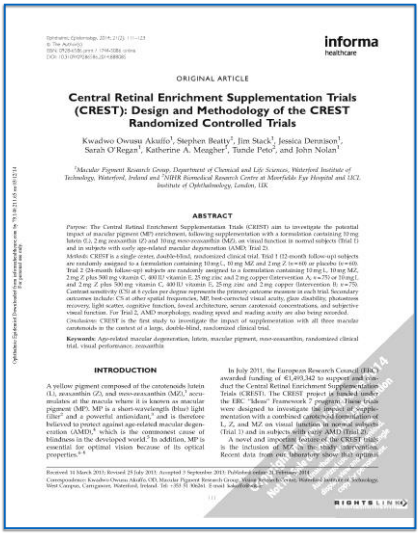
PART II: KEY PEER-REVIEWED STUDIES

CREST Studies: Setting the Gold Standard



informa
healthcare

ORIGINAL ARTICLE

Central Retinal Enrichment Supplementation Trials (CREST): Design and Methodology of the CREST Randomized Controlled Trials

Kwadwo Owusu Akuffo[1], Stephen Beatty[2], Jim Stack[1], Jessica Dennison[1], Sarah O'Regan[1], Katherine A. Mengher[2], Tunde Peto[2], and John Nolan[1]

[1]Macular Pigment Research Group, Department of Chemical and Life Sciences, Waterford Institute of Technology, Waterford, Ireland and [2]NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, UK

ABSTRACT

Purpose: The Central Retinal Enrichment Supplementation Trials (CREST) aim to investigate the potential impact of macular pigment (MP) enrichment, following supplementation with a formulation containing 10 mg lutein (L), 2 mg zeaxanthin (Z) and 10 mg meso-zeaxanthin (MZ), on visual function in normal subjects (Trial 1) and in subjects with early age-related macular degeneration (AMD; Trial 2).

Methods: CREST is a single-center, double-blind, randomized clinical trial. Trial 1 (12-month follow-up) subjects are randomly assigned to a formulation containing 10 mg L, 10 mg MZ and 2 mg Z (n=60) or placebo (n=60). Trial 2 (24-month follow-up) subjects are randomly assigned to a formulation containing 10 mg L, 10 mg MZ, 2 mg Z plus 500 mg vitamin C, 400 IU vitamin E, 25 mg zinc and 2 mg copper (intervention A; n=70) or 10 mg L and 2 mg Z plus 500 mg vitamin C, 400 IU vitamin E, 25 mg zinc and 2 mg copper (intervention B; n=70). Contrast sensitivity (CS) at 6 cycles per degree represents the primary outcome measure in each trial. Secondary outcomes include: CS at other spatial frequencies, MP, best-corrected visual acuity, glare disability, photostress recovery, light scatter, cognitive function, foveal architecture, serum carotenoid concentrations, and subjective visual function. For Trial 2, AMD morphology, reading speed and reading acuity are also being recorded.

Conclusions: CREST is the first study to investigate the impact of supplementation with all three macular carotenoids in the context of a large, double-blind, randomized clinical trial.

Keywords: Age-related macular degeneration, lutein, macular pigment, meso-zeaxanthin, randomized clinical trial, visual performance, zeaxanthin

INTRODUCTION

A yellow pigment composed of the carotenoids lutein (L), zeaxanthin (Z), and meso-zeaxanthin (MZ),[1] accumulates at the macula where it is known as macular pigment (MP). MP is a short-wavelength (blue) light filter[2] and a powerful antioxidant,[3] and is therefore believed to protect against age-related macular degeneration (AMD),[4] which is the commonest cause of blindness in the developed world.[5] In addition, MP is essential for optimal vision because of its optical properties.[6–8]

In July 2011, the European Research Council (ERC) awarded funding of €1,493,342 to support and conduct the Central Retinal Enrichment Supplementation Trials (CREST). The CREST project is funded under the ERC "Ideas" Framework 7 program. These trials were designed to investigate the impact of supplementation with a combined carotenoid formulation of L, Z, and MZ on visual function in normal subjects (Trial 1) and in subjects with early AMD (Trial 2).

A novel and important feature of the CREST trials is the inclusion of MZ in the study intervention. Recent data from our laboratory show that supple-

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Funded by the European Research Council (ERC)
The main goal of the ERC is to encourage the highest quality research in Europe on the basis of scientific excellence through competitive funding. €1,493,342 over five years; Grant No. 281096

CREST
NRCI Nutrition Research Centre Ireland

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PART II: KEY PEER-REVIEWED STUDIES

CREST Normal: Trial 1 Design

Retina

Enrichment of Macular Pigment Enhances Contrast Sensitivity in Subjects Free of Retinal Disease: Central Retinal Enrichment Supplementation Trials – Report 1

John M. Nolan,[1] Rebecca Power,[1] Jim Stringham,[2] Jessica Dennison,[1] Jim Stack,[1] David Kelly,[3] Rachel Moran,[1] Kwadwo O. Akuffo,[1] Laura Corcoran,[1] and Stephen Beatty[1]

Investigative Ophthalmology & Visual Science

- Sample size: N=105
- Study Design: Double blind placebo controlled RCT
- Population: Healthy participants with low MP
- Intervention:
  - L10mg:MZ10mg:Z2mg
  - Placebo
- Outcomes:
  - Contrast Sensitivity

CREST
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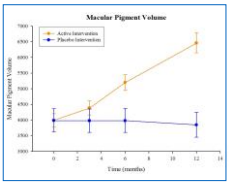
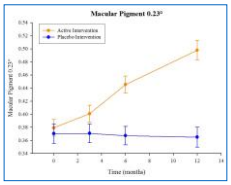
PART II: KEY PEER-REVIEWED STUDIES

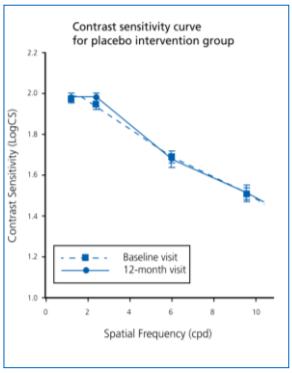
CREST Normal: Trial 1 Results

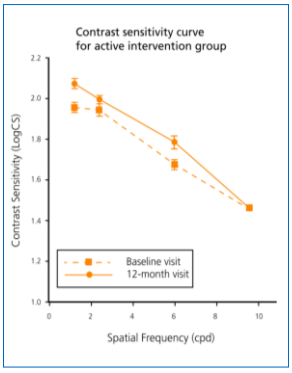
100% Response





Making the invisible visible





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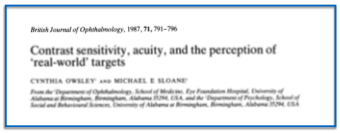
PART II: KEY PEER-REVIEWED STUDIES

Visual Performance in the Real World

Owsley & Sloane (1987): Contrast sensitivity at middle and low spatial frequencies (e.g. 6 cpd) was significant predictor of real-world object detection and identification. *Faces, road signs, basic objects.*

- CS determined to be a better predictor of performance than age!
- VA was not a significant contributor to real-world visual performance



British Journal of Ophthalmology, 1987, 71, 791–796

Contrast sensitivity, acuity, and the perception of 'real-world' targets

CYNTHIA OWSLEY AND MICHAEL E SLOANE

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PART II: IMPLICATION OF FINDINGS

Implication of Findings: Healthy Subjects

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PART II: IMPLICATION OF FINDINGS

Implication of Findings: Visually-Demanding Occupations

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PART II: IMPLICATION OF FINDINGS

Implication of Findings: Sports Performance


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PART II: KEY PEER-REVIEWED STUDIES

CREST AMD: Trial 2 Design

Clinical Trials

The Impact of Supplemental Antioxidants on Visual Function in Nonadvanced Age-Related Macular Degeneration: A Head-to-Head Randomized Clinical Trial

Kwadwo Owusu Akuffo,[1] Stephen Beatty,[1] Tunde Peto,[2] Jim Stack,[1] Jim Stringham,[3] David Kelly,[1] Irene Leung,[4] Laura Corcoran,[1] and John M. Nolan[1]

- Sample size: N=121
- Study Design: Double-blind RCT
- Population: Early AMD
- Intervention:
  - L10mg: MZ10mg: Z2mg + Vit C + Vit E + Zn + Cu
  - AREDS
- Time: 12 months
- Outcomes:
  - Visual Performance
  - Macular Pigment

CREST

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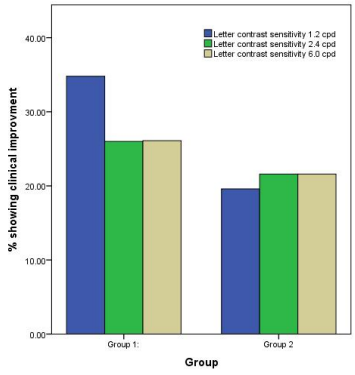
PART II: KEY PEER-REVIEWED STUDIES

CREST AMD: Trial 2 Results



75%** (24 of 32) of vision related measures (e.g. contrast sensitivity, glare disability, photo stress recovery) **exhibited significant improvements

TABLE 3. Change in Contrast Sensitivity of ≥1 Line of CS

	% Showing Clinical Improvement		% Showing Clinical Deterioration	
Variable	Group 1*	Group 2†	Group 1*	Group 2†
Letter CS 1.2 cpd	34.8	19.6	2.2	3.9
Letter CS 2.4 cpd	26.1	21.6	4.3	3.9
Letter CS 6 cpd	26.1	21.6	13	11.8

Clinical significance, which for present purposes we defined as one line or more on a letter CS chart. Letter CS measured using the Test Chart 2000 PRO (Thomson Software Solutions).

* Group 1, 10 mg/d MZ, 10 mg/d L, and 2 mg/d Z plus 500 mg/d vitamin C, 400 IU/d of vitamin E, 25 mg/d zinc, and 2 mg/d copper.

† Group 2, 10 mg/d L, 2 mg/d Z plus 500 mg/d vitamin C, 400 IU/d of vitamin E, 25 mg/d zinc, and 2 mg/d copper.

Supplementation with a formulation containing MZ *improves* visual function in patients with early AMD

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PART II: IMPLICATION OF FINDINGS

Implication of CREST Findings

Recommend a Triple-Carotenoid Formulation

10:10:20 mg/day (MZ:L:Z)

THE BENEFITS FOR YOUR PATIENTS:

↑ Optimize their vision

↓ Decrease the risk of progression of AMD

OPTION

IF THE DOCTOR PREFERS AN AREDS-LIKE FORMULA:

- Use low zinc (safer)
- Fortified with Meso-Zeaxanthin (better)

Please note the AREDS study demonstrated a benefit of the active ingredient for reducing risk of AMD progression for patients with intermediate AMD only.

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PART II: IMPLICATION OF FINDINGS

AREDS and AREDS 2


Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration
The Age-Related Eye Disease Study 2 (AREDS2)
Randomized Clinical Trial


NIH Public Access
Author Manuscript

A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation With Vitamins C and E, Beta Carotene, and Zinc for Age-Related Macular Degeneration and Vision Loss:


Secondary Analyses of the Effects of Lutein/Zeaxanthin on Age-Related Macular Degeneration Progression
AREDS2 Report No. 3

AREDS1 has shown a 25% risk reduction in progression from intermediate AMD to advanced AMD when supplemented with antioxidants and zinc

AREDS2 has shown that supplementation with lutein and zeaxanthin provided an additional 10% risk reduction in the progression from intermediate AMD to advanced AMD

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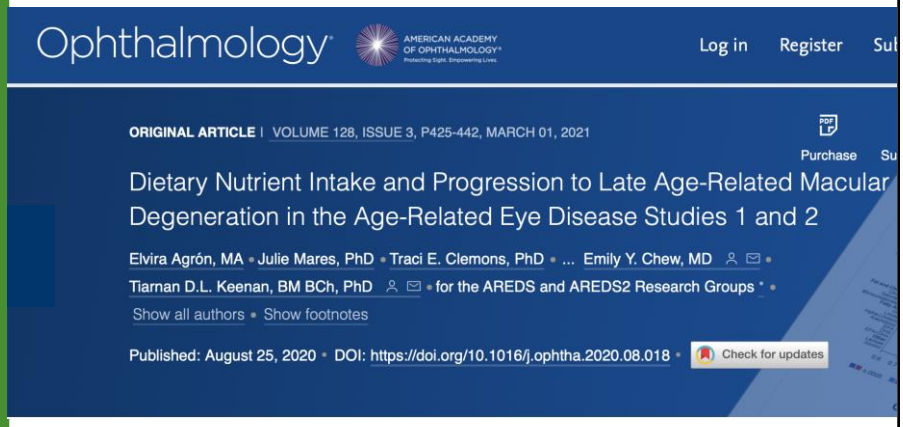
PART II: IMPLICATION OF FINDINGS

AREDS 3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ORIGINAL ARTICLE | VOLUME 128, ISSUE 3, P425-442, MARCH 01, 2021

Purchase Su

Dietary Nutrient Intake and Progression to Late Age-Related Macular Degeneration in the Age-Related Eye Disease Studies 1 and 2

Elvira Agrón, MA • Julie Mares, PhD • Traci E. Clemons, PhD • ... Emily Y. Chew, MD •
Tiarnan D.L. Keenan, BM BCh, PhD • for the AREDS and AREDS2 Research Groups * •
Show all authors • Show footnotes

Published: August 25, 2020 • DOI: https://doi.org/10.1016/j.ophtha.2020.08.018 • Check for updates

Higher dietary intake of multiple nutrients (including specific vitamins, minerals, carotenoids, and fatty acids) was associated with decreased progression to late age-related macular degeneration, particularly geographic atrophy.

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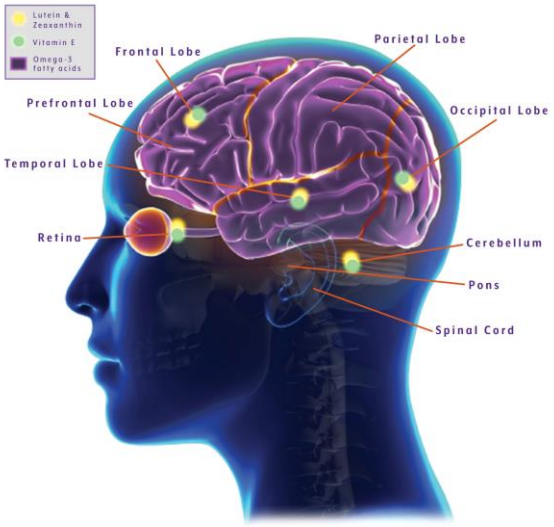
PART II: IMPLICATION OF FINDINGS

Targeted Nutrition and Cognition



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PART II: IMPLICATION OF FINDINGS

Carotenoid and Retinal Dementia Study (CARDS 1)

Macular Pigment, Visual Function, and Macular Disease among Subjects with Alzheimer's Disease: An Exploratory Study

John M. Nolan[a,*], Ekaterina Loskutova[a], Alan N. Howard[b,c], Rachel Moran[a], Riona Mulcahy[d], Jim Stack[a], Maggie Bolger[d], Jessica Dennison[a], Kwadwo Owusu Akuffo[a], Niamh Owens[a], David I. Thurnham[e] and Stephen Beatty[a]

[a]*Macular Pigment Research Group, Department of Chemical and Life Sciences, Waterford Institute of Technology, Waterford, Ireland*
[b]*Howard Foundation, Cambridge, UK*
[c]*Downing College, University of Cambridge, Cambridge, UK*
[d]*Waterford Regional Hospital, Age-Related Care Unit, Waterford, Ireland*
[e]*Northern Ireland, Centre for Food and Health (NICHE), University of Ulster, Coleraine, UK*

Accepted 2 May 2014

Abstract.
Background: The macula (central retina) contains a yellow pigment, comprising the dietary carotenoids lutein (L), zeaxanthin (Z), and *meso*-zeaxanthin, known as macular pigment (MP). The concentrations of MP's constituent carotenoids in retina and brain tissue correlate, and there is a biologically-plausible rationale, supported by emerging evidence, that MP's constituent carotenoids are also important for cognitive function.
Objective: To investigate if patients with Alzheimer's disease (AD) are comparable to controls in terms of MP and visual function.
Methods: 36 patients with moderate AD and 33 controls with the same age range participated. MP was measured using dual-wavelength autofluorescence (Heidelberg Spectralis®); cognitive function was assessed using a battery of cognition tests (including Cambridge Neuropsychological Test Automated Battery). Visual function was recorded by measuring best corrected visual acuity (BCVA) and contrast sensitivity (CS). Serum L and Z concentrations (by HPLC) and age-related macular degeneration (AMD, by retinal examination) status were also assessed.
Results: In the AD group, central MP (i.e., at 0.25°) and MP volume were significantly lower than the control group ($p < 0.001$ for both), as were measures of BCVA, CS, and serum L and Z concentrations ($p < 0.05$, for all).
Conclusion: AD patients were observed to exhibit significantly less MP, lower serum concentrations of L and Z, poorer vision, and a higher occurrence of AMD when compared to control subjects. A clinical trial in AD patients designed to investigate the impact of macular carotenoid supplementation with respect to MP, visual function, and cognitive function is merited.

Keywords: Age-related macular degeneration, Alzheimer's disease, cognitive function, contrast sensitivity, lutein, meso-zeaxanthin, visual function, zeaxanthin

Objective
To examine whether or not individuals with AD are comparable to controls in terms of macular pigment and visual function.

Design
- Cross-sectional
- Mild-moderate AD (n = 36)
- Controls (n = 33)

Primary outcome measures
- Macular pigment
- Visual function
- AMD status

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PART II: IMPLICATION OF FINDINGS

Carotenoid and Retinal Dementia Study (CARDS 1)

Macular Pigment, Visual Function, and Macular Disease among Subjects with Alzheimer's Disease: An Exploratory Study

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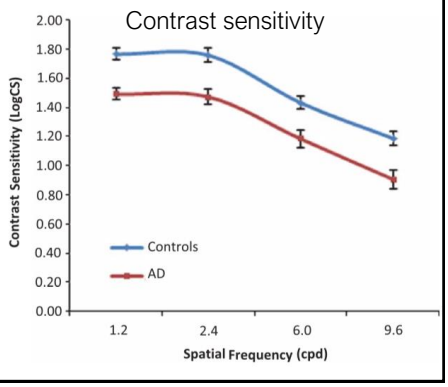
Keywords: Age-related macular degeneration, Alzheimer's disease, cognitive function, contrast sensitivity, lutein, meso-zeaxanthin, visual function, zeaxanthin

Patients with AD exhibited significantly lower MP levels and serum carotenoid concentrations and poorer vision compared to patients without the disease.



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PART II: IMPLICATION OF FINDINGS

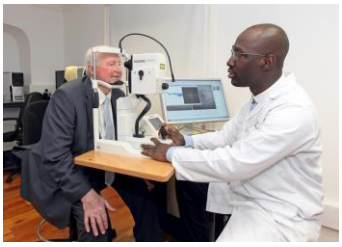
Carotenoid and Retinal Dementia Study (CARDS 2)

Objective
To investigate supplementation with the macular carotenoids on MP, vision and cognitive function in patients with AD versus controls.

Design
6-month, double-blind, placebo-controlled, RCT.
Intervention: 10mg L, 10mg MZ, 2mg Z (n = 31) Vs placebo (n = 31).
Study visits were performed at baseline and 6 months.

Primary outcome measures
Macular pigment

Secondary outcome measures
Visual function
Cognitive function



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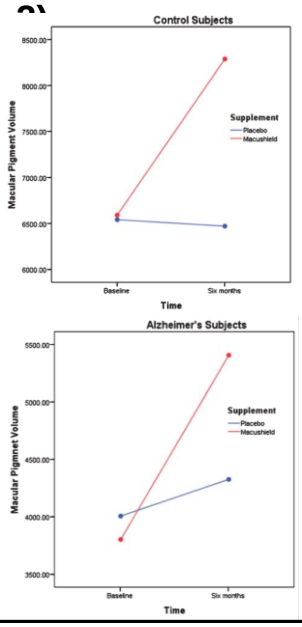
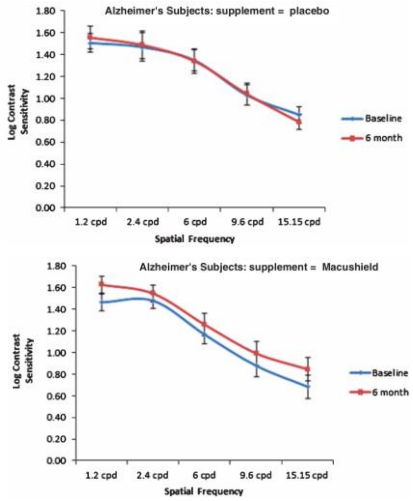
PART II: IMPLICATION OF FINDINGS

Carotenoid and Retinal Dementia Study (CARDS 2)





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PART II: IMPLICATION OF FINDINGS

Carotenoid and Retinal Dementia Study (CARDS 2)

The Impact of Supplemental Macular Carotenoids in Alzheimer's Disease: A Randomized Clinical Trial

John M. Nolan[a,*], Ekaterina Loskutova[a], Alan Howard[b,c], Riona Mulcahy[d], Rachel Moran[a], Jim Stack[a], Maggie Bolger[d], Robert F. Coen[e], Jessica Dennison[a], Kwadwo Owusu Akuffo[a], Niamh Owens[a], Rebecca Power[a], David Thurnham[f] and Stephen Beatty[g]

[a]*Macular Pigment Research Group, Department of Chemical and Life Sciences, Waterford Institute of Technology, Waterford, Ireland*
[b]*Howard Foundation, Cambridge, UK*
[c]*Downing College, University of Cambridge, Cambridge, UK*
[d]*University Hospital Waterford, Age-Related Care Unit, Waterford, Ireland*
[e]*Mercer's Institute for Successful Ageing, St. James's Hospital, Dublin, Ireland*
[f]*Northern Ireland, Centre for Food and Health (NICHE), University of Ulster, Coleraine, UK*

Accepted 15 October 2014

Abstract

Background: Patients with Alzheimer's disease (AD) exhibit significantly less macular pigment (MP) and poorer vision when compared to control subjects.

Objective: To investigate supplementation with the macular carotenoids on MP, vision, and cognitive function in patients with AD versus controls.

Methods: A randomized, double-blind clinical trial with placebo and active arms. 31 AD patients and 31 age-similar control subjects were supplemented for six months with either Macushield (10 mg meso-zeaxanthin [MZ]; 10 mg lutein [L]; 2 mg zeaxanthin [Z]) or placebo (sunflower oil). MP was measured using dual-wavelength autofluorescence (Heidelberg Spectralis®). Serum L, Z, and MZ were quantified by high performance liquid chromatography. Visual function was assessed by best corrected visual acuity and contrast sensitivity (CS). Cognitive function was assessed using a battery of cognition tests, including the Cambridge Neuropsychological Test Automated Battery (CANTAB).

Results: Subjects on the active supplement (for both AD and non-AD controls) exhibited statistically significant improvement in serum concentrations of L, Z, MZ, and MP ($p < 0.001$, for all) and also CS at ($p = 0.039$). Also, for subjects on the active supplement, paired samples *t*-tests exhibited four significant results (from five spatial frequencies tested) in the AD group, and two for the non-AD group, and all indicating improvements in CS. We found no significant changes in any of the cognitive function outcome variables measured ($p > 0.05$, for all).

Conclusion: Supplementation with the macular carotenoids (MZ, Z, and L) benefits patients with AD, in terms of clinically meaningful improvements in visual function and in terms of MP augmentation.

Keywords: Age-related macular degeneration, Alzheimer's disease, cognitive function, contrast sensitivity, lutein, meso-zeaxanthin, randomized clinical trial, visual function, zeaxanthin

CONCLUSIONS

Supplementation with all three macular carotenoids (in a MZ:L:Z [mg] ratio of 10:10:2) benefited patients with AD in terms of clinically meaningful improvements in visual function and in terms of MP augmentation.

No improvements in cognitive function were observed suggesting that cognition had deteriorated too far for nutritional intervention to have any meaningful effect.

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PART II: IMPLICATION OF FINDINGS

Carotenoid and Retinal Dementia Study (CARDS 3)

Objective

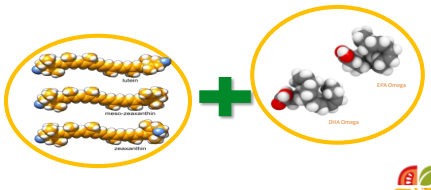
To investigate if supplementation with xanthophyll carotenoids in a ratio (mg/day) of 10:10:2 (L:MZ:Z) plus omega-3 fatty acids impacted on disease progression in patients with Alzheimer's disease.

Design

Trial 1: 12 patients supplemented with 10mg L, 10mg MZ and 2mg Z over 18 months.
Trial 2: 13 patients supplemented with 10mg L, 10mg MZ, 2mg Z, 430mg DHA and 90mg EPA over 18 months.
Trial 3: 15 control subjects were supplemented with 10mg L, 10mg MZ and 2mg Z over 6 months.

Primary outcome measures

Disease progression
Biochemical response



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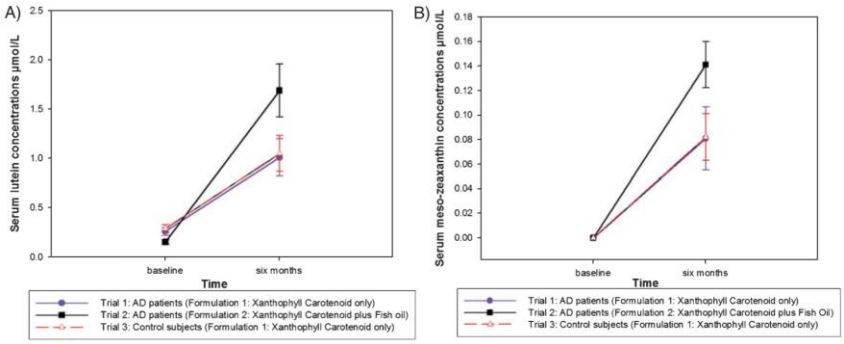
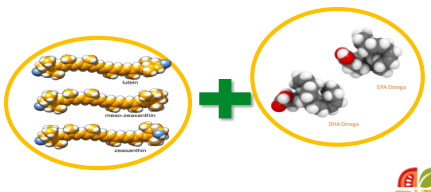
PART II: IMPLICATION OF FINDINGS

Carotenoid and Retinal Dementia Study (CARDS 3)





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PART II: IMPLICATION OF FINDINGS

Carotenoid and Retinal Dementia Study (CARDS 3)

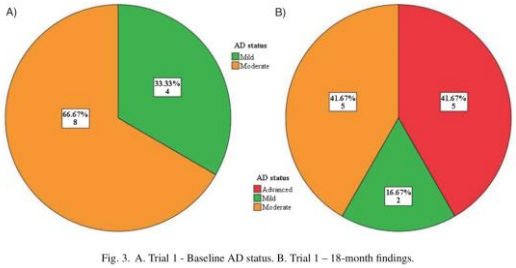

Fig. 3. A. Trial 1 - Baseline AD status. B. Trial 1 – 18-month findings.

Trial 1: Xanthophyll carotenoid formulation

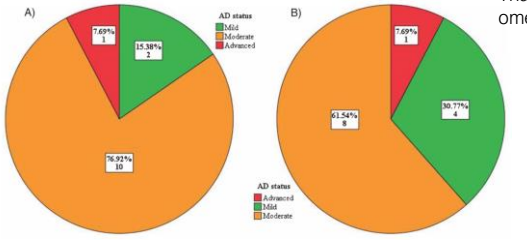

Fig. 4. A. Trial 2 – Baseline AD status. B. Trial 2 – 18-month findings.

Trial 2: Xanthophyll carotenoid plus omega-3 fatty acid formulation

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Targeted Nutrition and Cognition

The Howard Foundation

Macular Pigment, Visual Function, and Macular Disease among Subjects with Alzheimer's Disease: An Exploratory Study

John M. Nolan[a,*], Ekaterina Loskutova[a], Alan N. Howard[b,c], Rachel Moran[a], Riona Mulcahy[d], Jim Stack[a], Maggie Bolger[a], Jessica Dennison[a], Kwadwo Owusu Akuffo[a], Niamh Owens[a], David I. Thurnham[e] and Stephen Beatty[a]

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Objective: To investigate if patients with Alzheimer's disease (AD) are comparable to controls in terms of MP and visual function.

Methods: 36 patients with moderate AD and 33 controls with the same age range participated. MP was measured using customized, fully-validated, heterochromatic flicker photometry. Subjects was assessed using a battery of cognitive tests (including Cambridge Neuropsychological Test Automated Battery). Visual function was recorded by measuring best corrected visual acuity (BCVA) and contrast sensitivity (CS). Serum L and Z concentrations (by HPLC) and age-related macular degeneration (AMD, by retinal examination) status were also assessed.

Results: In the AD group, central MP (i.e., at 0.25°) and MP volume were significantly lower than the control group ($p<0.001$ for both), as were measures of BCVA, CS, and serum L and Z concentrations ($p<0.05$, for all).

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John M. Nolan[a,*], Ekaterina Loskutova[a], Alan Howard[b,c], Riona Mulcahy[d], Rachel Moran[a], Jim Stack[a], Maggie Bolger[a], Robert F. Coen[e], Jessica Dennison[a], Kwadwo Owusu Akuffo[a], Niamh Owens[a], Rebecca Power[a], David Thurnham[f] and Stephen Beatty[a]

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Accepted 15 October 2014

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Nutritional Intervention to Prevent Alzheimer's Disease: Potential Benefits of Xanthophyll Carotenoids and Omega-3 Fatty Acids Combined

John M. Nolan[a,*], Riona Mulcahy[b], Rebecca Power[a], Rachel Moran[a] and Alan N. Howard[c]

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[c]Howard Foundation, Cambridge, UK

Accepted 17 April 2018

Abstract.

Background: A growing body of scientific evidence suggests that enrichment of certain nutritional compounds in the brain may reduce the risk of Alzheimer's disease (AD).

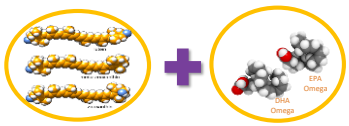
Objective: To investigate the impact of supplemental xanthophyll carotenoids plus omega-3 fatty acids on disease progression in patients with AD.

Methods: Three trial experiments were performed. In Trials 1 and 2 (performed on patients with AD over an 18-month period), 12 patients (AD status at baseline: 4 mild and 8 moderate) were supplemented with a xanthophyll carotenoid only formulation (Formulation 1; lutein:meso-zeaxanthin:zeaxanthin 10:10:2 mg/day) and 15 patients (AD status at baseline: 2 mild, 10 moderate, and 1 severe) were supplemented with a xanthophyll carotenoid and fish oil combination (Formulation 2; lutein:meso-zeaxanthin:zeaxanthin 10:10:2 mg/day plus 1 g/day of fish oil containing 450 mg docohexaenoic acid [DHA] and 90 mg eicopentaenoic acid [EPA], respectively. In Trial 3, 15 subjects free of AD (the control group) were supplemented for 6 months with Formulation 1. Blood xanthophyll carotenoid response was measured in all trials by HPLC. Omega-3 fatty acids were profiled by direct infusion mass spectrometry.

Results: Xanthophyll carotenoid concentration increases were significantly greater for Formulation 2 compared to Formulation 1 ($p<0.05$), and progression of AD was less for this group ($p=0.003$), with carers reporting functional benefits in memory, sight, and mood.

Conclusion: This preliminary report suggests positive outcomes for patients with AD who consumed a combination of xanthophyll carotenoids plus fish oil, but further study is required to confirm this important observation.

Keywords: Alzheimer's disease, dementia, DHA, fatty acids, lutein, meso-zeaxanthin, nutrition, omega-3, prevention, xanthophyll carotenoids



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COAST

Carotenoid Omega BioAvailability STudy

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PART II: COAST

COAST: Boosting Bioavailability

The latest research

antioxidants

MDPI

Article

The Impact of Formulation on Lutein, Zeaxanthin, and *meso*-Zeaxanthin Bioavailability: A Randomised Double-Blind Placebo-Controlled Study

Marina Green-Gomez [1], Alfonso Prado-Cabrero [1], Rachel Moran [1], Tommy Power [1], Laura G. Gómez-Mascaraque [2], Jim Stack [1] and John M. Nolan [1,*]

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check for updates

Abstract: Lutein (L), zeaxanthin (Z), and *meso*-zeaxanthin (MZ) have been the focus of research and commercial interest for their applications in human health. Research into formulations to enhance their bioavailability is merited. This 6 month randomised placebo-controlled trial involving 81 healthy volunteers compared the bioavailability of different formulations of free L, Z, and MZ in sunflower or omega-3 oil versus L, Z, and MZ diacetates (Ld, Zd, and MZd) in a micromicellar formulation. Fasting serum carotenoids, macular pigment, and skin carotenoid score were analysed at baseline and 6 months. Serum L, Z, and MZ concentrations increased in all active interventions compared to placebo ($p < 0.001$ to $p = 0.008$). The diacetate micromicelle formulation exhibited a significantly higher mean response in serum concentrations of Z and MZ compared to the other active interventions ($p = 0.002$ to 0.019). A micromicellar formulation with solubilised Z and MZ diacetates is a promising technology advancement that enhances the bioavailability of these carotenoids when compared to traditional carotenoid formulations (ISRCTN clinical trial registration number: ISRCTN18206561).

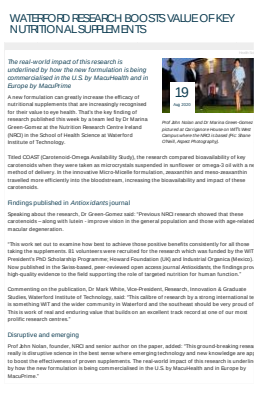
Keywords: *meso*-zeaxanthin; zeaxanthin; lutein; carotenoid diacetates; bioavailability; micromicelles

1. Introduction

Lutein (L), zeaxanthin (Z), and meso-zeaxanthin (MZ) are xanthophyll carotenoids (XC) that singularly deposit in the human macula lutea [1], where they are known as macular pigment (MP). L and Z are obtained solely through dietary intake [2]. MZ has been proposed to be obtained from the endogenous conversion of L in the retinal pigment epithelium [3], but it can be also found in trace amounts in diet [4]. Over the last two decades, intervention trials have studied the role of L, Z, and MZ in human health using nutritional supplements [2]. Reports confirmed that these carotenoids enhance visual performance [5–7] and cognitive function [7,8], and are potential preventive and therapeutic agents in retinal pathology, such as non-advanced age-related macular degeneration (AMD) [1,6].

L used in nutritional supplements is extracted from the marigold flower (*Tagetes erecta* L.) [9], while Z is obtained from specific varieties of this flower [10] and peppers [11]. MZ is obtained from L through a process that promotes the migration of a double bond that turns the ε-ring of L into a β-ring [12]. In every case, the final purification step forms XC microcrystals [7,9] (Figure 1). Nutraceutical companies continually seek to develop new methods to protect these microcrystals from oxidation, improve their solubility in aqueous matrices, and increase their bioavailability in the

Antioxidants **2020**, *9*, 707; doi:10.3390/antiox9080707 www.mdpi.com/journal/antioxidants



WATERFORD RESEARCH BOOSTS VALUE OF KEY NUTRITIONAL SUPPLEMENTS

The real-world impact of this research is underlined by how the new formulation is being commercialised in the U.S by MacuHealth and in Europe by MacuPrime

A new formulation can greatly increase the efficacy of nutritional supplements that are increasingly recognised for their value to eye health. That's the key finding of research published this week by a team led by Dr Marina Green-Gomez at the Nutrition Research Centre Ireland (NRCI) in the School of Health Science at Waterford Institute of Technology.

19 Aug 2020

Prof John Nolan and Dr Marina Green-Gomez pictured at Carrigtwohill Campus where the NRCI is based. (Pic: Maire O'Neill, Aquac Photography).

Titled COAST (Carotenoid-Omega Availability Study), the research compared bioavailability of key carotenoids when they were taken as microcrystals suspended in sunflower or omega-3 oil with a new method of delivery. In the innovative Micro-Micelle formulation, zeaxanthin and meso-zeaxanthin travelled more efficiently into the bloodstream, increasing the bioavailability and impact of these carotenoids.

Findings published in Antioxidants journal

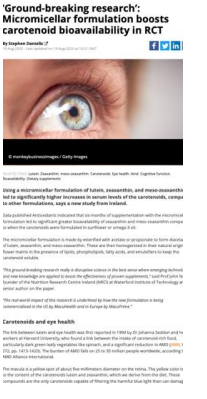
Speaking about the research, Dr Green-Gomez said: "Previous NRCI research showed that these carotenoids – along with lutein - improve vision in the general population and those with age-related macular degeneration.

"This work set out to examine how best to achieve those positive benefits consistently for all those taking the supplements. 81 volunteers were recruited for the research which was funded by the WIT President's PhD Scholarship Programme, Howard Foundation (UK) and Industrial Organica (Mexico). Now published in the Swiss-based, peer-reviewed open access journal *Antioxidants*, the findings provide high-quality evidence to the field supporting the role of targeted nutrition for human function."

Commenting on the publication, Dr Mark White, Vice-President, Research, Innovation & Graduate Studies, Waterford Institute of Technology, said: "This calibre of research by a strong international team is something WIT and the wider community in Waterford and the southeast should be very proud of. This is work of real and enduring value that builds on an excellent track record at one of our most prolific research centres."

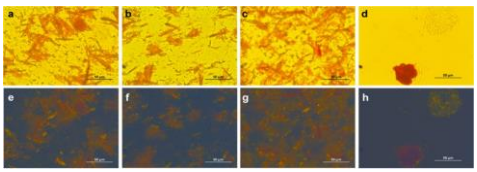
Disruptive and emerging

Prof John Nolan, founder, NRCI and senior author on the paper, added: "This ground-breaking research really is disruptive science in the best sense where emerging technology and new knowledge are applied to boost the effectiveness of proven supplements. The real-world impact of this research is underlined by how the new formulation is being commercialised in the U.S. by MacuHealth and in Europe by MacuPrime."



'Ground-breaking research': Micromicellar formulation boosts carotenoid bioavailability in RCT

Carotenoids and eye health



CONCLUSIONS

COAST

Conclusions

Z and MZ diacetates presented an increased bioavailability most likely due to improved bioaccesibility. Micellarization and absorption efficiency is a plausible rationale for their enhanced bioavailability.

Advanced supplement technology with solubilized L, Z, and MZ diacetates instead of crystals enhances the bioavailability when compared to traditional carotenoid supplements.

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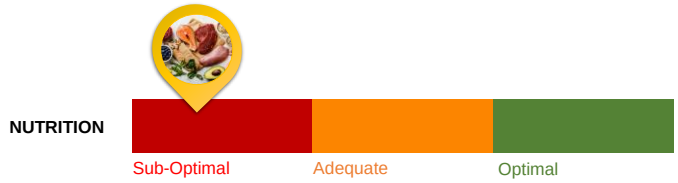
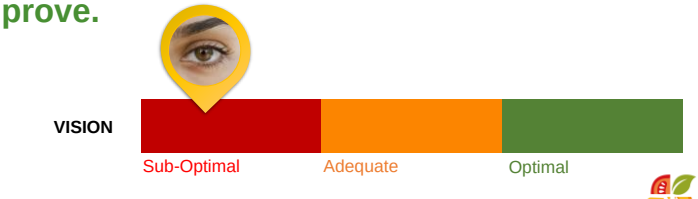
CONCLUSIONS

Take-home Message

Enriching diet with carotenoids and omegas,



vision and cognition function will improve.



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ON TOP OF INNOVATION!

www.profjohnnolan.com

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THANK YOU

Questions?

Find my work at profjohnnolan.com

NRCI

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Ocular Disease: Part I

Presented by MBKU | SCCO

Retinal Grand Rounds

Presented by Julie Rodman, OD, MSc

Live CE Webinar | Day One | AM Session

Saturday | March 20, 2021 | 8:55 a.m. - 9:50 a.m.

Marshall B.
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Retinal Grand Rounds

JULIE RODMAN OD, MSC, FAAO
PROFESSOR, NOVA SOUTHEASTERN UNIVERSITY
COLLEGE OF OPTOMETRY

1

Disclosures

Optovue: Speaker, Consultant, Advisory Board

Maculogix: Speaker, Consultant, Advisory Board

2

Chloroquine and Hydoxychloroquine (Plaquenil) Retinopathy

GUIDELINES AND SCREENING RECOMMENDATIONS

3

What is Hydroxychloroquine (Plaquenil)?

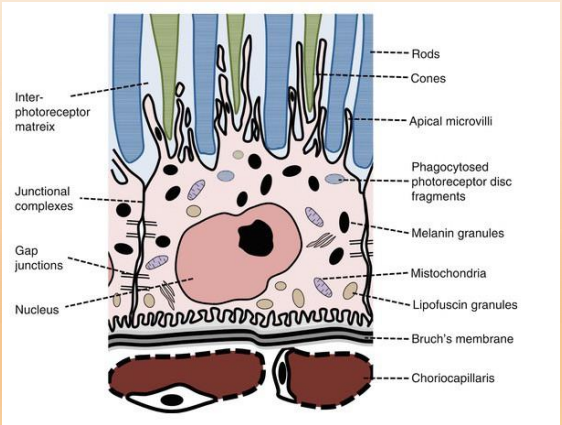
- Disease-modifying anti-rheumatic drug (DMARD)
- Originally anti-malarial

- Used to treat rheumatoid arthritis, lupus, and other inflammatory and dermatologic conditions

4

What is Hydroxychloroquine (Plaquenil)?

- Metabolite of chloroquine
- Longer half life
  - Less drug needed for efficacy



- Binds to melanin in RPE
  - Results in Bulls-Eye Maculopathy

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Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

- *Dose:*
  - Maximum daily HCQ use of ≤ 5.0 mg/kg real weight
- *Duration:*
  - At recommended dosage, risk of toxicity up to 5 years is under 1% and up to 10 years is under 2%... BUT 20% AFTER 20 YEARS!!!

High dose and long duration of use are most significant risk factors

6

Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)

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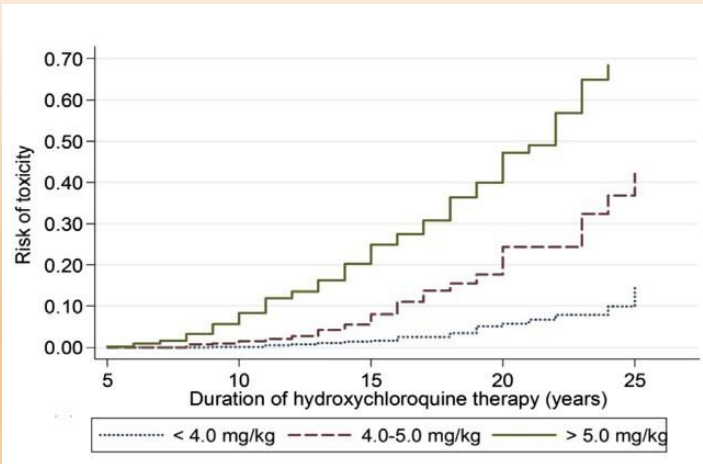

JAMA Ophthalmol 2014;132:1453e60

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Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

- *Major Risk Factors:*
  - Concomitant renal disease
    - Subnormal glomerular filtration rate
  - Concomitant Drugs
    - Tamoxifen Use

Retinopathy is not reversible!!

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Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Screening Schedule

- Baseline Screening
  - Fundus examination within first year of use
  - Add VFs and OCT if maculopathy is present
- Annual Screening
  - Begin after 5 years of use
  - Sooner in the presence of major risk factors

JAMA Ophthalmol 2014;132:1453e60

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65-year-old Caucasian Female

- Complaints of "central darkening" OU
  - Progressive worsening
- History of rheumatoid arthritis (20+ years)
- BCVA:
  - OD 20/40; OS 20/40-

Medications:

- *Methotrexate*
- *Plaquenil: 400 mg x 20 years*

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Risk of Plaquenil Maculopathy

Step 1: Evaluate the dosage:

- ***Dose:***
  - Maximum daily HCQ use of ≤ 5.0 mg/kg real weight

150 lb. converts to 68 kg

400mg/68 kg = 5.88 mg/kg

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Risk of Plaquenil Maculopathy

Step 2: Evaluate the duration:

- ***Duration:***
  - At recommended dosage, risk of toxicity up to 5 years is under 1% and up to 10 years is under 2%... **BUT 20% AFTER 20 YEARS!!!**

20 years of use and dosage higher than recommended

12

Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)

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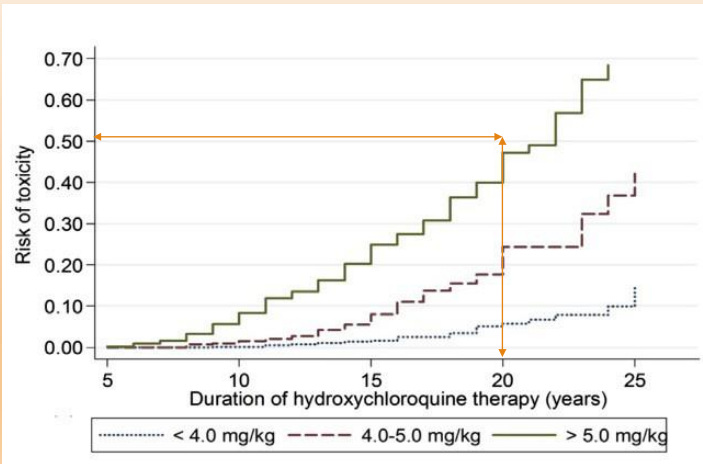

JAMA Ophthalmol 2014;132:1453e60

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Risk of Plaquenil Maculopathy

Step 3: Assess other major risk factors:

- ***Major Risk Factors:***
  - Concomitant renal disease
    - Subnormal glomerular filtration rate
  - Concomitant Drugs
    - Tamoxifen Use

This patient does not have any other major risk factors

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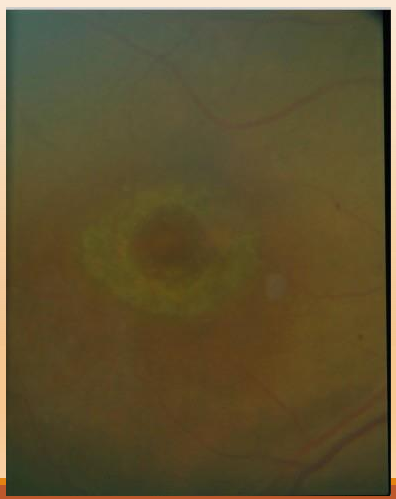
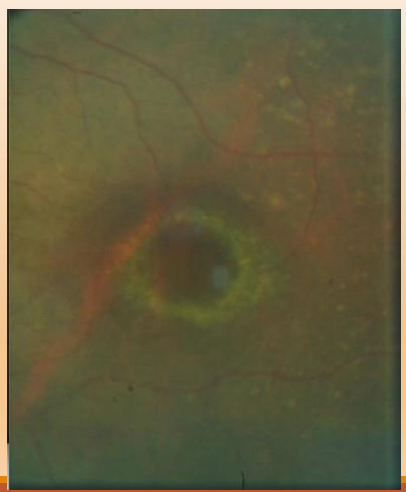
Dilated Fundus Examination





Ring of parafoveal RPE depigmentation sparing fovea

"Bull's Eye Maculopathy"

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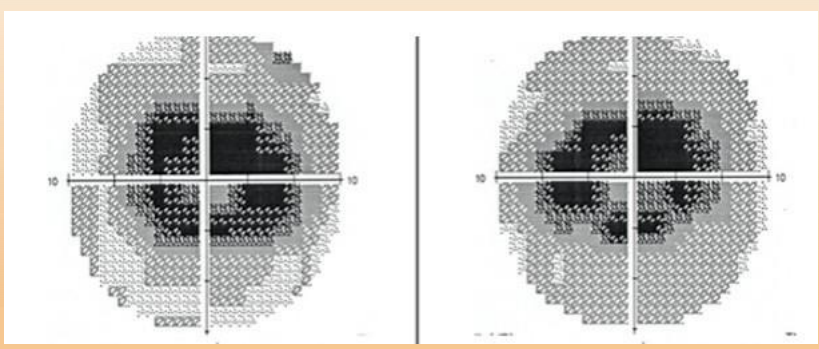
Ancillary Testing

10-2 Humphrey Visual Field



Dense ring scotoma bilaterally

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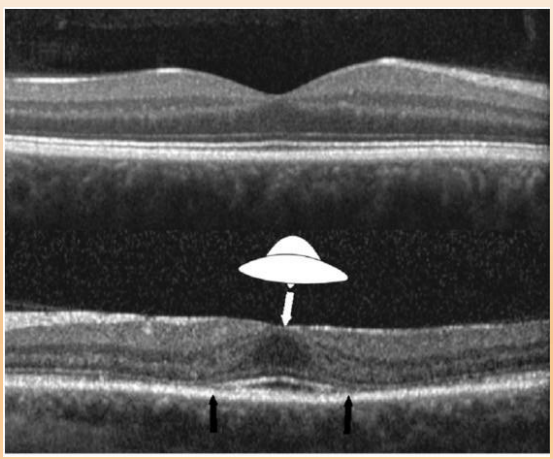
Ancillary Testing: Optical Coherence Tomography



https://www.researchgate.net/figure/Top-Normal-Spectralis-spectral-domain-optical-coherence-tomography-SD-OCT-image-with_fig3_49602243
Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)

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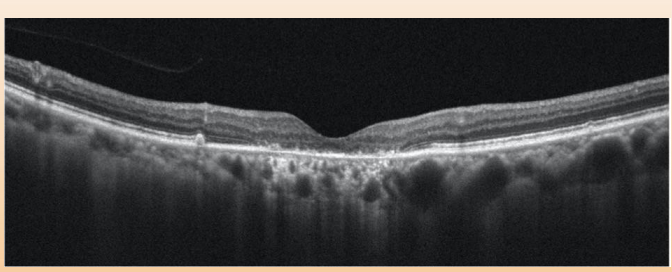
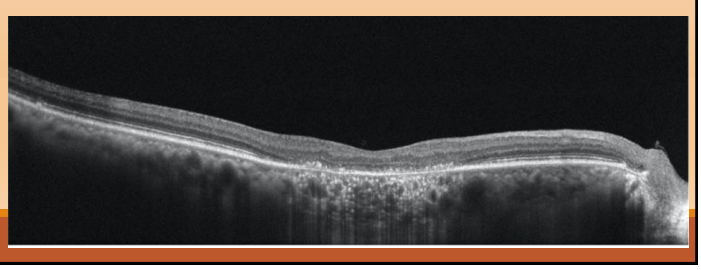
Ancillary Testing: This patient





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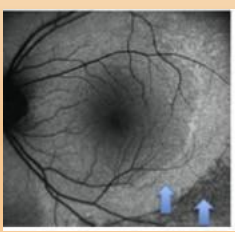
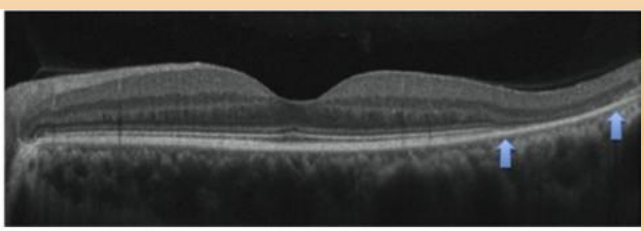
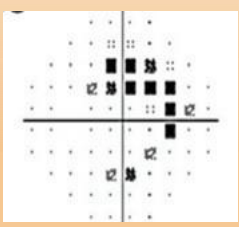
Toxicity Variation: Asians

Classic "bulls-eye" pattern of toxicity is infrequent in Asian patients; initial damage is seen in a more peripheral extramacular distribution near the arcades.







Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)

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Clinical Pearl

Maculopathy is NOT reversible and damage may progress even after drug cessation. Once "bull's eye" is seen… we are too late!!!

However, when retinopathy is identified early, there is only mild and limited progression after discontinuing the medication.

SCREENING ENABLES EARLY DETECTION!!

Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision)

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Mystery Case

WHAT COULD THIS BE?

21

What type of bilateral disease is this?

a) AMD
b) Macular Dystrophy
c) Bull's Eye Maculopathy
d) Macular Hole
e) Something else?

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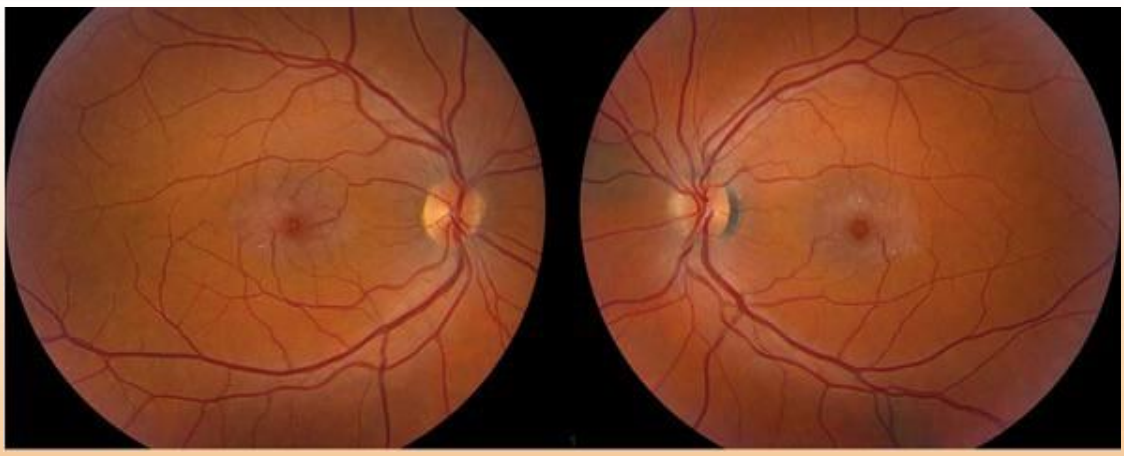

What type of bilateral disease is this?

a) AMD
b) Macular Dystrophy
c) Bull's Eye Maculopathy
d) Macular Hole
e) Something else?

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Macular Telangiectasia 2

GUIDELINES AND SCREENING RECOMMENDATIONS

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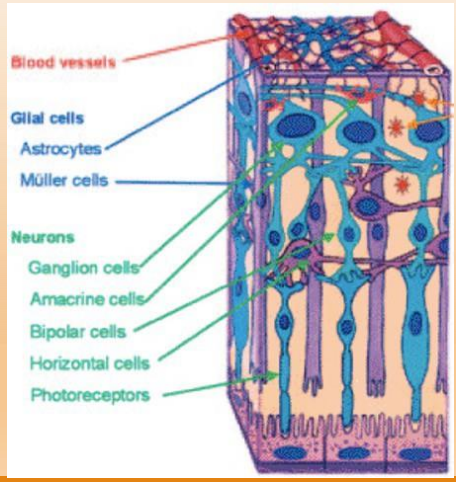
What is Macular Telangiectasia 2?

Proposed hypothesis: Neuro-degenerative disorder

1. *Originates from abnormality in the Muller Cells*
2. *Integrity of retinal vasculature affected*



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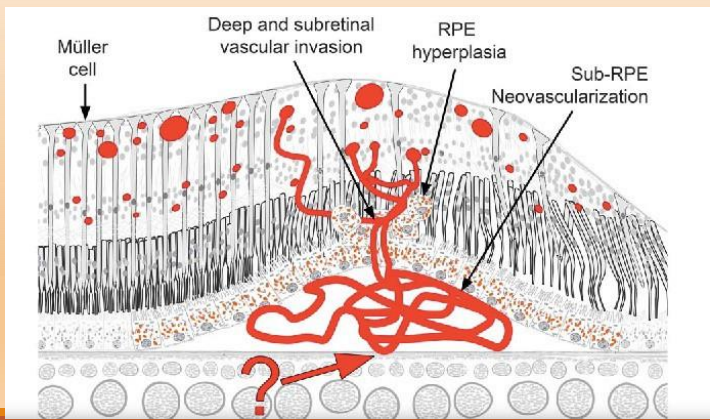
What is Macular Telangiectasia 2?

Proposed hypothesis: Neurodegenerative disorder



3. *Muller cell depletion: telangiectasia and vessel dilation*
4. *Photoreceptor death*
5. *Weakening of blood retinal barrier*

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Let's Learn More About It…

- Bilateral, acquired
- Idiopathic
- Occurs in either sex
- 5th-6th decade of life
- Often Asymmetric

- Slow loss of vision
- Distorted vision
- Blurriness
- Variable scotoma

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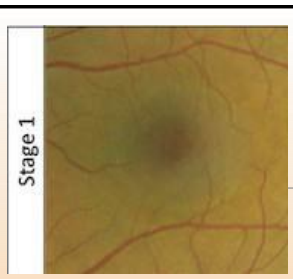
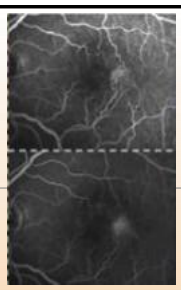
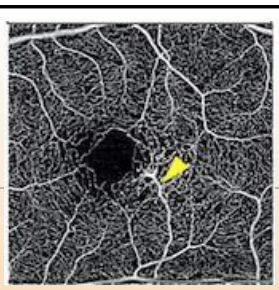
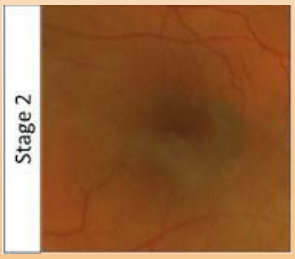


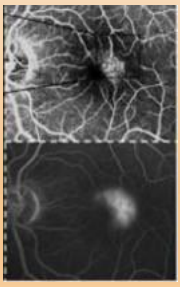


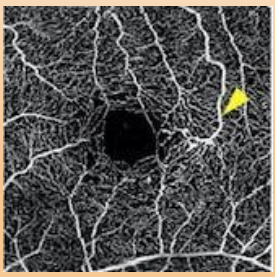


Lack of fundoscopic findings; leakage on FA

Right angle (dilated) venules visible on OCTA before fundus exam







Loss of retinal transparency, Crystalline deposits

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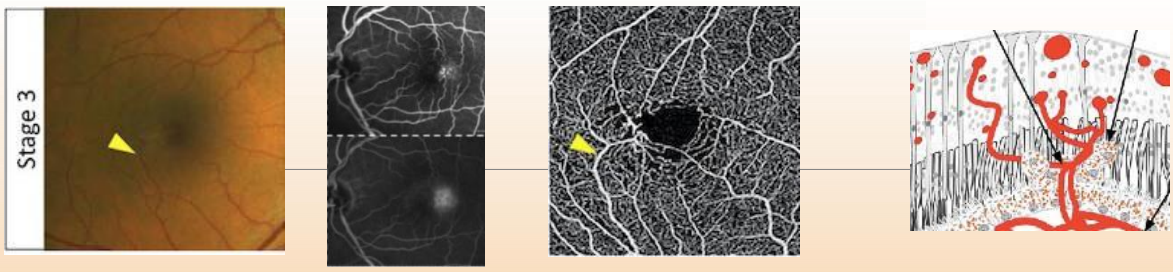
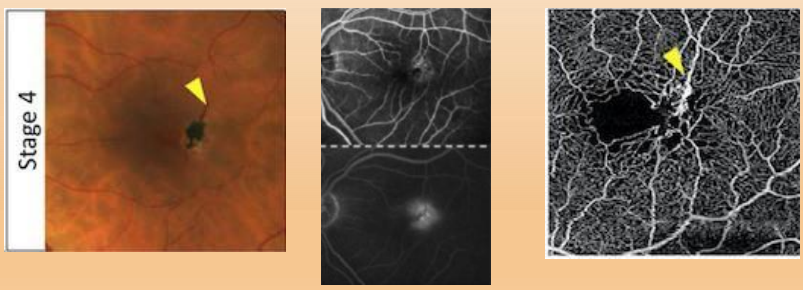
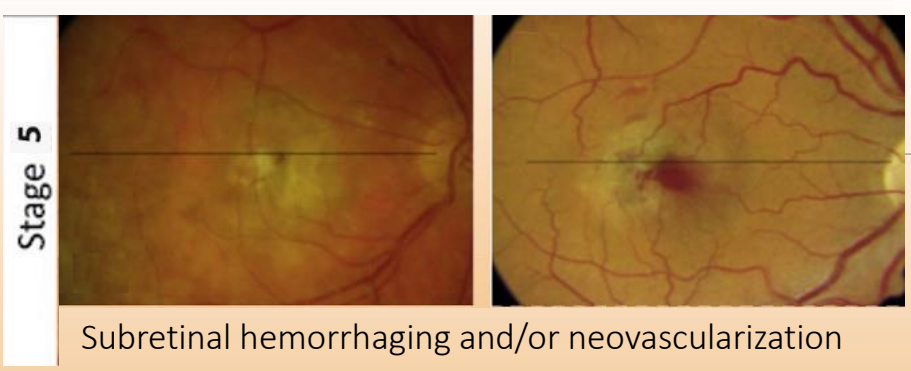


Occurrence of prominent, blunted vessels (dive into deeper retinal layers at a ”right angle”)

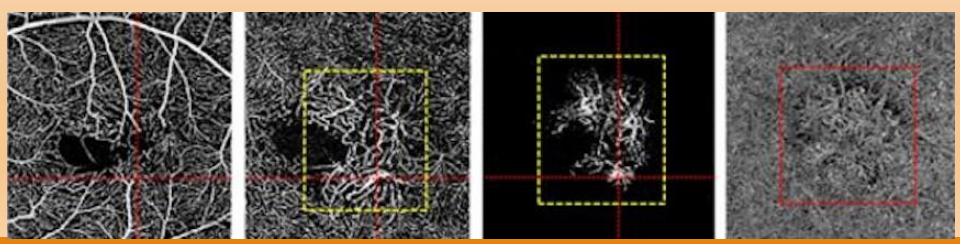


Intraretinal pigment migration

29



Subretinal hemorrhaging and/or neovascularization



Neovascular complex in choroid

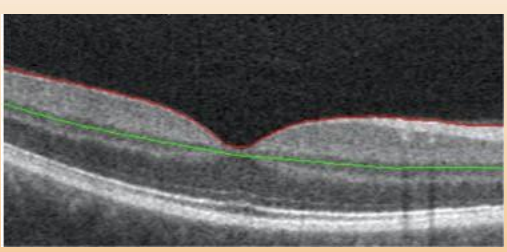
30

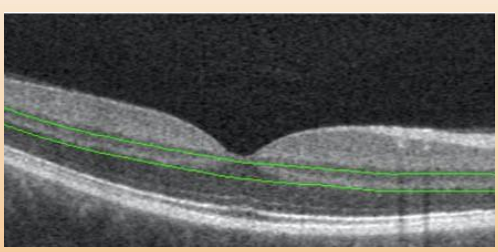
Management

- Non-neovascular: No proven treatment
- Neovascular
  - Anti-VEGF: Mainstay
  - Transpupillary therapy and PDT
  - ?Neuro-protective agents- Ciliary neurotrophic factor Decreased EZ loss, Increased macular thickness

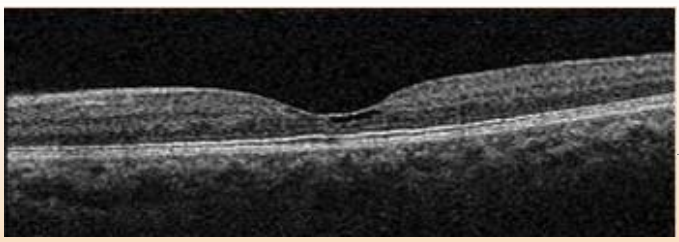
31

OCT: Normal





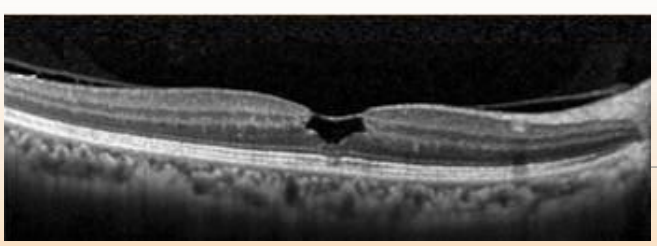
32

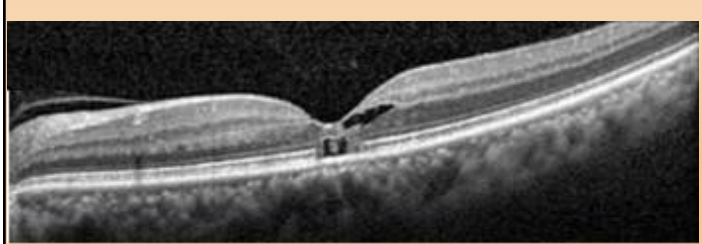


Hypo-reflective cavities in inner retina

"ILM DRAPE"

33

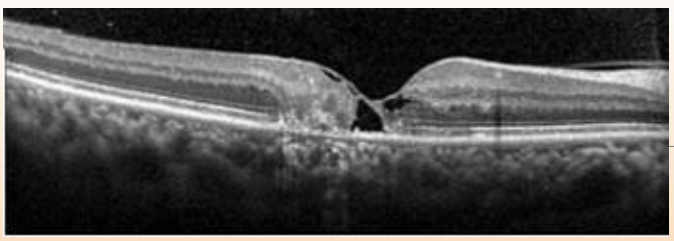




ENLARGEMENT OF ILM DRAPE

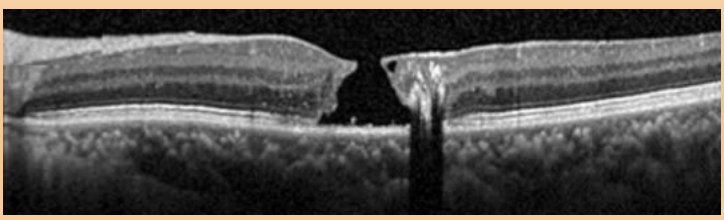
INVOLVEMENT OF OUTER RETINA; IS/OS

34



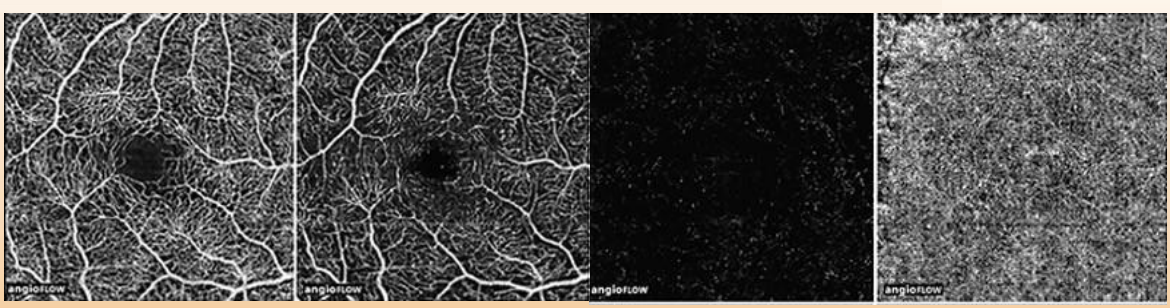
CAVITY SPANS TO OUTER RETINA

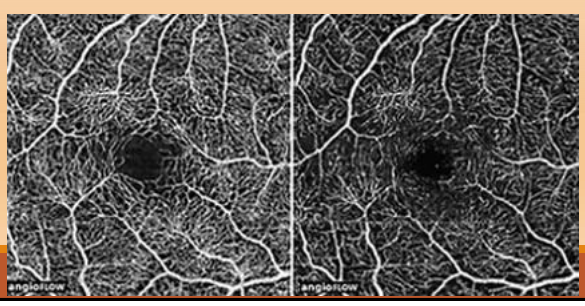
MACULAR HOLE FORMATION

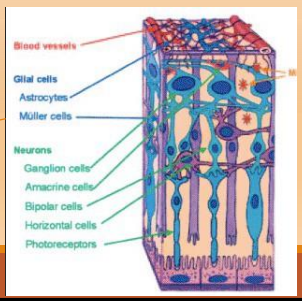


35

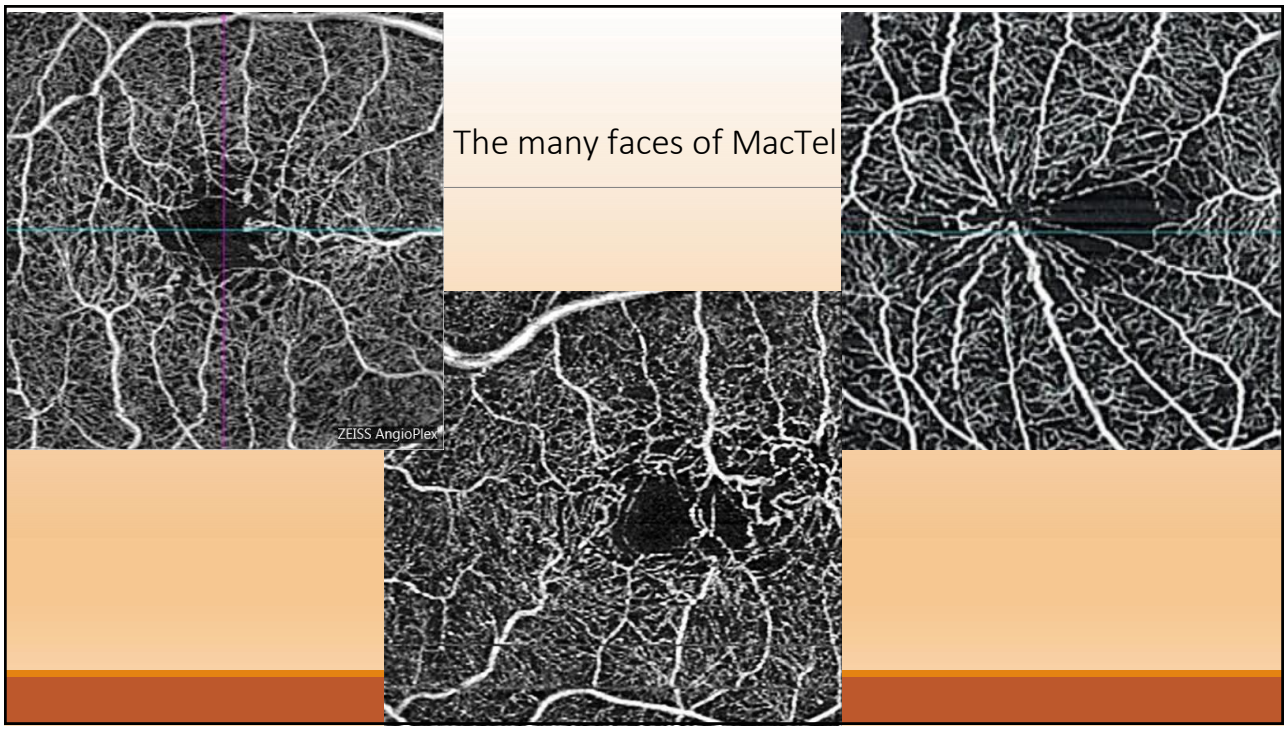
Normal OCT Angiography





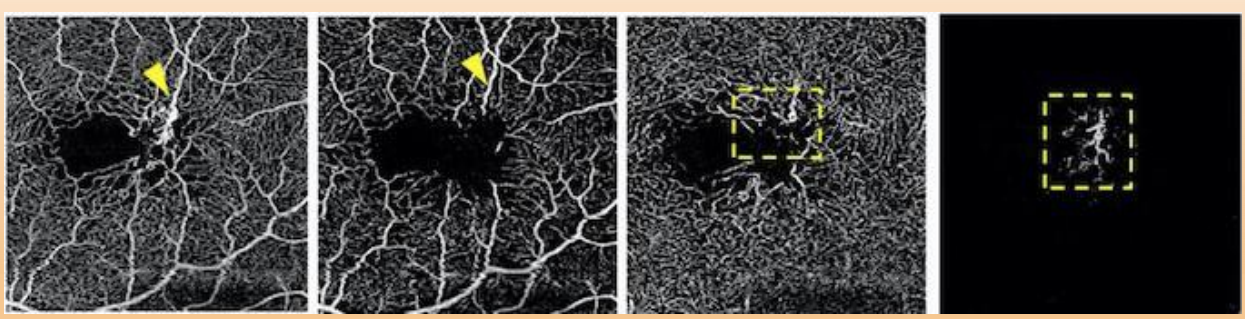


36



37

Right Angled Venules: yellow arrowheads.
Anastomoses: yellow-dotted box in the deep and avascular layer, respectively.



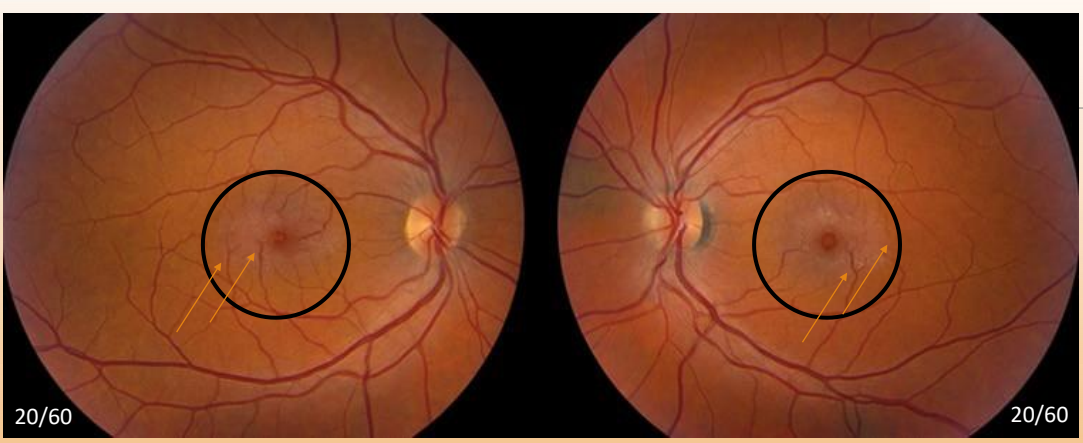
38

Back to our Case: 43-year-old Male

"My vision has decreased, and I see black in the center of my vision… 10 years… getting worse!!"

39

What do we see?



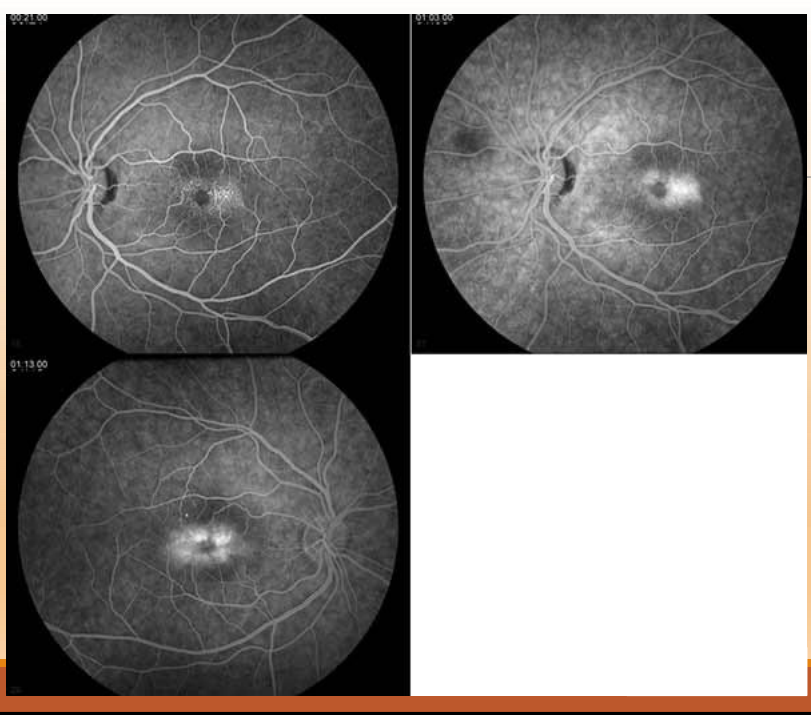
1. Loss of transparency, crystals
2. Right Angled Venules
3. Telangiectatic vessels more prominent temporally
4. All of the above

40

What do we see?

1. Loss of transparency, crystals
2. Right Angled Venules
3. Telangiectatic vessels more prominent temporally
4. All of the above

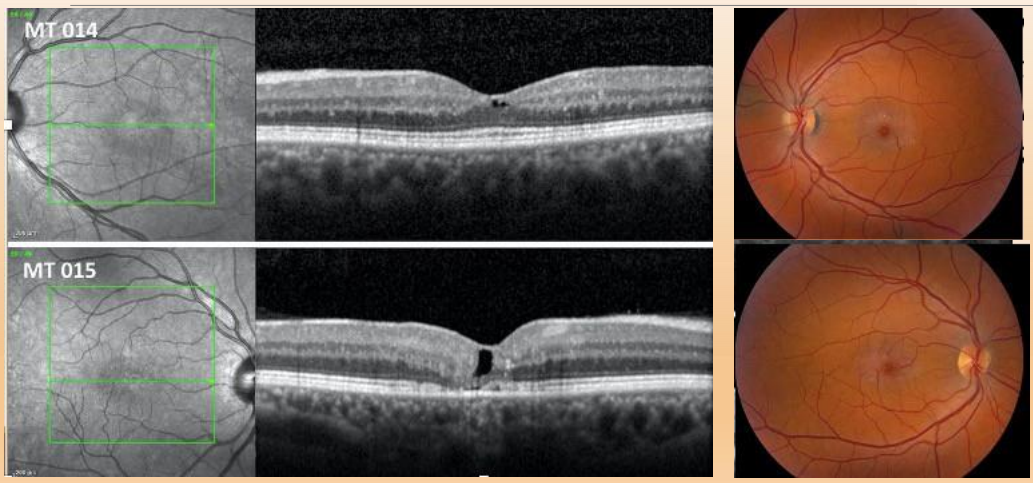
41



Fluorescein angiography demonstrates telangiectatic vessels surrounding the fovea more prominent temporally with leakage OU

42

SD-OCT demonstrates small foveal cystoid cavities in both the right and left eyes; OS>OD



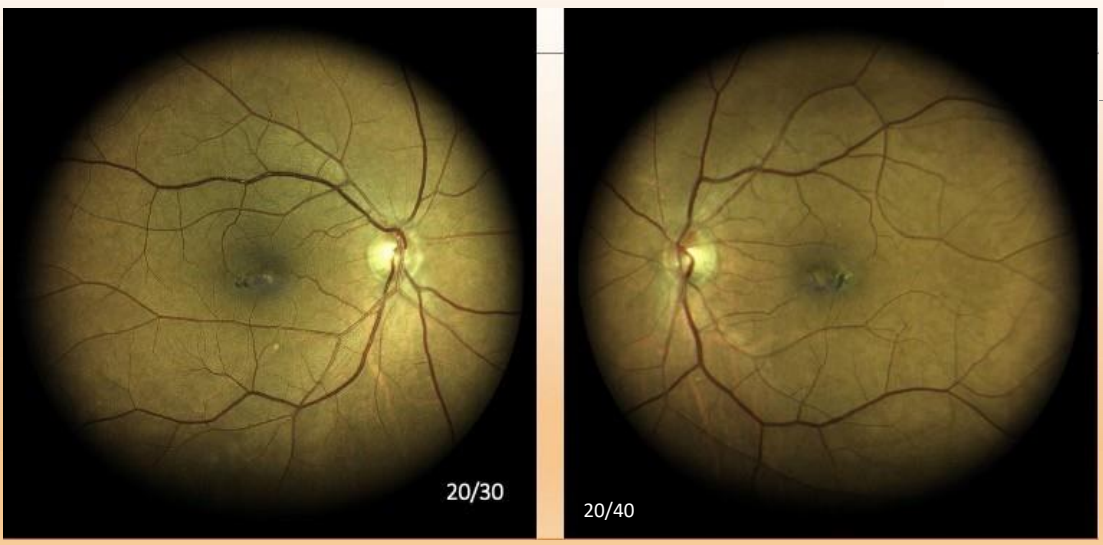
43

70-year-old Hispanic female

- Presents for a second opinion
- Told she had dry AMD OU
- H/O Diabetes, Hypertension, Hypercholesterolemia

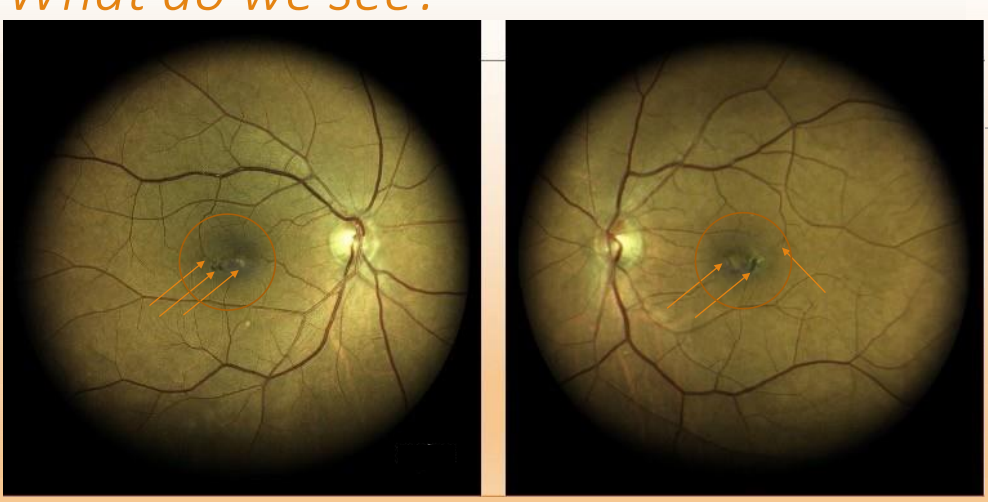
"In the last two weeks, I noticed in my left eye a blurry area on that grid that my last doctor gave me…It's almost like a veil"

44



45

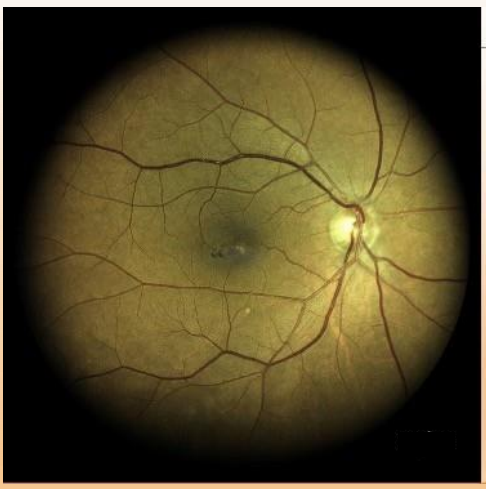
What do we see?

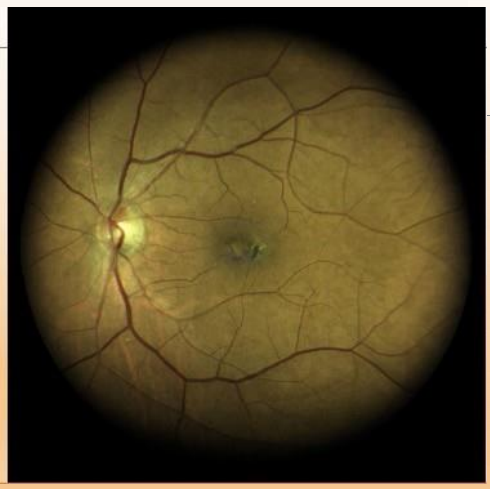


1. Perifoveal telangiectatic vessels
2. Crystalline deposits
3. Pigment plaques
4. RPE atrophy

46

What do we see?

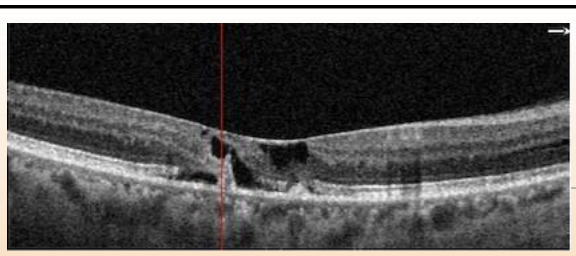




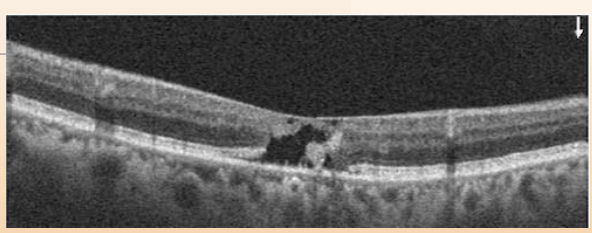
1. Perifoveal telangiectatic vessels
2. Crystalline deposits
3. Pigment plaques
4. RPE atrophy

ALL!!!

47

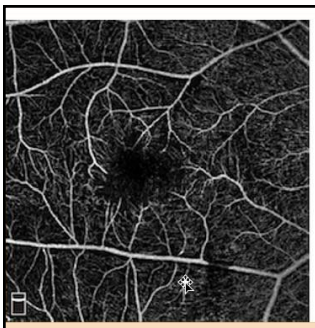


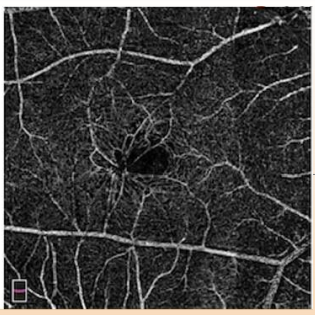
OD

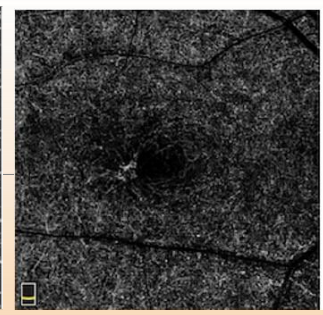


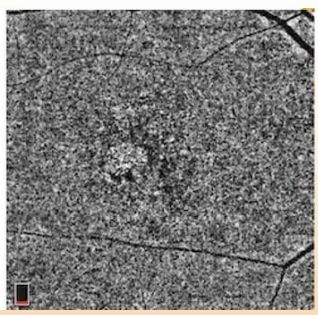
- *ILM drape*
- *Collapse of outer retina*
- *Disruption of EZ*
- *Large hypo-reflective cavity spanning from inner retina to outer retina above and below ELM*

48


Superficial Plexus


Deep Plexus

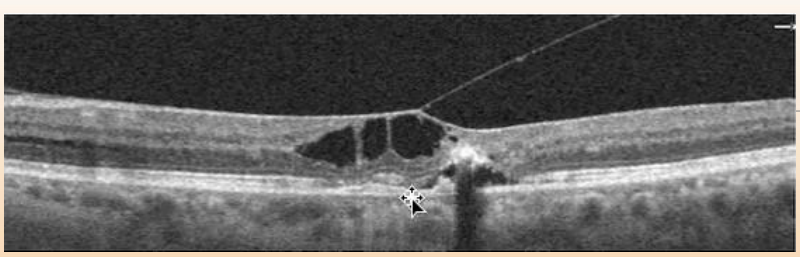

Avascular


Choroid

Juxtafoveal capillary telangiectasia

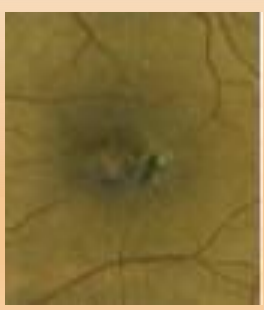
Early retinal-retinal anastomoses

49

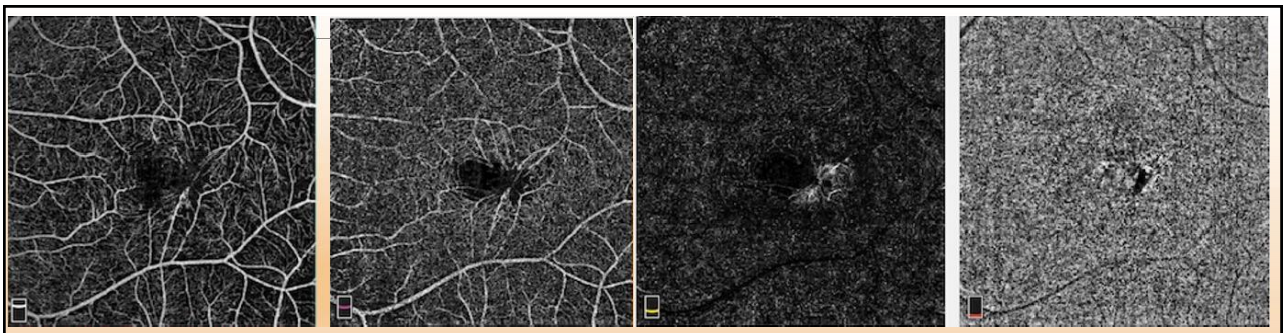


OS

- *ILM drape*
- *Collapse of outer retina*
- *Disruption of EZ*
- *Large hypo-reflective cavity spanning from inner retina to outer retina above and below ELM*
- *Intraretinal hyper-reflective foci*



50



Superficial Plexus | Deep Plexus | Avascular | Choroid

Right angled venules parafoveally

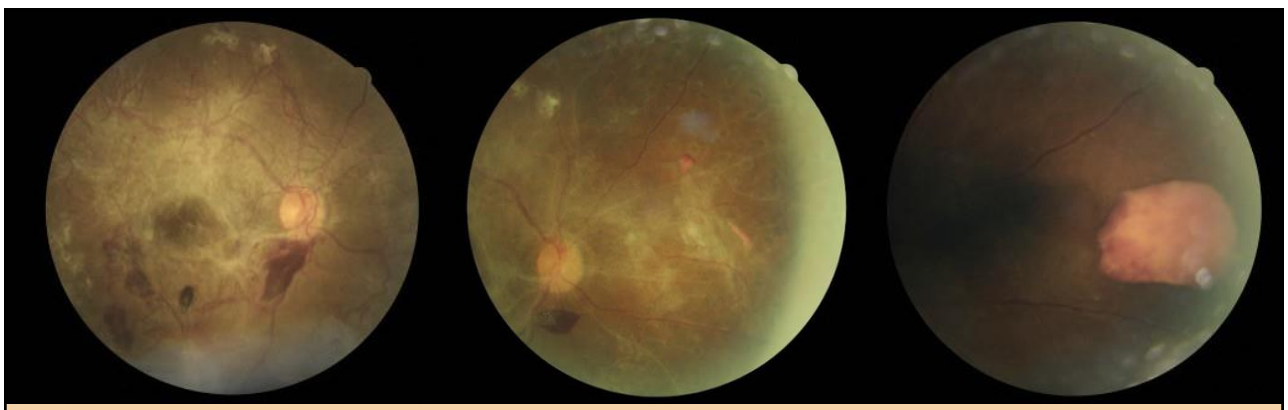
Retinal-Retinal anastomoses

51

Mystery Case #2

WHAT COULD THIS BE?

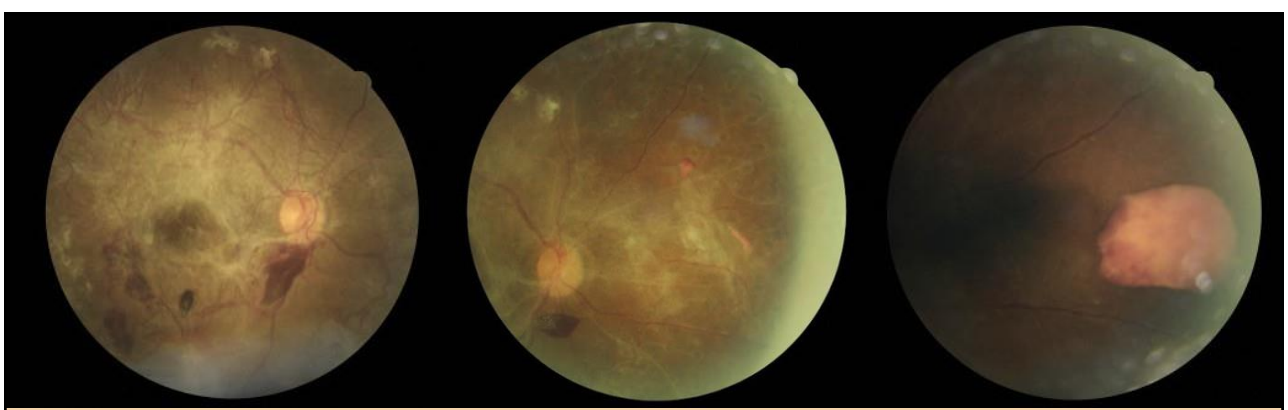
52



What are possible diagnoses?

1. Old retinal vascular occlusion
2. Retinal vasculitis
3. Diabetic Retinopathy
4. Something else??

53



What are possible diagnoses?

1. Old retinal vascular occlusion
2. Retinal vasculitis
3. Diabetic Retinopathy
4. Something else??

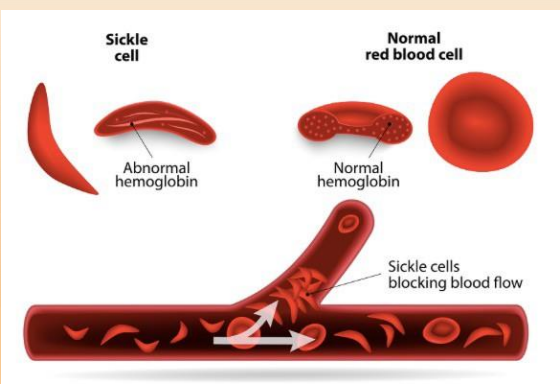
54

Sickle Cell Retinopathy

GUIDELINES AND SCREENING RECOMMENDATIONS

55

Sickle Cell Retinopathy: Epidemiology



- Genetic
- Compromise of normal retinal circulation by abnormal hemoglobin (sickled)
- Results in retinal hypoxia which stimulates abnormal vascular growth

56

Ocular Findings: Non-Proliferative

- *Signs*
  - Salmon Patch Hemorrhages

Ischemia causes weakening of vessel wall with rupture and resultant hemorrhage

57

Ocular Findings: Non-Proliferative

- *Signs*
  - Black Sunburst lesions

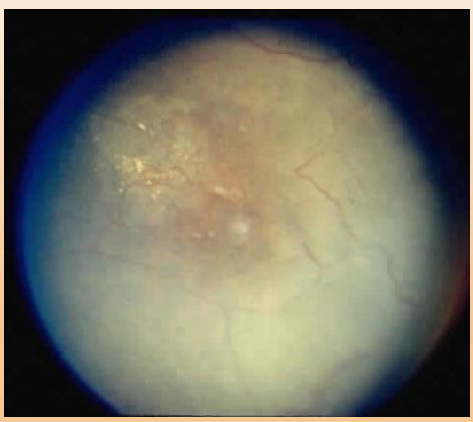
Sequelae of salmon patches caused by proliferation and migration of the RPE

58

Ocular Findings: Non-Proliferative

- *Signs*
  - Refractile (iridescent) deposits/spots

Intraretinal blood breakdown products



59

Clinical Pearl: Non-Proliferative to Proliferative

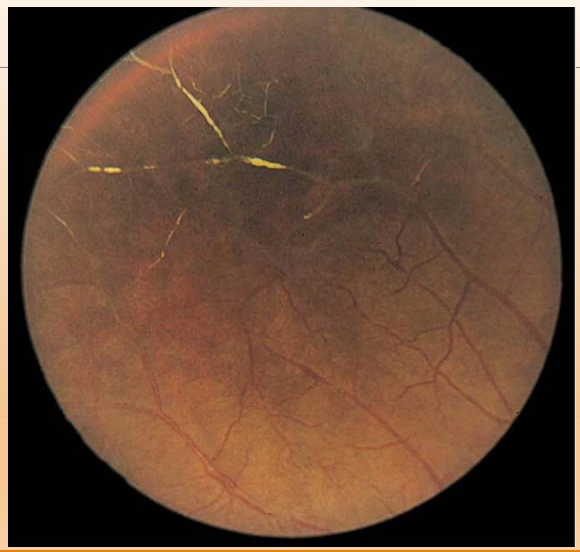
The retinal capillary network in the retinal periphery thins to a single layer near the ora. A similar thinning occurs near the fovea. These are the two areas most susceptible to vascular occlusions.

http://www.oculist.net/downaton502/prof/ebook/duanes/pages/v3/ch017/020f.html

60

Ocular Findings: Proliferative

- *Stage 1*
  - Peripheral arteriolar occlusion



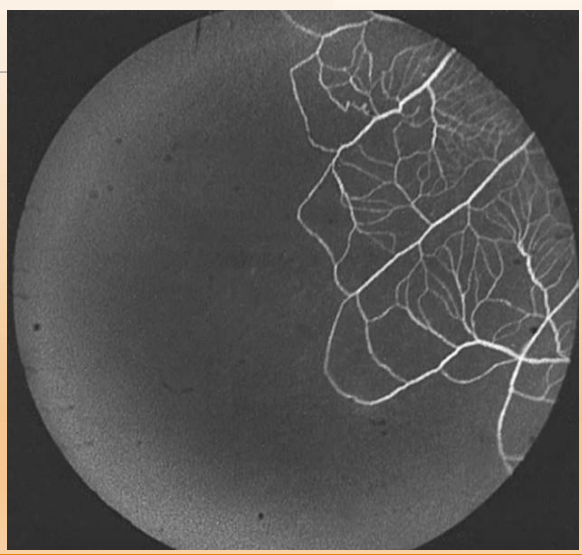
retinaatals

61

Ocular Findings: Proliferative

- *Stage 2*
  - Peripheral arteriolar-venular anastomosis

Reduction in blood flow results in anastomosis at the border of perfused and non-perfused retina

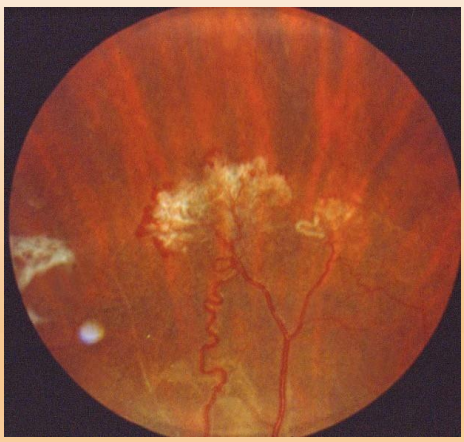


62

Ocular Findings: Proliferative

- *Stage 3*
  - Neovascularization

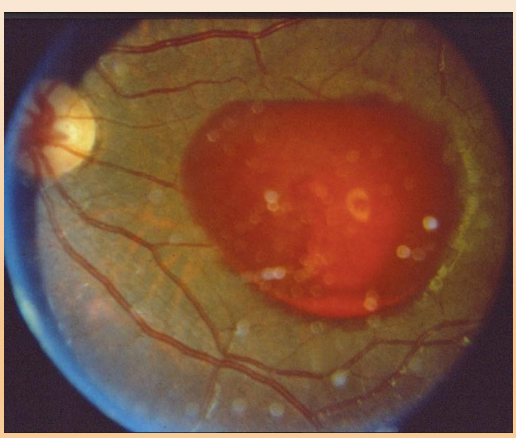
Occur near areas of arterio-venous anastomoses



63

Ocular Findings: Proliferative

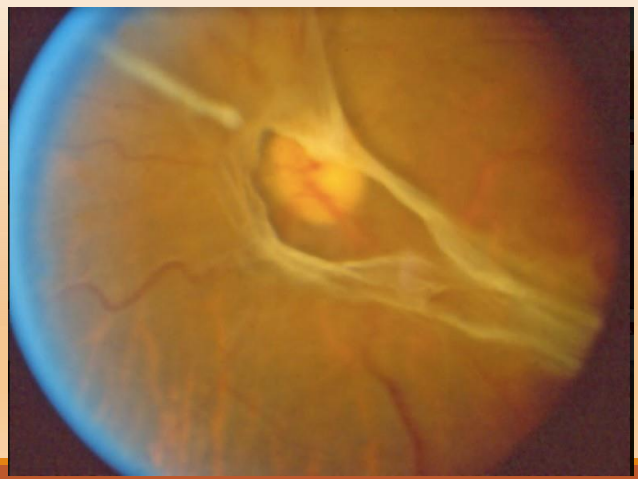
- *Stage 4*
  - Vitreous hemorrhage



64

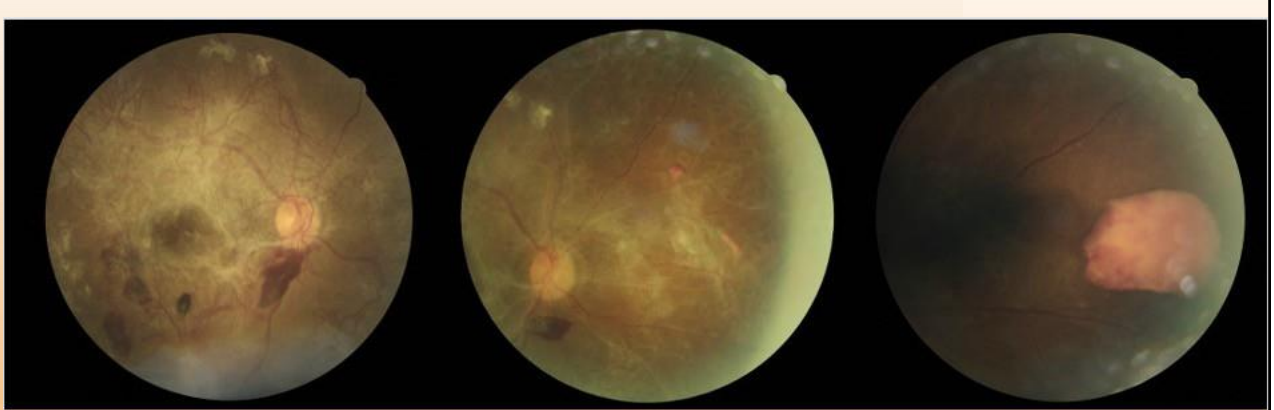
Ocular Findings: Proliferative

- *Stage 5*
  - Retinal Detachment



65

Back to our patient… 60 y/o BF



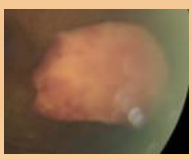
History of DM and Sickle Cell Trait

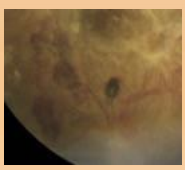
"I'm blind doc… Something is wrong with my vision"

66

What are the clinical findings?

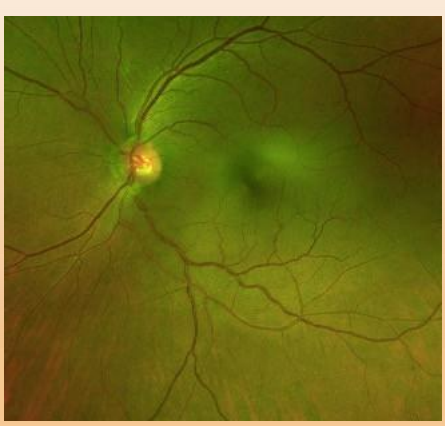
Do We See??
*Salmon Patch hemorrhages
*Arterio-Venous Anastomoses
*Neovascularization



67

Meet Amy: A 45-year-old AA Female
Sickle Cell Anemia (SC Disease)



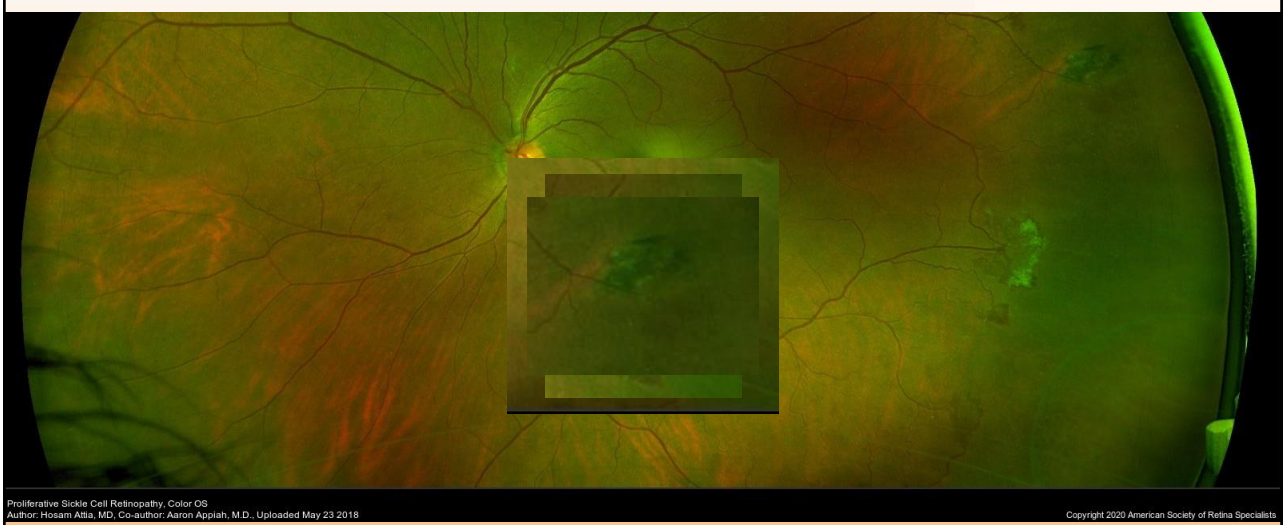
"No ocular complaints; just saw internist.. GREAT EXAM!"

Arteriolar attenuation,
mild venous tortuosity…
but NO Sickle Cell!!

https://imagebank.asrs.org/file/28238/proliferative-sickle-cell-retinopathy-color-os

68

What did we miss???

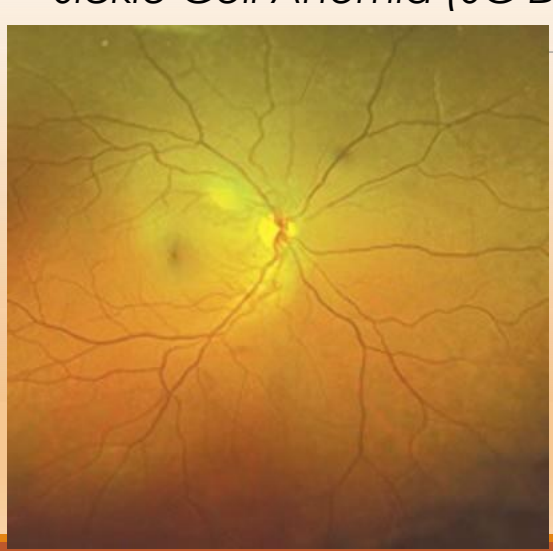


Proliferative Sickle Cell Retinopathy, Color OS
Author: Hosam Attia, MD, Co-author: Aaron Appiah, M.D., Uploaded May 23 2018

- Peripheral arterio-venous anastomoses
- Multiple, small NVE
- Sunburst

69

Meet Marge: A 34-year-old AA Female
Sickle Cell Anemia (SC Disease)

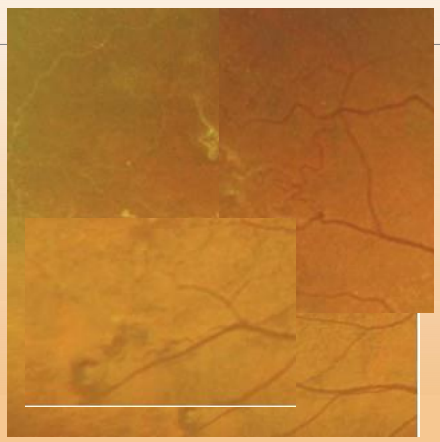


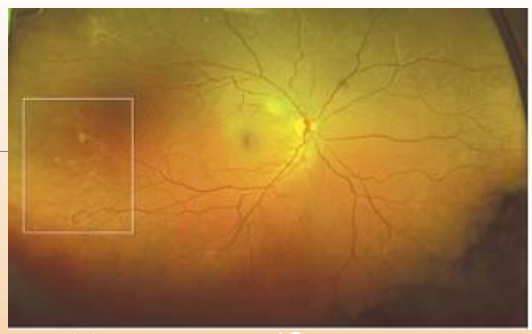
What would you do?
Management?
Follow-Up?

https://journals-lww-com.ezproxylocal.library.nova.edu/retinajournal/Fulltext/2011/04000/DETECTION_AND_MONITORING_OF_SICKLE_CELL.16.aspx

70

What about now???





Management?
Follow-Up?

https://journals-lww-com.ezproxylocal.library.nova.edu/retinajournal/Fulltext/2011/04000/DETECTION_AND_MONITORING_OF_SICKLE_CELL.16.aspx

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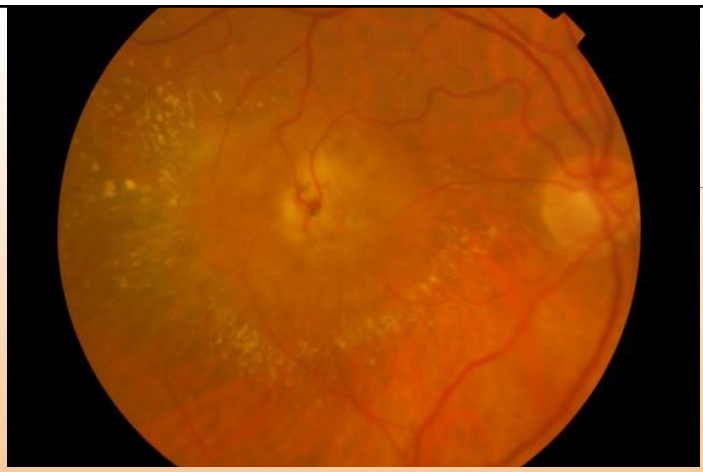
Mystery Case #3

WHAT COULD THIS BE?

72



Could this be…
1. AMD
2. Diabetic Retinopathy
3. Hypertensive Retinopathy
4. Others??

73

Retinal Angiomatous Proliferation (RAP)

GUIDELINES AND SCREENING RECOMMENDATIONS

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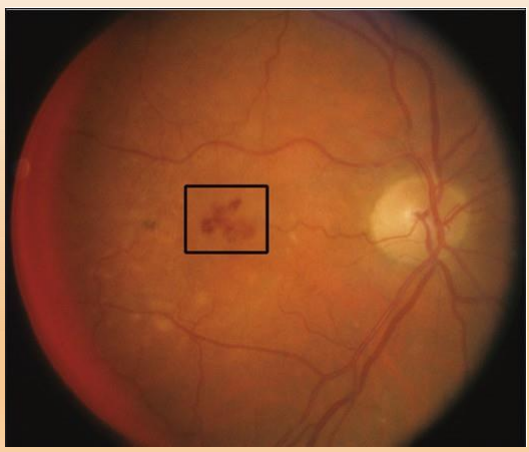
Retinal Angiomatous Proliferation

- Variant of exudative age-related macular degeneration
- Occurs in **older age group** than AMD
- Type 3 Neovascularization **(intra-retinal)**



75

Retinal Angiomatous Proliferation

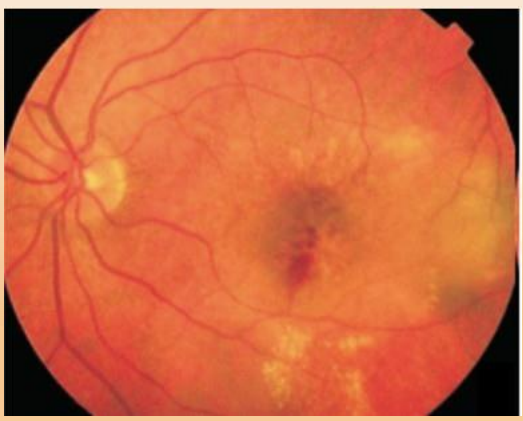
Stage 1: Intraretinal Proliferation

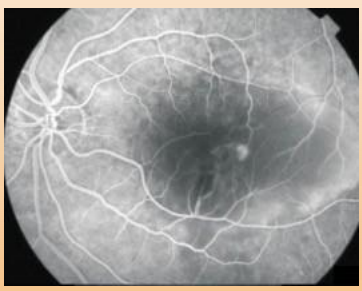
What might you see clinically?

Hemorrhages
Edema
Exudate

76

Stage 1: Intraretinal Proliferation



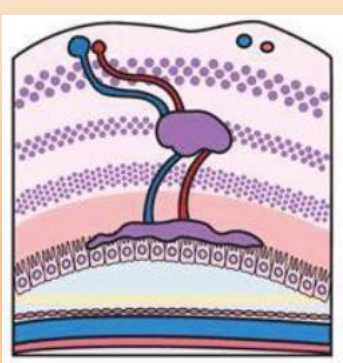


https://jamanetwork.com/journals/jamaophthalmology/fullarticle/420...
https://www.researchgate.net/figure/In-retinal-angiomatous-pro...

77

Retinal Angiomatous Proliferation

Stage 2: Subretinal capillary extension

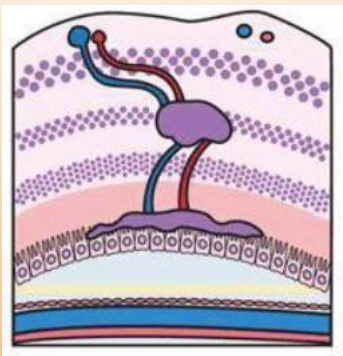


What might you see clinically?

Neurosensory detachment
Serous PED

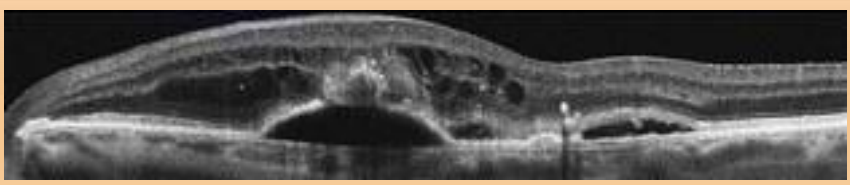
78

Stage 2: Subretinal capillary extension



What might you see clinically?

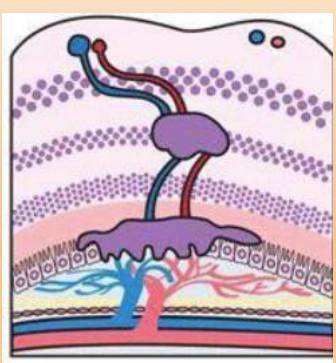
Neurosensory detachment
Serous PED



79

Retinal Angiomatous Proliferation

Stage 3: Retinal-choroidal anastomoses

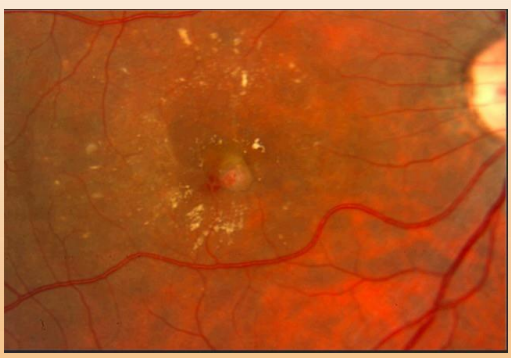


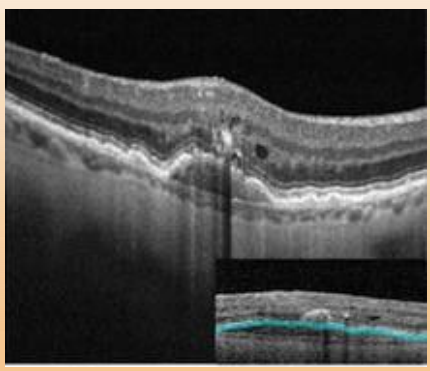
What might you see clinically?

Vascularized PED
CNVM

80

Stage 3: Retinal-choroidal anastomoses

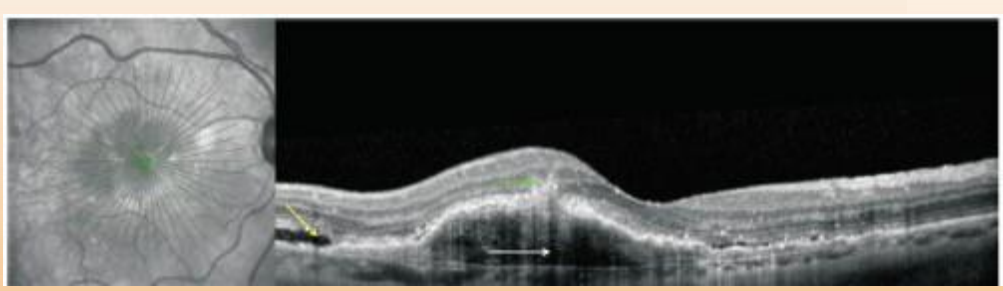


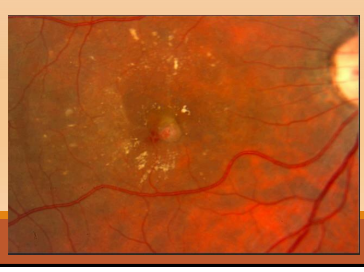


http://imagebank.asrs.org/file/26943/retinal-angiomatous-proliferation

81

Stage 3: Retinal-choroidal anastomoses

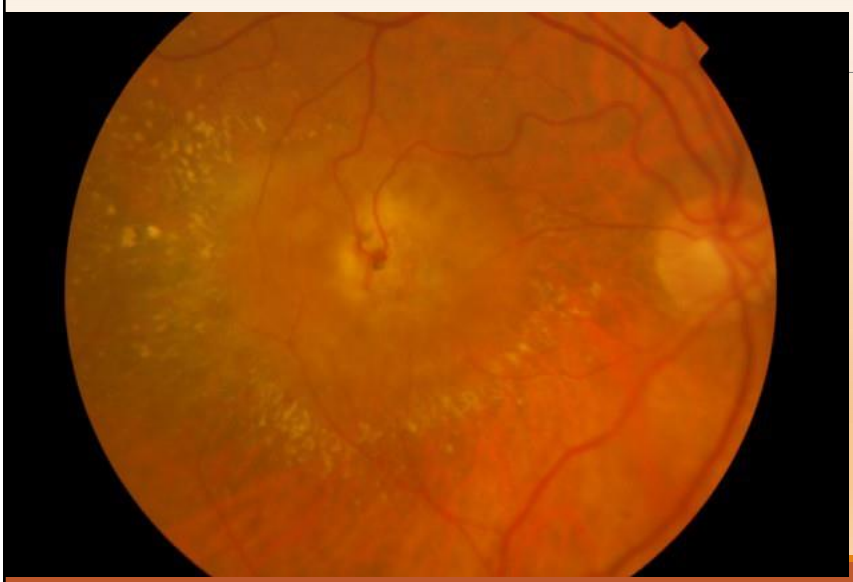




https://amdbook.org/content/neovascular-phenotypesrap-retinal-angiomatous-proliferation

82

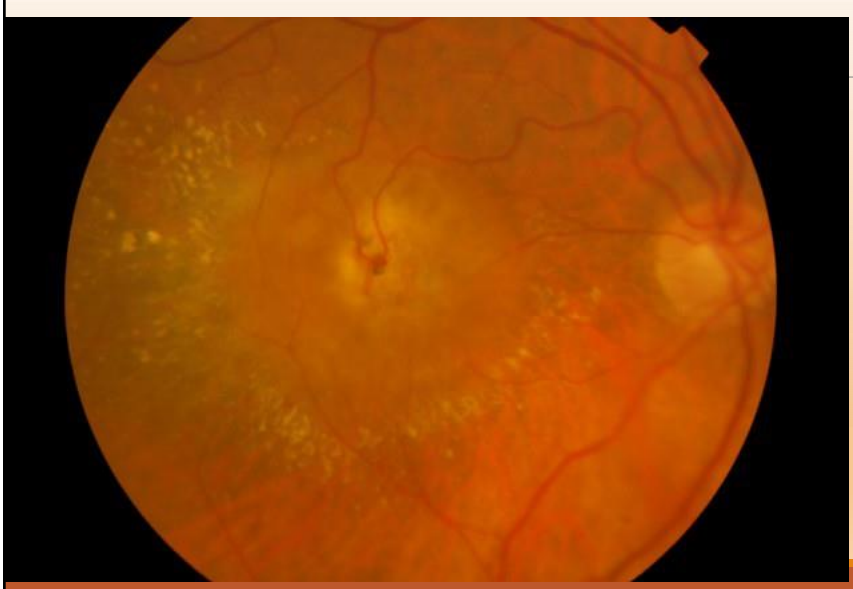
Back to our patient… 89 y/o female



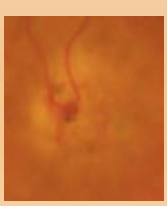
Told in past that she had AMD

83

What are the clinical findings?

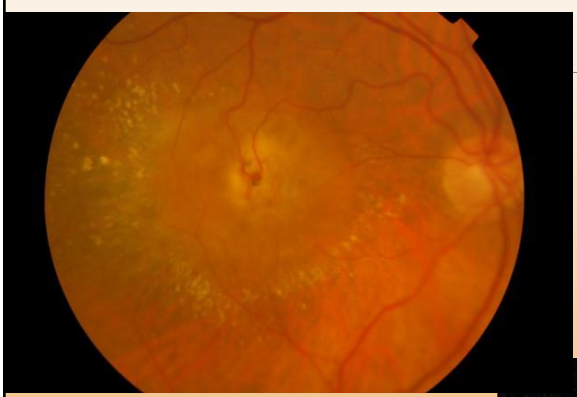


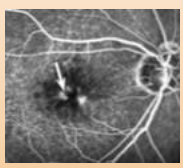
- Exudate
- Localized neurosensory detachment
- Abnormal vasculature over macula

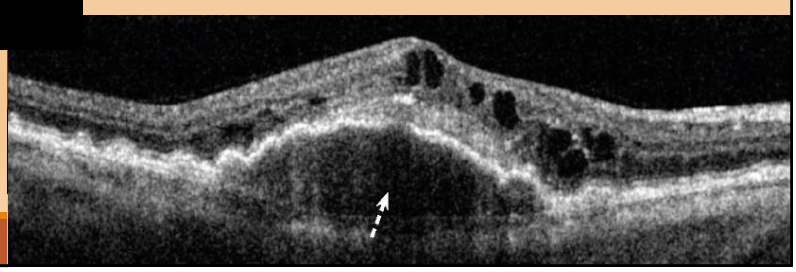


84

What is the abnormal vasculature?







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Questions: rjulie@nova.edu

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Ocular Disease: Part I

Presented by MBKU | SCCO

Diseases of the Vitreomacular Interface

Presented by Julie Rodman, OD, MSc

Live CE Webinar | Day One | AM Session

Saturday | March 20, 2021 | 10:00 a.m. - 10:55 a.m.

Marshall B.
KETCHUM UNIVERSITY
Southern California College of Optometry

Department of Continuing Education

ketchum.edu /ce | ce@ketchum.edu

Diseases of the Vitreoretinal Interface

Julie Rodman OD,MS,FAAO
Professor, Nova Southeastern University
College of Optometry

1

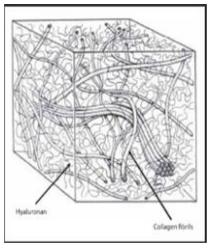
Disclosures:

- Optovue: Speaker, Consultant, Advisory Board
- Maculogix: Speaker, Consultant, Advisory Board

- There are no financial conflicts that will affect the content of this presentation

2

Anatomy of the Vitreous

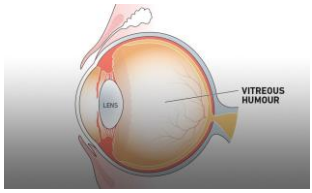


Physical Properties of the Vitreous:

- Volume of approximately 4 ml (adults)
- 80% volume of the eye

Composed of:

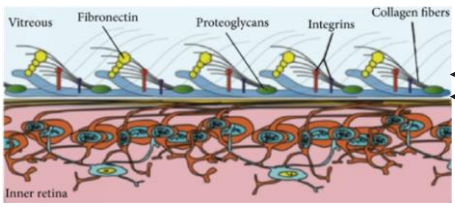
- 98% water
- 2% Solids
  - Proteins, hyaluronic acid, collagen fibrils



3

Anatomy of the vitreous

Densely packed collagen fibrils of the posterior vitreous cortex lie over the macula and are superficially inserted into the ILM by means of adhesion molecules (laminin, fibronectin, proteoglycans)



Posterior Vitreous Cortex
Inner Limiting Membrane of Retina

4

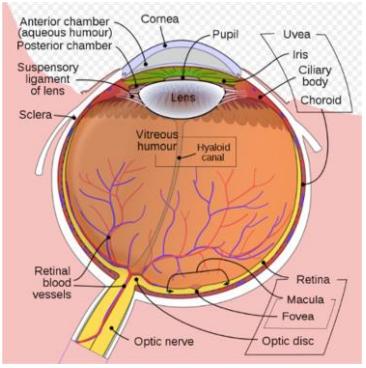
Anatomy of the vitreous

Points of attachment (Retina)

- Vitreous Base at Ora
- Macula
- Optic Nerve Head
- Retinal Blood Vessels

Points of attachment (Lens)

- Wieger's ligament



5

Strength of Vitreous Attachment

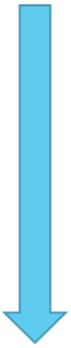
Vitreous Base at Ora

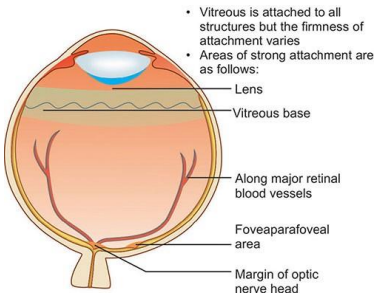
Posterior Lens

Optic Nerve Head

Macula

Retinal Blood Vessels

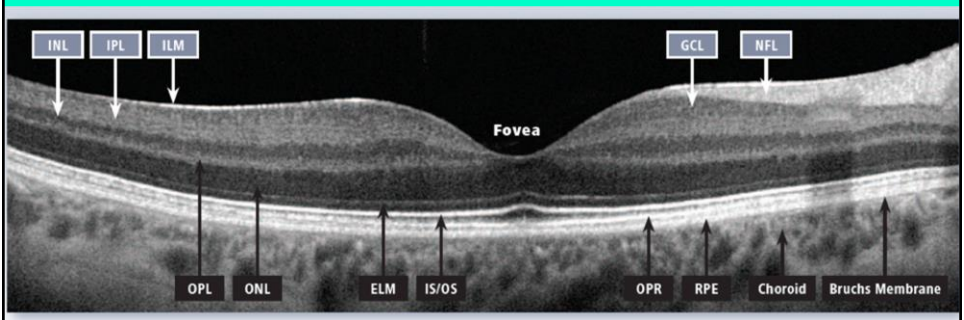




6

Vitreous: Friend or Foe?

7



ILM: Inner limiting membrane
IPL: Inner plexiform layer
INL: Inner nuclear layer
OPL: Outer plexiform layer
ONL: Outer nuclear layer

ELM: External limiting membrane
IS/OS: Junction of inner and outer photoreceptor segments
OPR: Outer segment PR/RPE complex

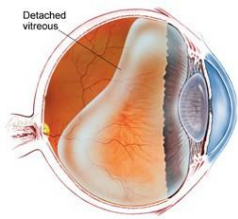
NFL: Nerve fiber layer
GCL: Ganglion cell layer
RPE: Retinal pigment epithelium + Bruch's Membrane

8

Aging of the Vitreous: Two Processes

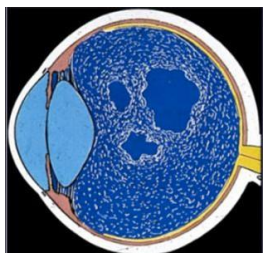
Synchysis (Liquefaction of the Vitreous Gel)

Syneresis (Contraction of the Vitreous Gel)

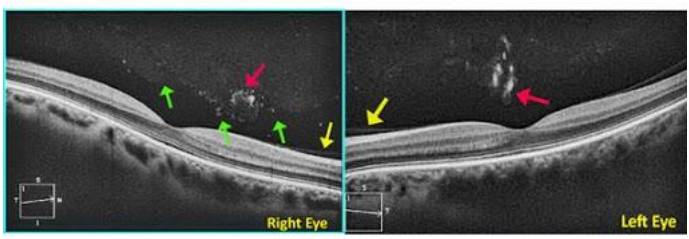


9

Aging of the Vitreous: Two Processes



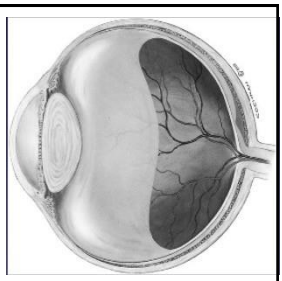
Synchysis (liquefaction of the vitreous gel)



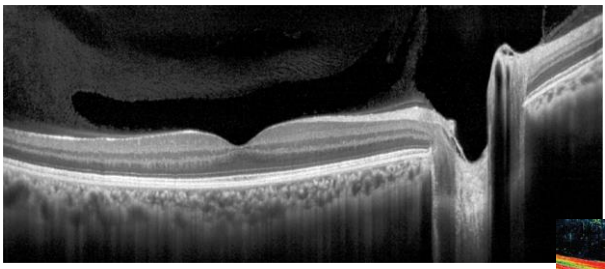
http://www.retinareference.com/diseases/e653d43e66671105/images/0296e8a61b/

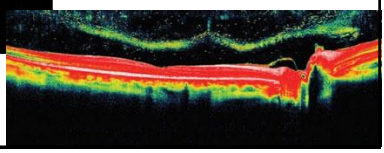
10

Aging of the Vitreous: Two Processes



Syneresis (Contraction of the Vitreous Gel)

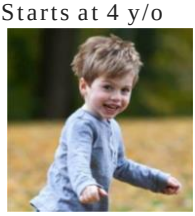




11

Fun Facts about Vitreous Liquefaction

Starts at 4 y/o



Late teens

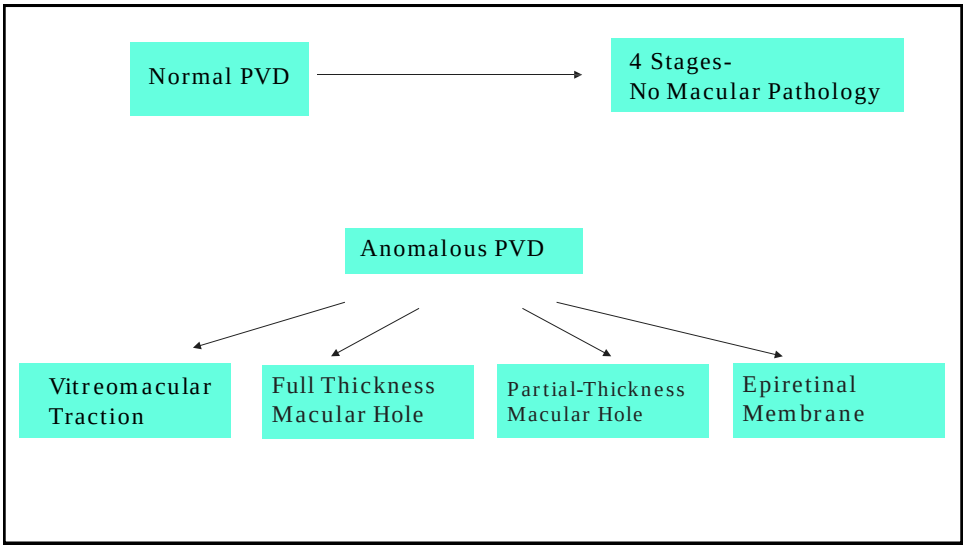
20% of vitreous is liquefied

70++

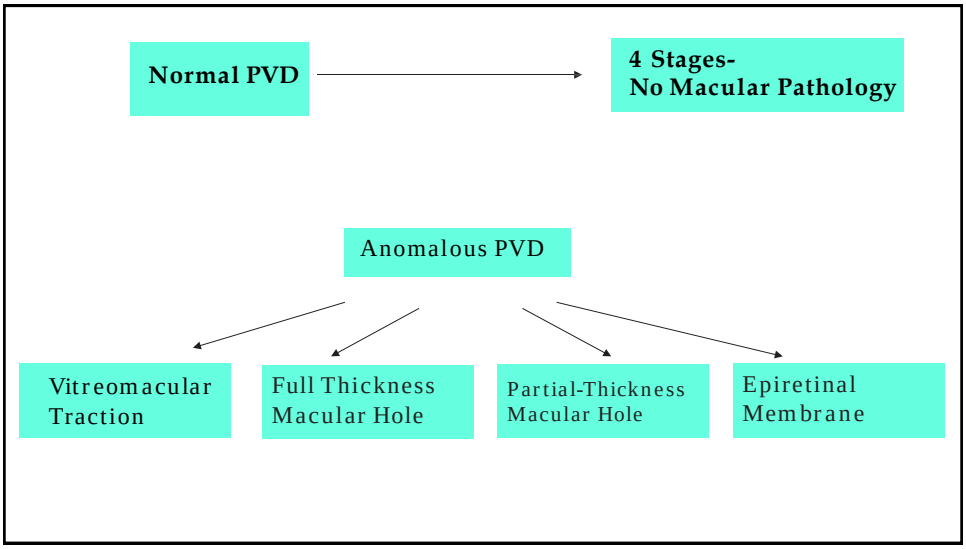
>50% liquefied

Liquefaction increases with age

12


Normal PVD
4 Stages-
No Macular Pathology
Anomalous PVD
Vitreomacular Traction
Full Thickness Macular Hole
Partial-Thickness Macular Hole
Epiretinal Membrane

13


Normal PVD
4 Stages-
No Macular Pathology
Anomalous PVD
Vitreomacular Traction
Full Thickness Macular Hole
Partial-Thickness Macular Hole
Epiretinal Membrane

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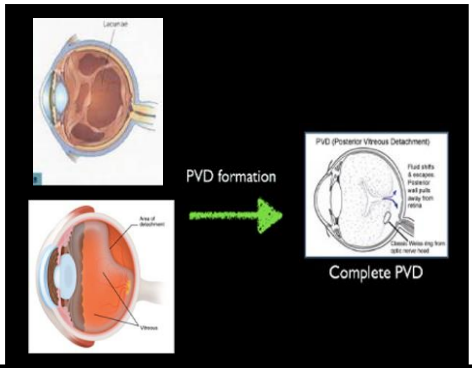
When the vitreous behaves…

Synchysis and Syneresis Occur Simultaneously

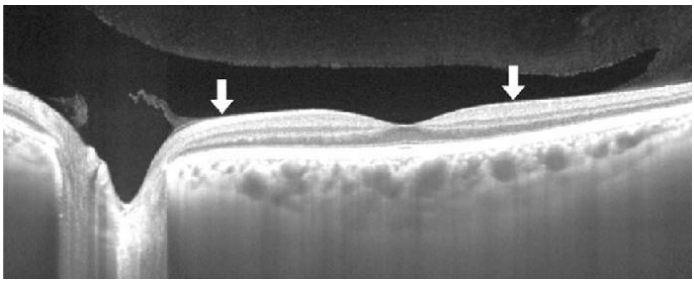


…A POSTERIOR VITREOUS DETACHMENT (PVD) OCCURS!

❖Insidious process over time (decades) with abrupt end stage

15

Stages of PVD: Stage 0



No PVD

Stage 0: visualization of the posterior cortex with no detached cortex

https://www.researchgate.net/figure/Representative-OCT-images-of-the-stages-of-posterior-vitreous-detachment-PVD-classified_fig1_328832211

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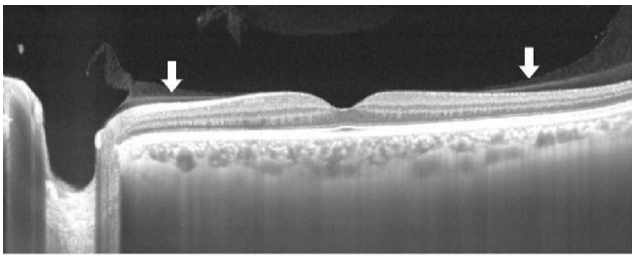
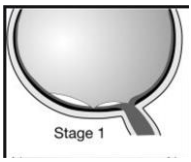
Stages of PVD: Stage 1





Perifoveal separation with adhesion of vitreous to fovea

Vitreomacular Adhesion represents a specific stage of partial vitreous detachment in the perifoveal area without retinal abnormalities (Stage 1)

https://www.researchgate.net/figure/Representative-OCT-images-of-the-stages-of-posterior-vitreous-detachment-PVD-classified_fig2_329832211

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How do we classify Vitreomacular Adhesion?

18

Two VMA subclassifications

Focal versus Broad

Isolated versus Concurrent

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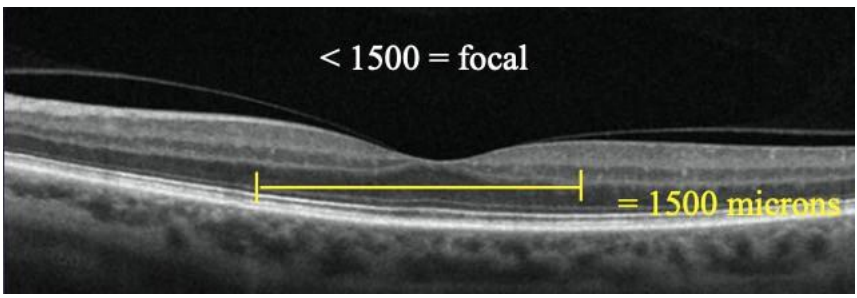
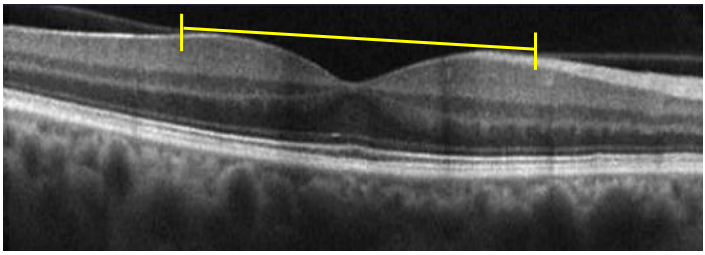
Focal VMA: <1500 *u*m



20

Broad VMA: >1500 *u*m



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Two VMA subclassifications

Focal versus Broad

Isolated versus Concurrent

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Isolated versus Concurrent

Isolated

- Normal macula
  - No other associated diseases or findings on OCT

Concurrent

- Associated with another posterior segment disease

Symptoms NOT part of classification!!

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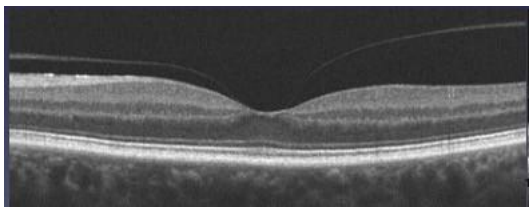
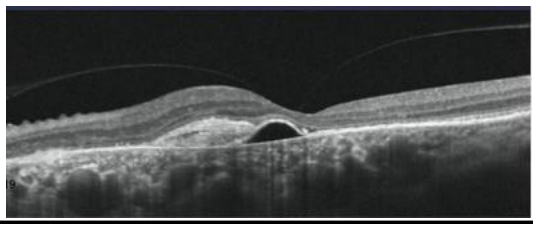
Isolated versus Concurrent

Isolated



Concurrent



24

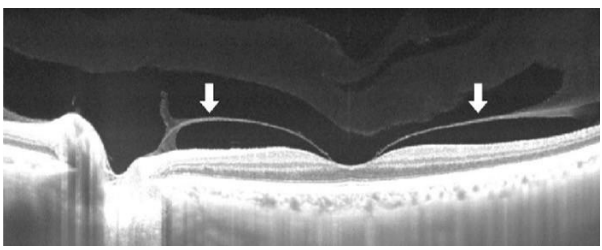
Management

Re-examine in 6 months with OCT….

But, if concurrent…. Re-consider!!

25

Stages of PVD: Stage 2

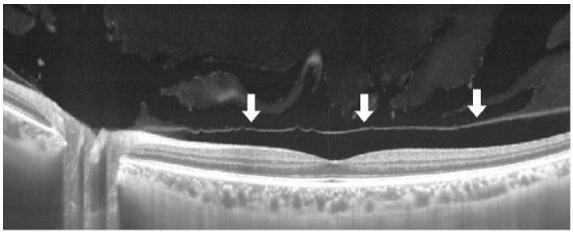


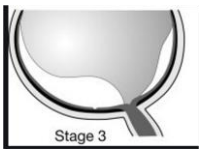
Separation of the vitreous from the macula occurs

https://www.researchgate.net/figure/Representative-OCT-images-of-the-stages-of-posterior-vitreous-detachment-PVD-classified_fig1_329883211

26

Stages of PVD: Stage 3



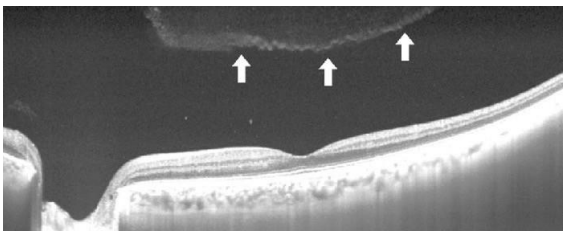


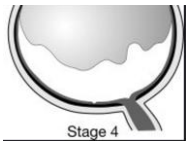
Vitreous has detached from macula with residual adhesion to the disc

https://www.researchgate.net/figure/Representative-OCT-images-of-the-stages-of-posterior-vitreous-detachment-PVD-classified_fig1_328832211

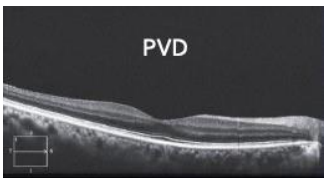
27

Stages of PVD: Stage 4





Complete PVD:
Detachment from ONH+macula



https://www.researchgate.net/figure/Representative-OCT-images-of-the-stages-of-posterior-vitreous-detachment-PVD-classified_fig1_328832211

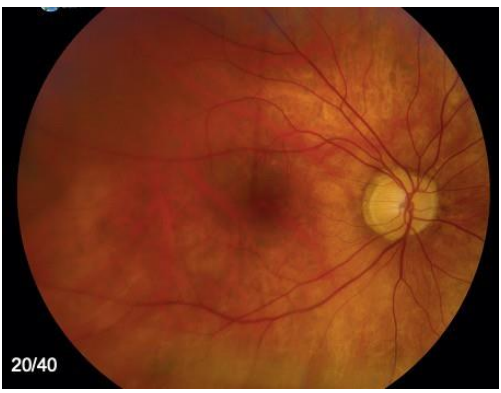
28

PVD Management:

Patients with *symptomatic* (floaters and/or photopsia) PVD without vitreous hemorrhage or peripheral retinal breaks *require no immediate treatment* but may be re-examined in *one to two weeks*, since some retinal breaks appear to develop days to weeks after the onset of symptoms.

29

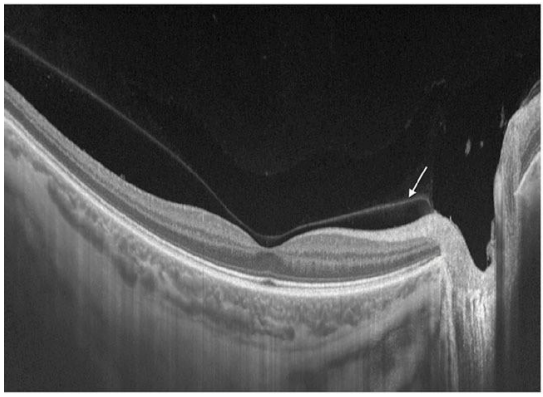
Case: 73 year-old female



"I feel a film of cobwebs over my right eye. It started a year ago but is progressively getting worse. I had cataract surgery in both eyes a few years ago.. Is it related??"

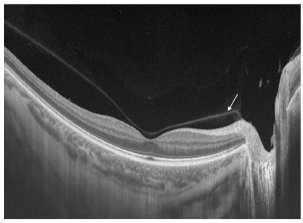
30

Case: 73 year-old female



31

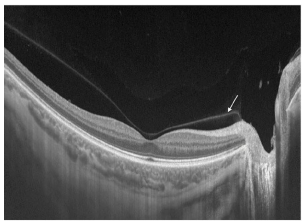
Case: 73 year-old female



The above OCT illustrates the following:
1. Complete PVD
2. There is partial detachment of the posterior hyaloid from the central fovea with persistent attachment at the ONH
3. There is vitreomacular traction resulting in obscuration of the foveal contour

32

Case: 73 year-old female



The above OCT illustrates the following:
1. Complete PVD
2.There is partial detachment of the posterior hyaloid from the central fovea with persistent attachment at the ONH
3. There is vitreomacular traction resulting in obscuration of the foveal contour

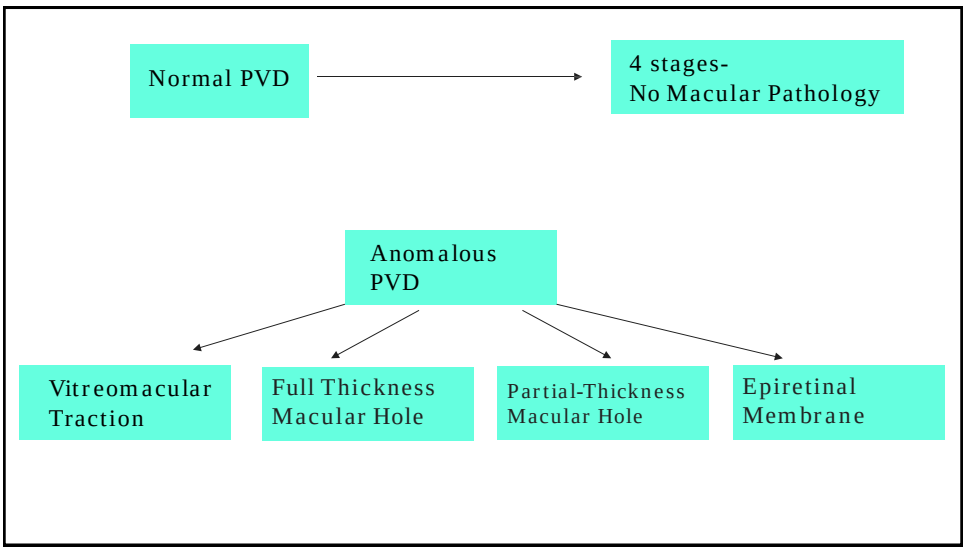
33

Case: Management

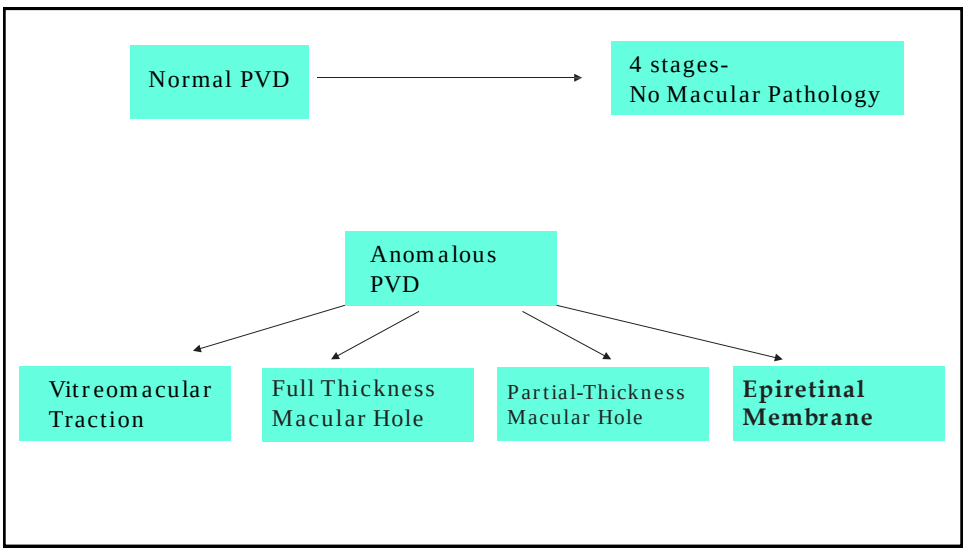
Patients with *symptomatic* (floaters and/or photopsia) PVD without vitreous hemorrhage or peripheral retinal breaks *require no immediate treatment* but may be re-examined in *one to two weeks*, since some retinal breaks appear to develop days to weeks after the onset of symptoms.

Chronic or acute? **Chronic…acute?**
Symptomatic or asymptomatic? **Symptomatic**

34


Normal PVD
4 stages-
No Macular Pathology
Anomalous
PVD
Vitreomacular
Traction
Full Thickness
Macular Hole
Partial-Thickness
Macular Hole
Epiretinal
Membrane

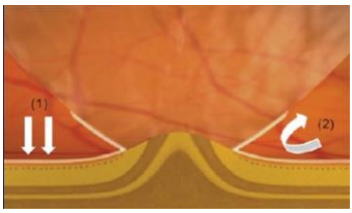
35

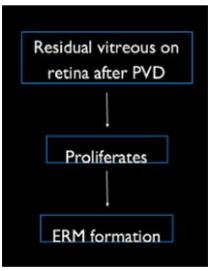

Normal PVD
4 stages-
No Macular Pathology
Anomalous
PVD
Vitreomacular
Traction
Full Thickness
Macular Hole
Partial-Thickness
Macular Hole
Epiretinal
Membrane

36

With PVD progression, residual vitreous tissue is left on inner retinal surface…

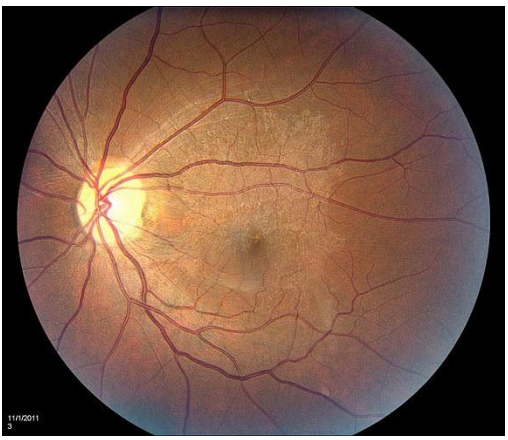
Residual vitreous proliferates to form ERM





37

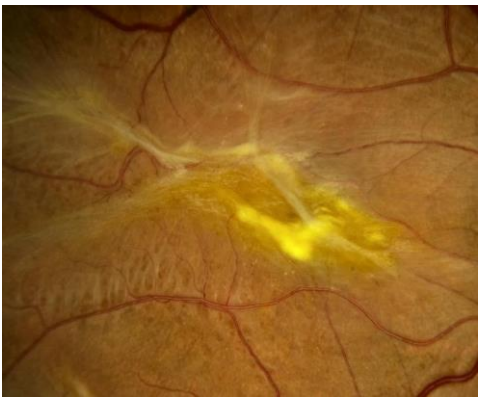
Epiretinal membrane: Grade 1



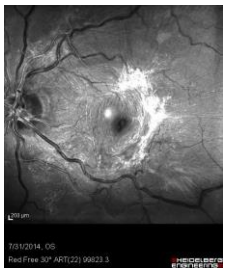
A cellophane-like sheen is observed over the macular area, causing very *mild wrinkling* of the inner retinal surface, with *little or no modification of retinal vessel trajectory*. These membranes are rarely symptomatic.

38

Epiretinal membrane: Grade 2

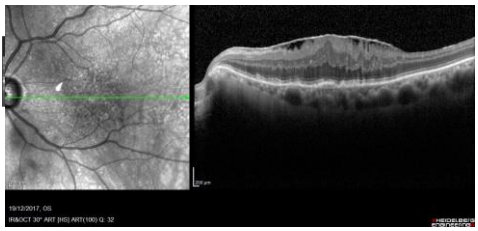


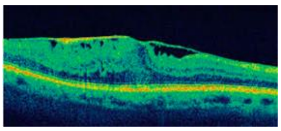
Fibrous tissue is observed over the macular area, causing *significant wrinkling of the retinal surface and modification of the retinal vessel trajectory*.

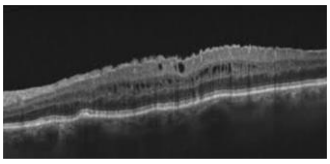


39

Epiretinal Membrane: OCT







40

Epiretinal membrane: Treatment

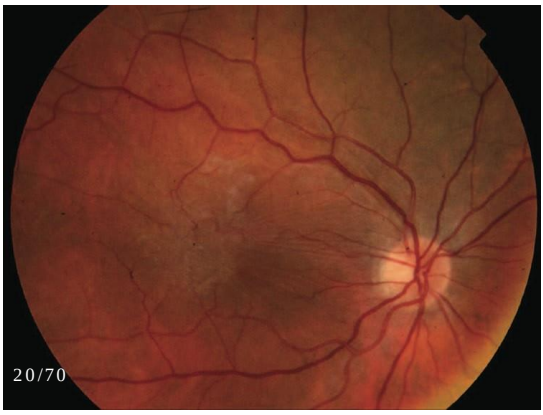
Vitrectomy may be indicated if:

- Vision is less than 20/60
- Severe metamorphopsia, double vision

80% of patients with ERM or VMT will improve by at least 2 lines of visual acuity following vitrectomy

41

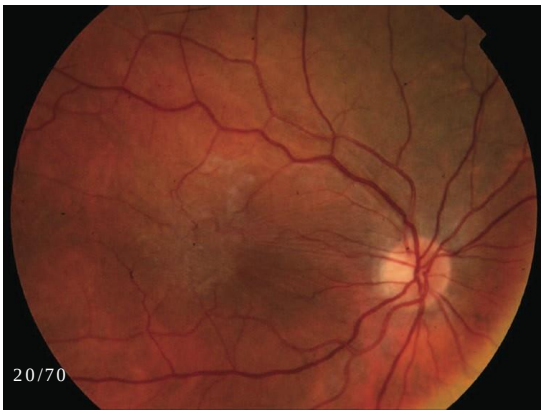
Case: 67 year-old male

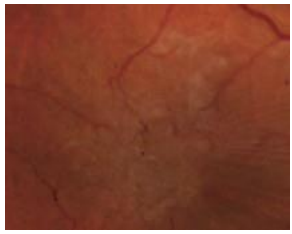


"I am seeing shadowing and doubling of images…. It started yesterday…"

42

What do we see?



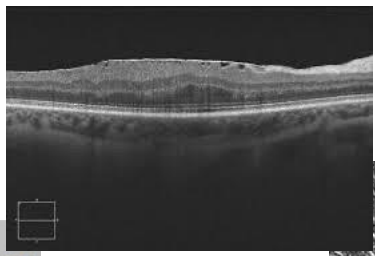


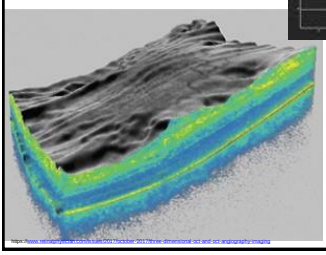
Fibrous tissue is observed over the macular area, causing *significant wrinkling of the retinal surface and modification of the retinal vessel trajectory*.

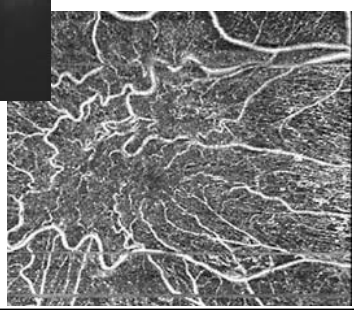
Grade 2

43

Case: 67 year-old male

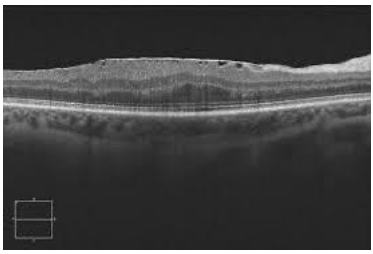






44

Case: 67 year-old male

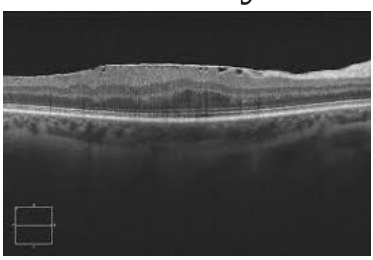


Which is not true of this OCT?

1. Epiretinal membrane and foveal thickening from traction
2. Disruption of the IS/OS junction
3. Intraretinal cystoid spaces from traction
4. Full thickness macular hole formation

45

Case: 67 year-old male

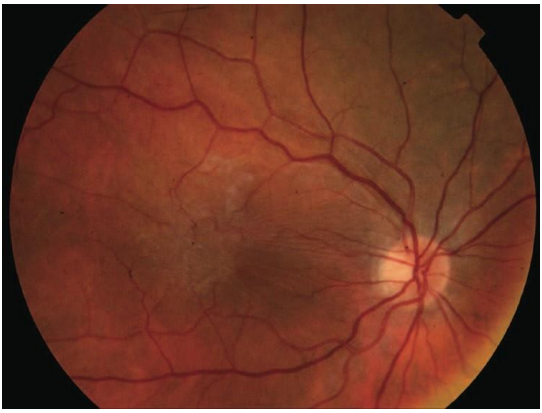


Which is not true of this OCT?

1. Epiretinal membrane and foveal thickening from traction
2. Disruption of the IS/OS junction
3. Intraretinal cystoid spaces from traction
4. **Full thickness macular hole formation**

46

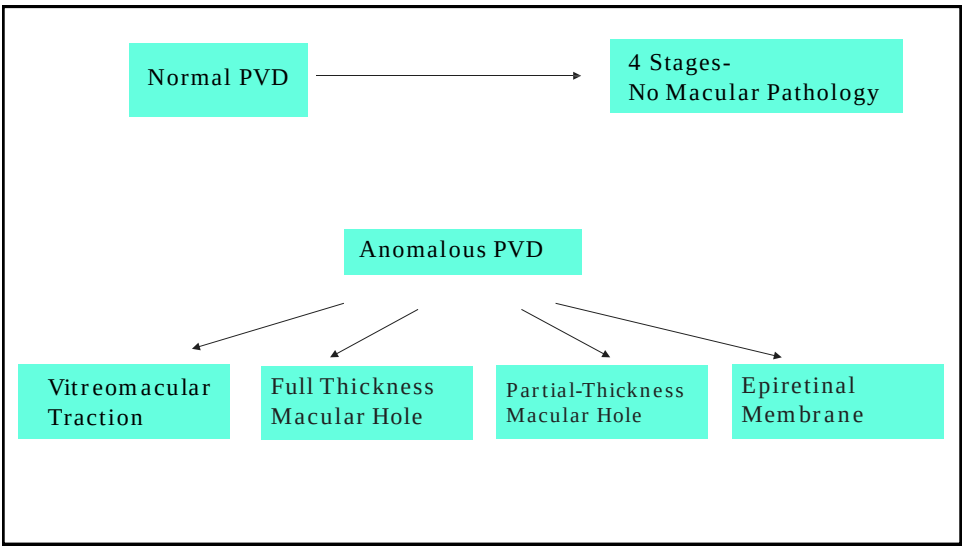
Case: Management



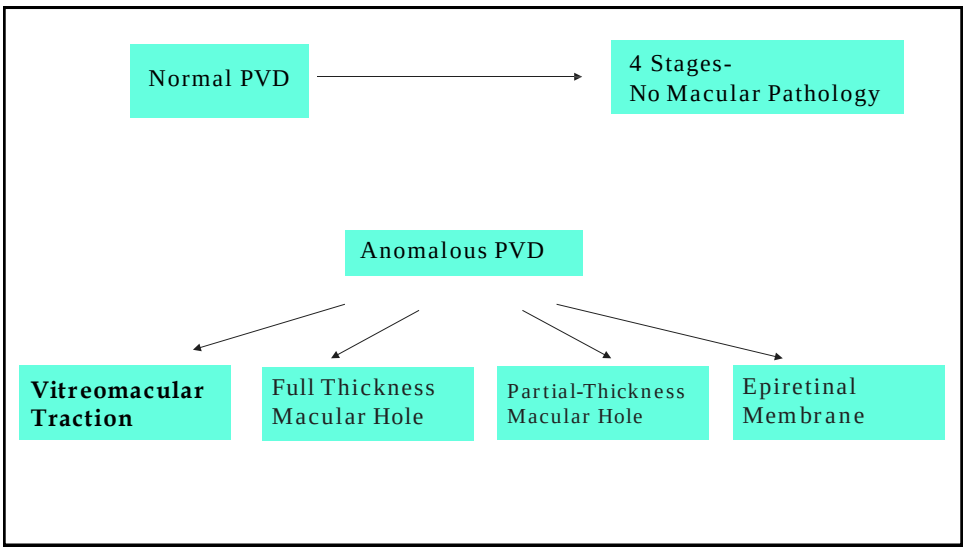
Vision? 20/70
Symptomatology?
Shadowing/Doubling!!

Vitrectomy!!

47

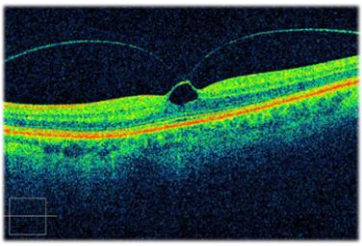


48



49

Vitreomacular Traction



Attachment of the vitreous cortex to the macula within a 3 mm radius of the fovea resulting in distortion of the foveal surface

50

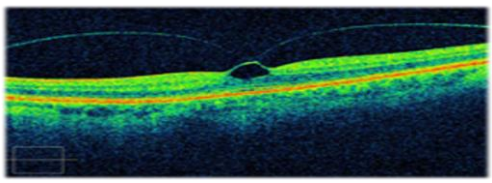
Two VMT subclassifications

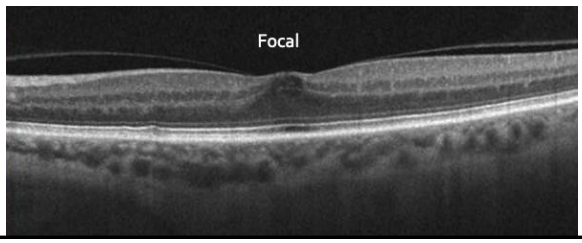
Focal versus Broad

Isolated versus Concurrent

51

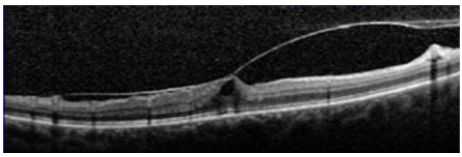
Focal VMT: <1500 um

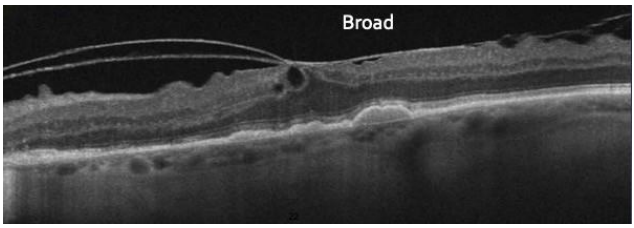




52

Broad VMT: >1500 um





53

Isolated versus Concurrent

Isolated

- Normal macula
  - No other associated diseases or findings on OCT

Concurrent

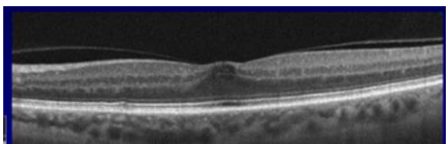
- Associated with another posterior segment disease

Symptoms NOT part of classification!!

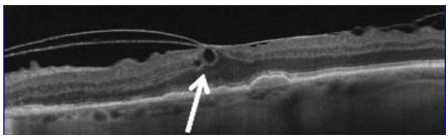
54

Isolated versus Concurrent

Isolated



Concurrent



55

Clinical Pearl

In patients who have areas of VMT ≤ 1500 um, the incidence of spontaneous release occurs in approximately 30-40% of eyes over 1-2 years

56

Management

Natural History of VMT Includes:
*Spontaneous resolution
*No change in VMT over time
*Increased tractional forces and MH formation

57

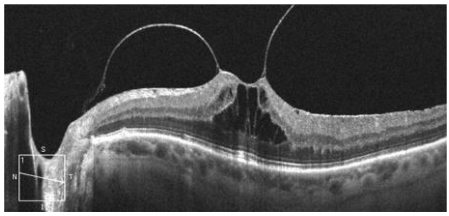
Management

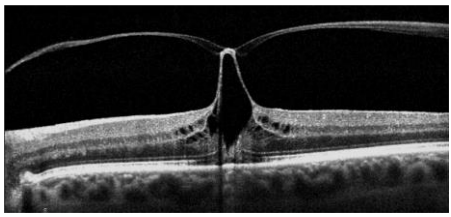
Asymptomatic VMT: Observation (especially NO ERM)

Symptomatic VMT:
* Pars plana vitrectomy (gold standard)
* Ocriplasmin (rarely used: side effects)
* Pneumatic vitreolysis

58

Which eye has the better visual prognosis?

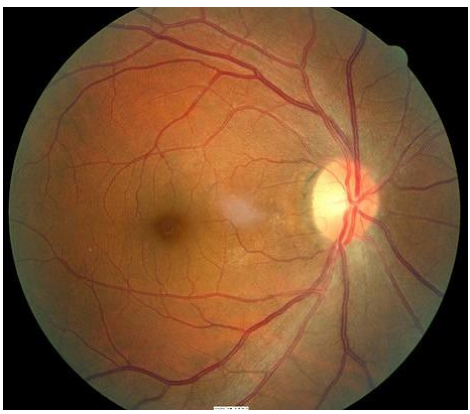




- Focal or Broad??
- Isolated or Concurrent?
- Integrity of PIL?

59

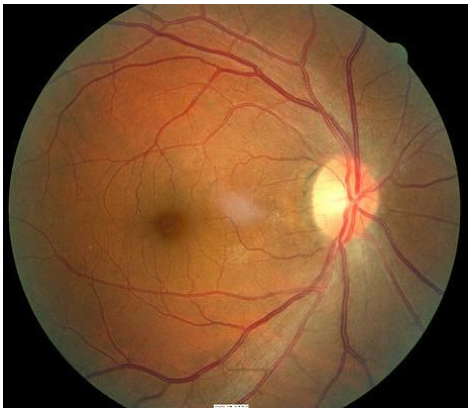
Case: 71 year-old female



"The vision in my right eye has gotten progressively worse over the last three months and everything looks wavy!!"

60

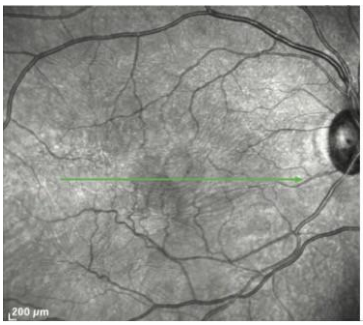
Case: Pertinent Findings

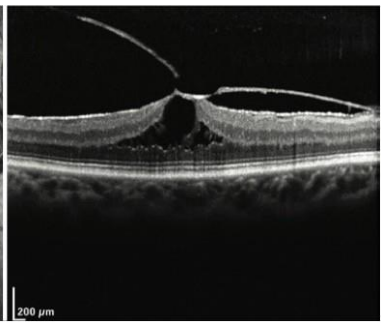


- BCVA *OD: 20/80*, OS: 20/20
- Fundoscopy: Vitreous condensation in fovea OD

61

Case: OCT



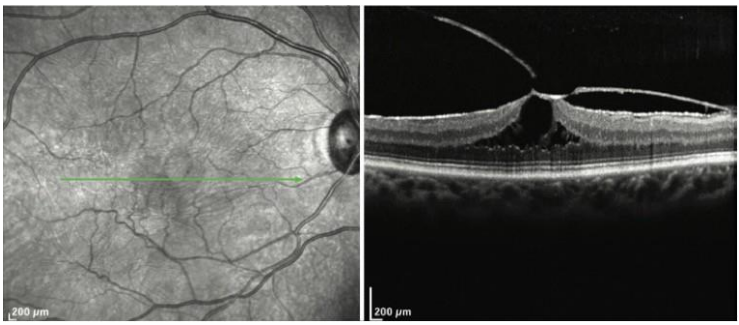


The following is not true of the above OCT:

1. VMT due to anomalous PVD that disorganized the foveal structure
2. ERM causing traction on the retinal surface
3. Broad vitreomacular traction (>1500 um)

62

Case: OCT

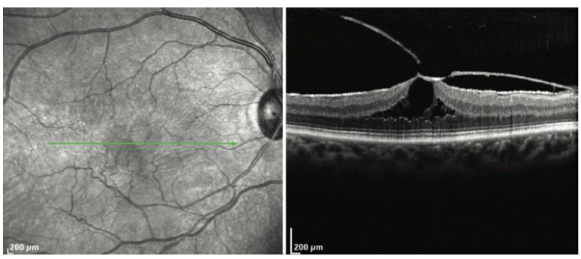


The following is not true of the above OCT:

1. VMT due to anomalous PVD that disorganized the foveal structure
2. ERM causing traction on the retinal surface
3. **Broad vitreomacular traction (>1500 um)**

63

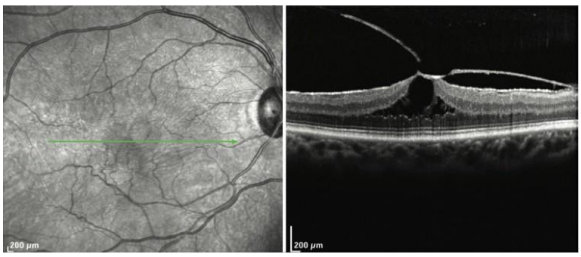
Case: Management Decisions



1. Is patient symptomatic?
2. What is the size of the VMT?
3. Is there an associated ERM?

64

Case: Management Decisions



1. Is patient symptomatic? Yes
2. What is the size of the VMT? <1500 um (focal)
3. Is there an associated ERM? Yes

65

Case: This patient

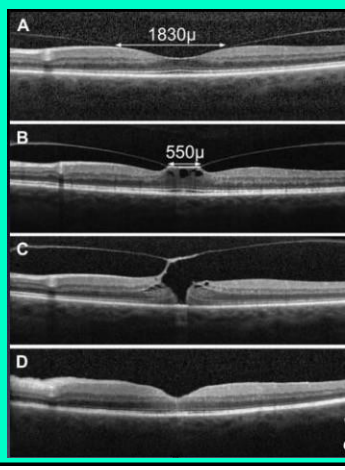
A vitrectomy and ERM peel were performed

<u>Other viable option:</u>
Intravitreal ocriplasmin
(more effective if MH <400 um present)

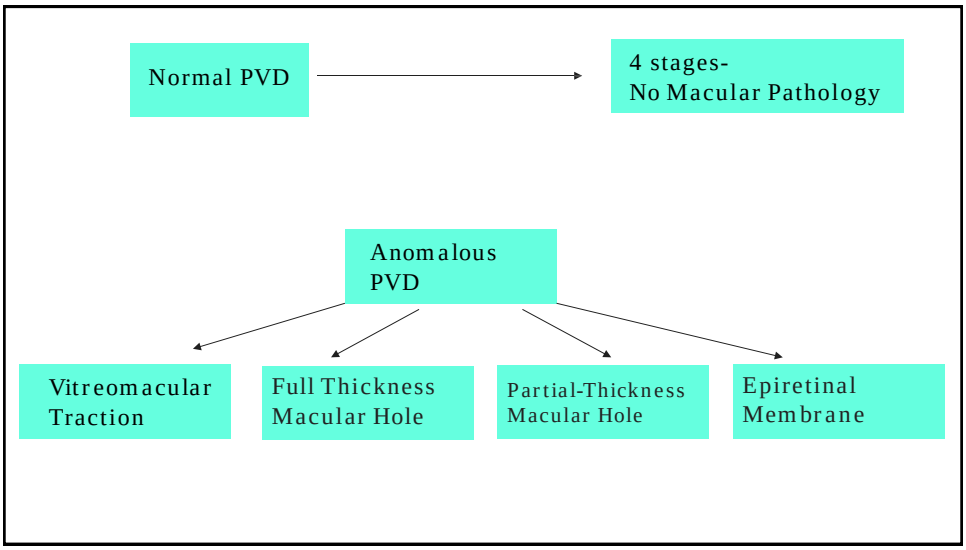
66

Case Example: When they don't resolve!!!

American Academy of Ophthalmology

Presentation		Broad VMA
One year later		Focal VMT
3 months later		FTMH
Post treatment		Resolved

67



68

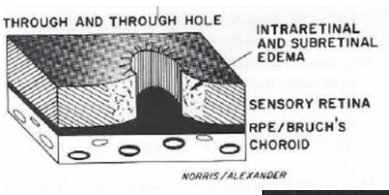
Normal PVD → 4 stages- No Macular Pathology

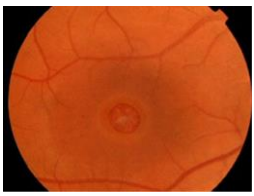
Anomalous PVD

- Vitreomacular Traction
- **Full Thickness Macular Hole**
- Partial-Thickness Macular Hole
- Epiretinal Membrane

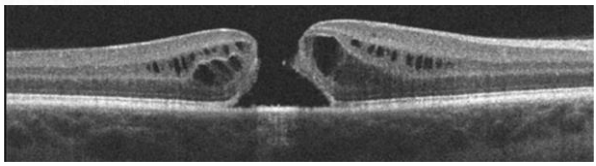
69

Full Thickness Macular Hole





Defect spans entire width of neurosensory retina



70

FTMH Classification *IVTS*

Anatomy and Outcome Based Classification

71

#1:Size of defect

What is the size of the aperture?
(Size critical for surgical outcome)

Small: Full thickness defect; ≤ 250 um
Medium: Full thickness defect; >250 um and ≤400 um
Large: Full thickness defect; >400 um

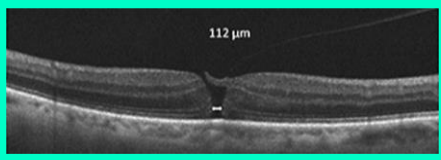
Measure at narrowest point on OCT
Parallel to RPE

72

Size of defect

Small: Full thickness defect; ≤ 250 um

- *Visual acuity may be relatively good*
- *Optimal size for successful repair by pharmacologic vitreolysis (Ocriplasmin)*
- *Very high probability of success with vitrectomy*

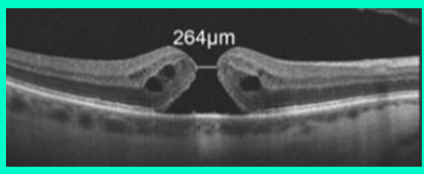


73

Size of defect

Medium: Full thickness defect; >250 um and ≤400 um

- *High probability of success with vitrectomy surgery*

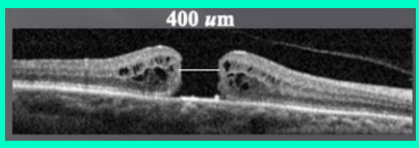


74

Size of defect

Large: Full thickness defect; >400 um

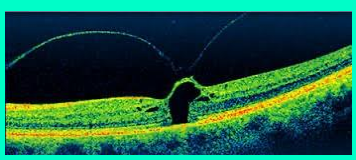
- *Less probability of successful closure with vitrectomy surgery*



75

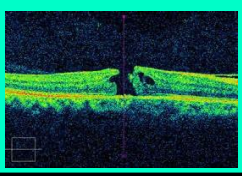
#2: Presence or absence of VMT

Primary: VMT present



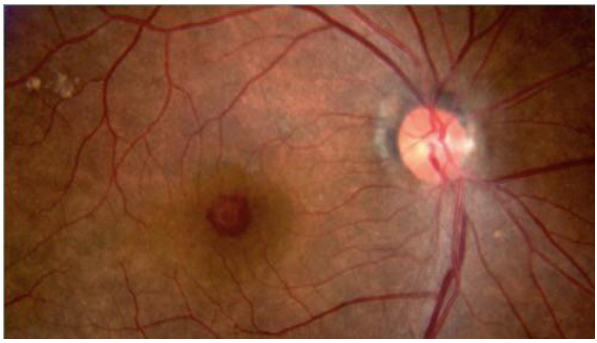
Secondary: VMT absent, secondary to pre-existing or concurrent disease

Examples: Trauma, myopia, macular edema, macular schisis, CNV, surgery, ERM



76

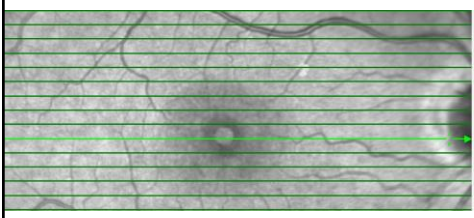
Case: 71 year-old Hispanic female

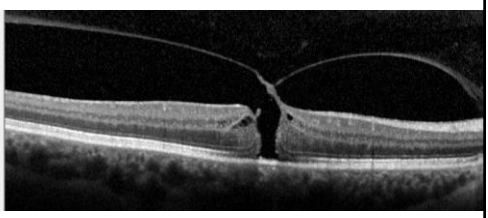


- BCVA OD: 20/80 eccentrically
- Scattered soft drusen throughout arcades
- Pseudophakia OU

77

Case: OCT





What best describes this OCT?

1. FTMH; Large; VMT present, ERM present
2. FTMH; Small; VMT present, ERM present
3. FTMH; Small; VMT absent, ERM absent

https://www.aropc.org/patient-education/macular-hole/

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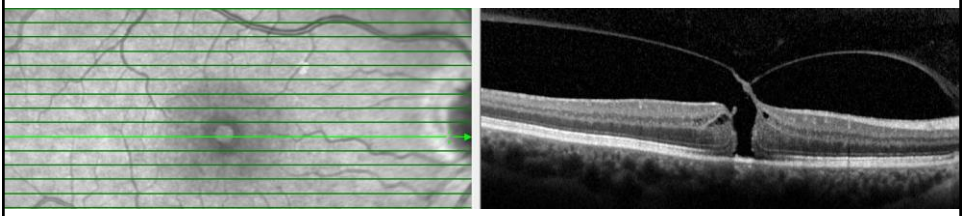
Case 2: OCT



What best describes this OCT?

1. FTMH; Large; VMT present, ERM present
2. **FTMH; Small; VMT present, ERM present**
3. FTMH; Small; VMT absent, ERM absent

https://www.aropc.org/patient-education/macular-hole/

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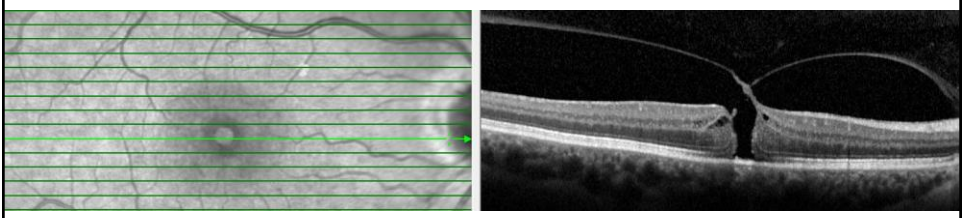
Case 2: Management Decisions

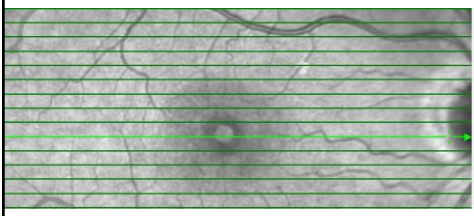


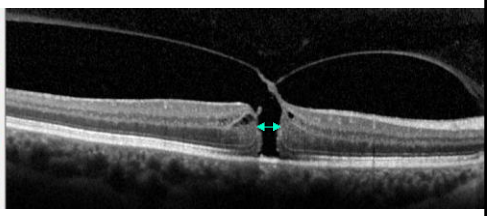
1. Is there an ERM?
2. How large is the hole?

https://www.aropc.org/patient-education/macular-hole/

80

Case 2: Management Decisions



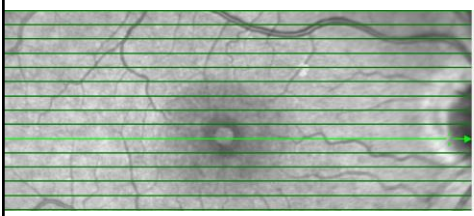


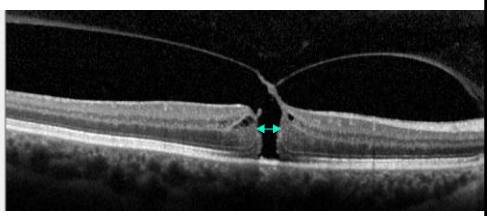
1. Is there an ERM? yes
2. How large is the hole? <400 um

https://www.aropc.org/patient-education/macular-hole/

81

Case 2: Treatment



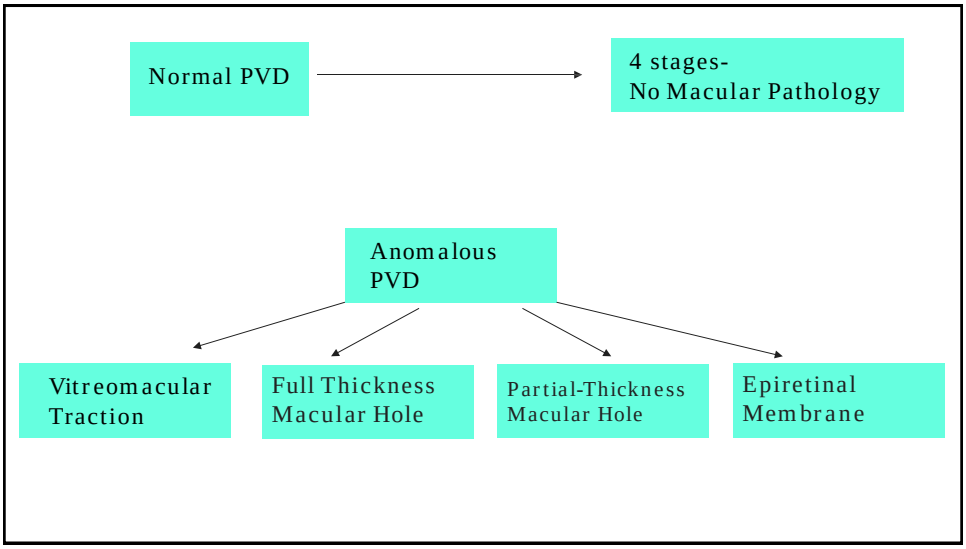


Vitrectomy OR

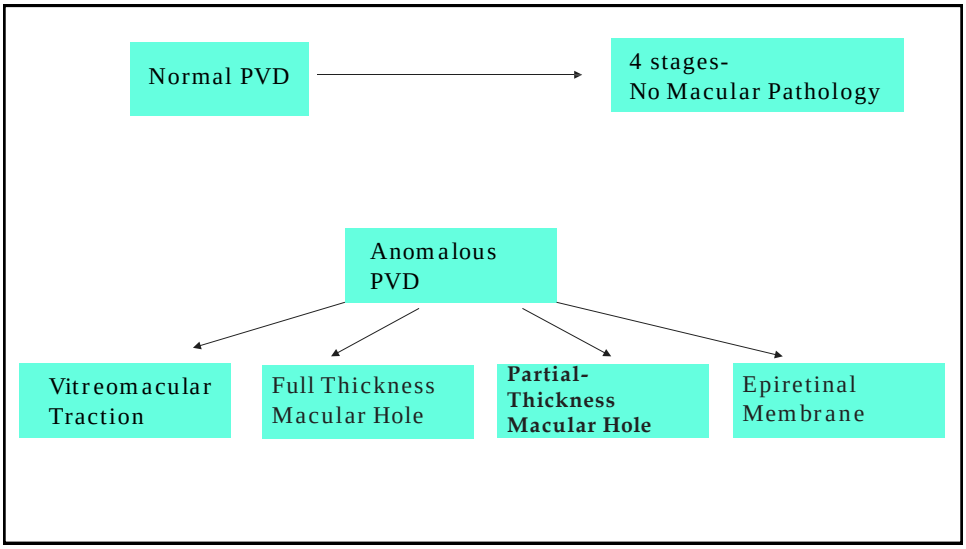
Ocriplasmin….(Size and VMT)

https://www.aropc.org/patient-education/macular-hole/

82


Normal PVD
4 stages-
No Macular Pathology
Anomalous
PVD
Vitreomacular
Traction
Full Thickness
Macular Hole
Partial-Thickness
Macular Hole
Epiretinal
Membrane

83


Normal PVD
4 stages-
No Macular Pathology
Anomalous
PVD
Vitreomacular
Traction
Full Thickness
Macular Hole
Partial-
Thickness
Macular Hole
Epiretinal
Membrane

84

Partial Thickness Macular Hole

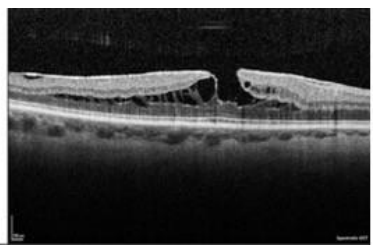
Lamellar Hole: Tractional and Degenerative

85

Lamellar hole: 2 Types

Tractional: "Moustache" appearance

- Must Have:
  ERM and foveoschisis



https://eyesthatdiabeticeyedoctor.com/wp-content/uploads/2016/04/Lamellar_Macular_Hole_Two_Distinct_Clinical_Entities_04-25-16.pdf

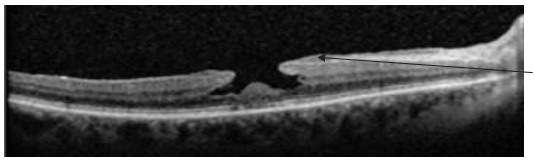
86

Lamellar hole: 2 Types

Degenerative: "Top Hat" appearance

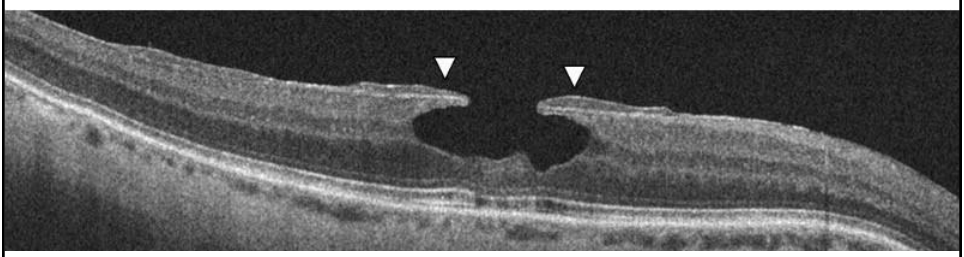
MUST HAVE:

- Irregular foveal contour
- Foveal cavitation with round edges
- Loss of foveal tissue (thinning)



87

What is Epiretinal Proliferation?



A thick, homogeneous, isoreflective layer covered by a thin hyper-reflective line at the edges of the hole contiguous with the inner retina

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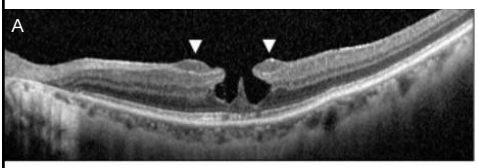
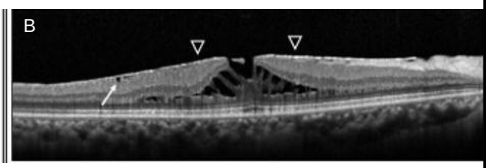
Quiz: Degenerative or tractional?





A: Degenerative

- Irregular foveal contour
- Foveal cavitation with round edges
- Loss of foveal tissue (thinning)

B: Tractional

- ERM and foveoschisis

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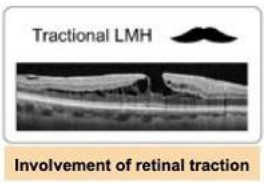
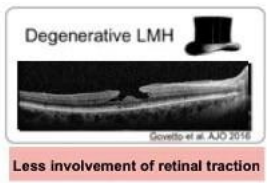
Lamellar Holes: Management



Involvement of retinal traction

Vitrectomy with membrane peeling improves BCVA



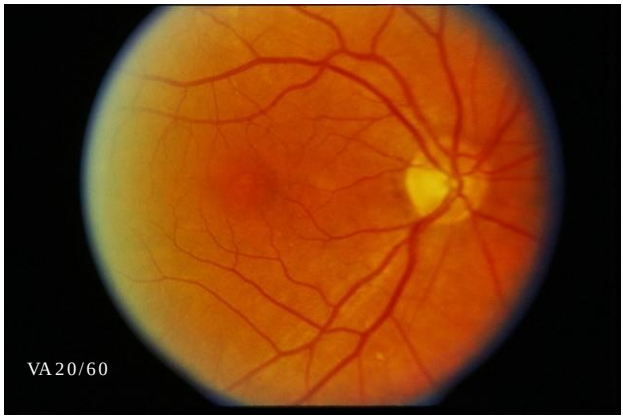
Less involvement of retinal traction

A standardized therapy or treatment algorithm does not exist. It is important to take into account the subjective complaints of the patient and the evolution of his BCVA

LHEP?

90

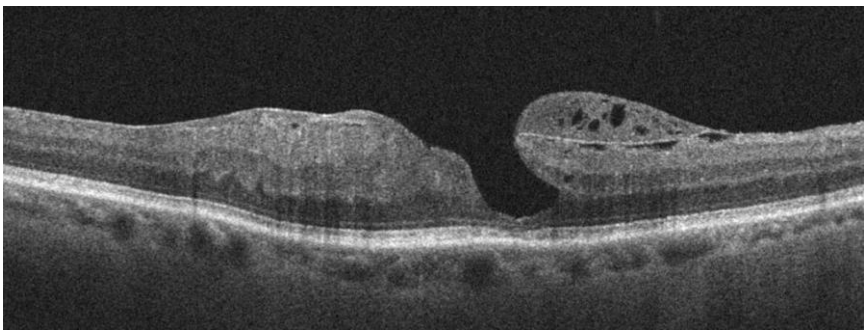
Case: 70 year-old Hispanic Male



https://imagebank.asrs.org/file/15844/macular-hole-evolving-lamellar-hole

91

Case: 70 year-old Hispanic Male

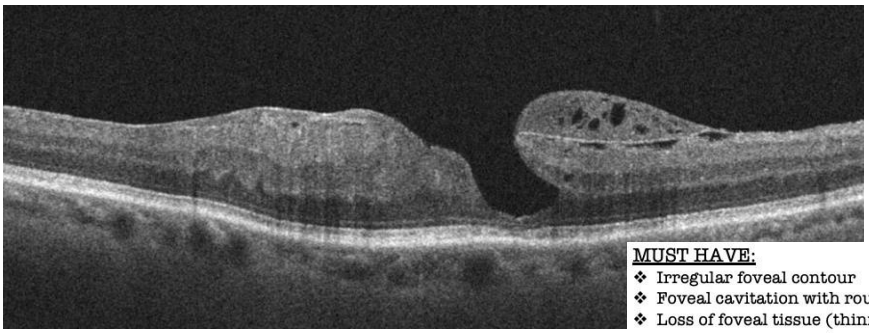


What classification is the lamellar macular hole above?
1. Tractional
2. Degenerative

https://imagebank.asrs.org/file/15844/macular-hole-evolving-lamellar-hole

92

Case: 70 year-old Hispanic Male



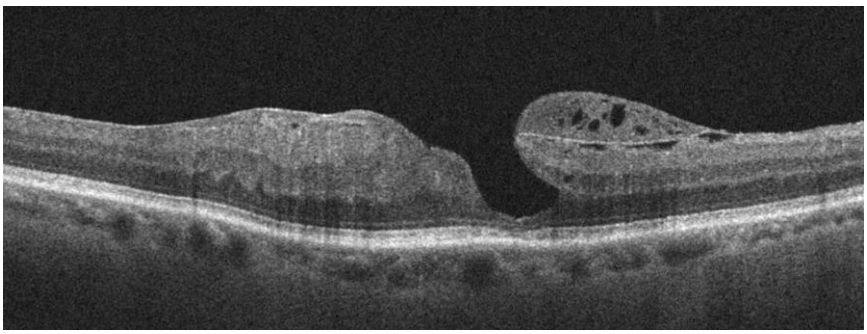
MUST HAVE:
- Irregular foveal contour
- Foveal cavitation with round edges
- Loss of foveal tissue (thinning)

What classification is the lamellar macular hole above?
1. Tractional
2. Degenerative : Absence of retinal traction

https://imagebank.asrs.org/file/15844/macular-hole-evolving-lamellar-hole

93

Case: 70 year-old Hispanic Male

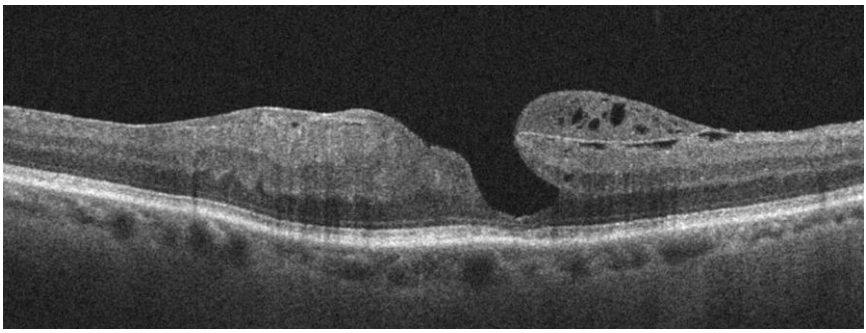


What is the optimal treatment?
1. Epiretinal membrane and ILM peel
2. Lamellar Hole Epiretinal Proliferation Embedding Technique

https://imagebank.asrs.org/file/15844/macular-hole-evolving-lamellar-hole

94

Case: 70 year-old Hispanic Male



What is the optimal treatment?

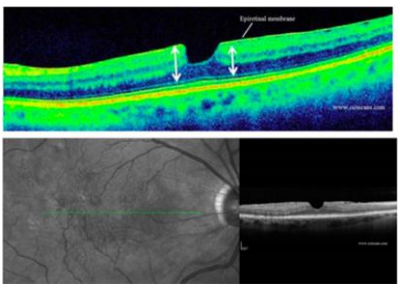
1. Epiretinal membrane and ILM peel
2. **Lamellar Hole Epiretinal Proliferation Embedding Technique**

https://imagebank.asrs.org/file/15844/macular-hole-evolving-lamellar-hole

95

Macular Pseudohole: Partial thickness

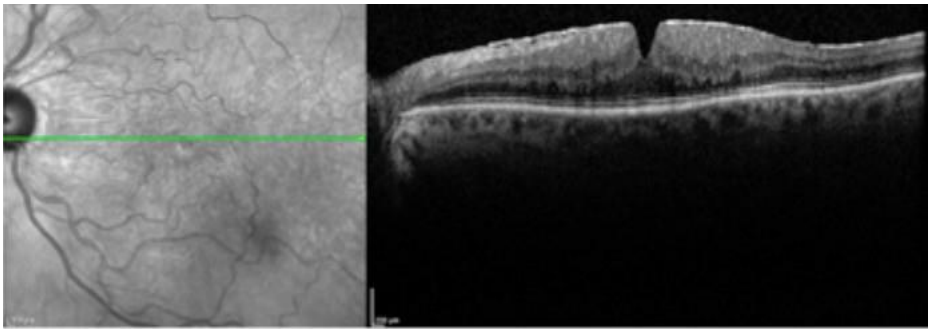
Circular or oval configuration of foveal depression



Can result in perifoveal traction from an ERM

96

Macular Pseudohole: Partial thickness



97

Thank you!!!

rjulie@nova.edu

98

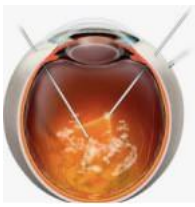
Treatment options

Quick Review

99

Jetrea (Ocriplasmin)

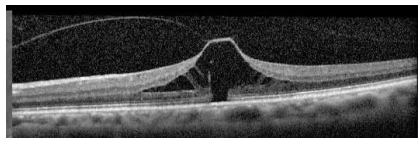
- Form of human plasmin: Induces liquefaction of vitreous and separation of vitreous cortex from ILM
- Intravitreal injection
- **MIVI-TRUST**: Microplasmin for intravitreal injection; Traction Release without Surgical Treatment



100

Jetrea (Ocriplasmin):
Reported factors that aid in higher success rates

- <65 years old
- Small adhesion diameter (≤ 1500 um)
- Presence of FTMH (<250 um)
- Absence of ERM
- Absence of concurrent retinal disease
- Shorter duration of VMT



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Ocular Disease: Part I

Presented by MBKU | SCCO

Retinal Vascular Occlusive Disease

Presented by Julie Rodman, OD, MSc

Live CE Webinar | Day One | AM Session

Saturday | March 20, 2021 | 10:55 a.m. - 11:50 a.m.

Marshall B.
KETCHUM UNIVERSITY
Southern California College of Optometry

Department of Continuing Education

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Retinal Vascular Occlusive Disease

JULIE RODMAN OD, MSC, FAAO
PROFESSOR, NOVA SOUTHEASTERN UNIVERSITY
COLLEGE OF OPTOMETRY

1

Financial Disclosures

Julie Rodman OD, MS, FAAO

- Optovue, Maculogix
  - Consultant and Speaker
- **There are no financial relationships that affect the content of this program**

2

Retinal Vascular Occlusive Disease: IMPORTANT TOPIC!!!

- Retinal vein occlusion is the second most prevalent retinal vascular disease (DR #1)
- Strong association with systemic disease
  - Morbidity and mortality highly associated

Main Risk Factors: AGE and SYSTEMIC VASCULAR DISEASE

3

Retinal Vein Occlusions

GUIDELINES AND SCREENING RECOMMENDATIONS

4

Definition of Retinal Vein Occlusion

Partial or complete obstruction of a retinal vein

- Classified by location of occlusion

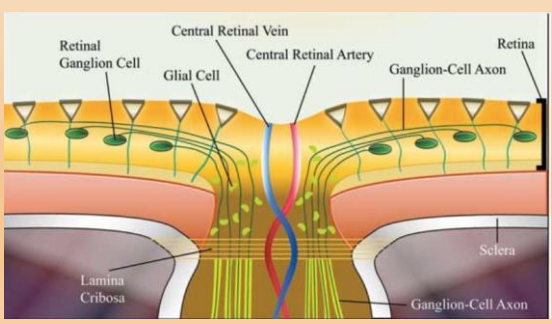
CRVO: Central Retinal Vein Occlusion
BRVO: Branch Retinal Vein Occlusion
HRVO: Hemi-Retinal Vein Occlusion

- Classified by extent of retinal ischemia
  - Ischemic vs. Non-Ischemic

5

Retinal Vein Occlusion: Etiology

- Atherosclerosis of the adjacent Central Retinal Artery
- The CRA compresses the CRV in the region of the lamina cribrosa
- This induces thrombosis (blood clot) in the lumen of the vein



6

Systemic Etiology: CRVO

- Hypertension (most common systemic)
- Diabetes
- Hyperlipidemia
- Cardiovascular Disease
- Hyperviscosity Syndromes
- Vasculitis: Sarcoid, Syphilis, SLE

- Miscellaneous:
  - Drugs (Oral Contraceptives, diuretics)
  - Migraine

More detailed evaluations for bilateral cases or in patients who are <50 years.

7

Ocular Etiology: CRVO

- **Ocular Hypertension/Glaucoma (most common ocular)**
  - (Causes increased pressure in the ONH sheath causing further compression and contributes to occlusion)

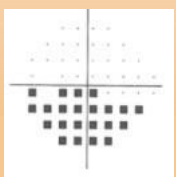
- Optic Disc Edema
- Optic Disc Drusen
- Orbital Tumor and abscess
- Cavernous Sinus Thrombosis
- Thyroid Eye Disease

Other factors that result in compression

8

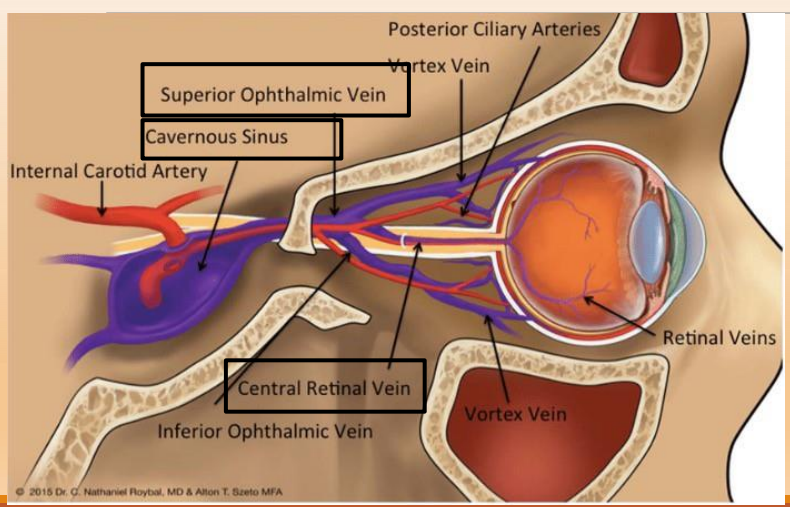
What are patient's going to report?

- Progressive, painless decrease in vision and field of vision
  - *Extent varies on type of occlusion*
  - Unilateral
  - Loss of VA; varies with degree of ischemia



9

Let's Review the Anatomy; CRVO



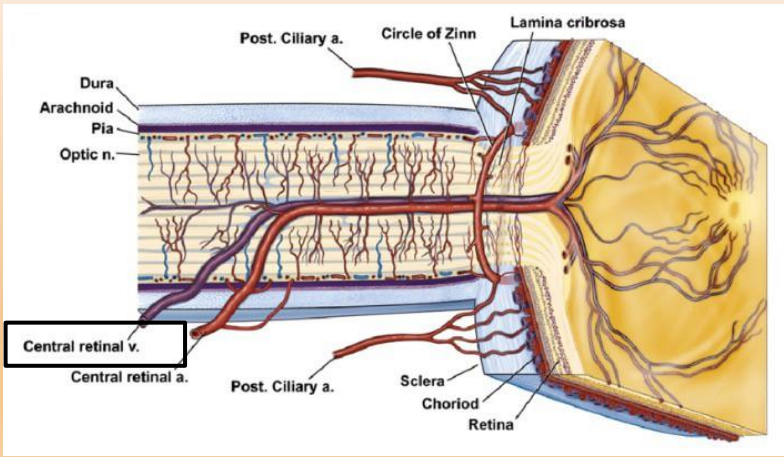
Central Retinal Vein:

Short vein that runs through the ONH

Retinal circulation drains into the CRV, which drains into the superior ophthalmic vein and then the cavernous sinus

10

Let's Review the Anatomy; CRVO



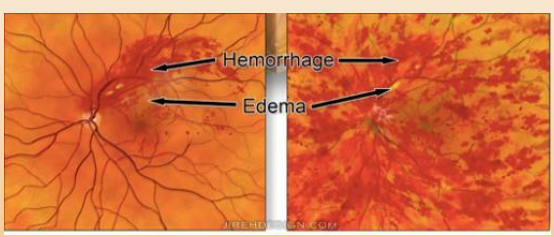
- Obstruction at/or posterior to the ONH

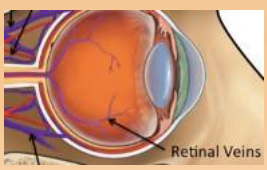
https://www.researchgate.net/figure/Anatomy-of-ocular-circulation-a-artery-b-vein-n-nerve-A-Cut-away-drawing-along-the_fig17_224949360

11

General Sequelae….RVO

- Complete or partial decrease in venous outflow within the retinal circulation
- Retinal vascular leakage
- Sequalae…..Varies depending on type of occlusion

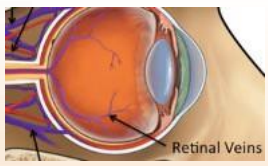




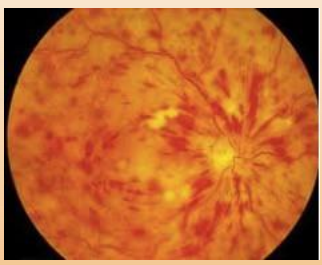
https://retinaeyedoctor.com/central-retinal-vein-occlusions/

12

Evaluation of CRVO

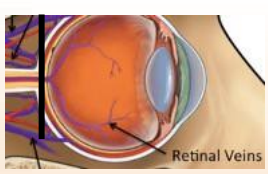


- Clinical findings:
  - Retinal hemorrhages (4 Quadrants)
  - Dilated, tortuous retinal veins
  - Superficial hemorrhages
  - CWS
  - Macular edema

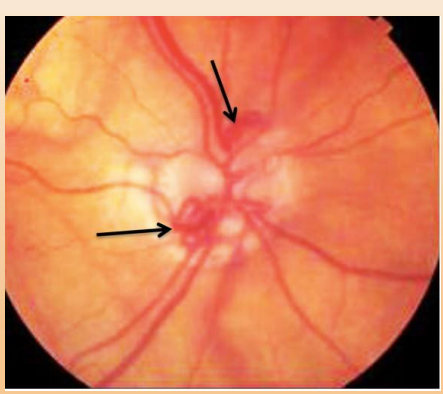


13

Evaluation of CRVO



- Later clinical findings:
  - <u>Collaterals</u>
    - CRVO: Between retinal venules and choroidal circulation at the disc
  - <u>Optic Disc Edema</u>



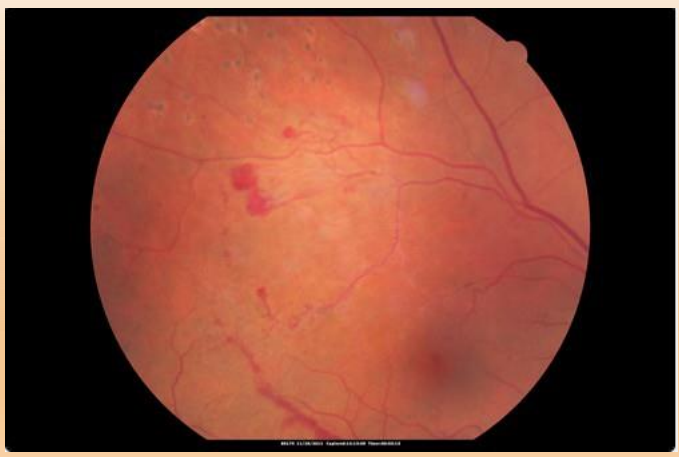
Black arrows: The identified veins are dilated, pre-existing channels connecting retinal venous return to choroidal veins.

http://www.retinareference.com/diseases/28f9641cc2c160e4/images/0a84f11b51

14

Evaluation of CRVO

- Later clinical findings:
  - Neovascularization
    - iris and retina
  - Vitreous hemorrhage
  - Neovascular glaucoma



https://retinagallery.com/displayimage.php?album=953&pid=7716#top_display_media

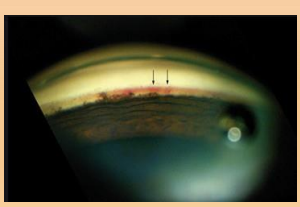
15

Evaluation of RVO

- Later clinical findings:
  Neovascular glaucoma

60% of patients with ischemic CRVO will develop neovascular glaucoma

90 Day Glaucoma!



https://retinagallery.com/displayimage.php?album=953&pid=7716#top_display_media

16

Ischemic vs. Non-Ischemic RVO

- Visual Acuity
  - <20/200 associated with non-perfusion
- Pupillary assessment for RAPD
  - Corresponds to level of ischemia; (+)APD if ischemic
  - Predictive of eyes at risk for neovascularization
- FA is used to evaluate the degree of ischemia
  - Defined by CVOS as eyes with 10-disc areas of capillary non-perfusion
  - CWS, extensive retinal hemorrhages

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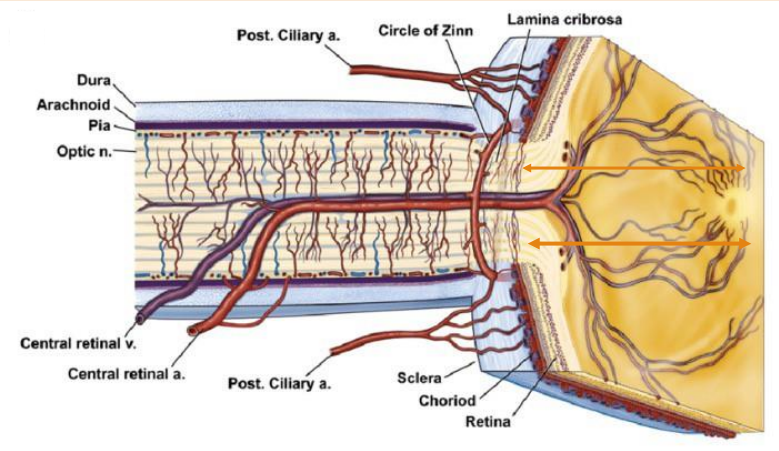
Retinal Imaging: Ischemic vs. Non-Ischemic

- *Optical Coherence Tomography*
  - Macular edema
- *Optical Coherence Tomography Angiography*
  - Accurately evaluates change in microvasculature (vessel density, size of FAZ)
- *Visual Field Testing*

18

Let's Review the Anatomy; HRVO



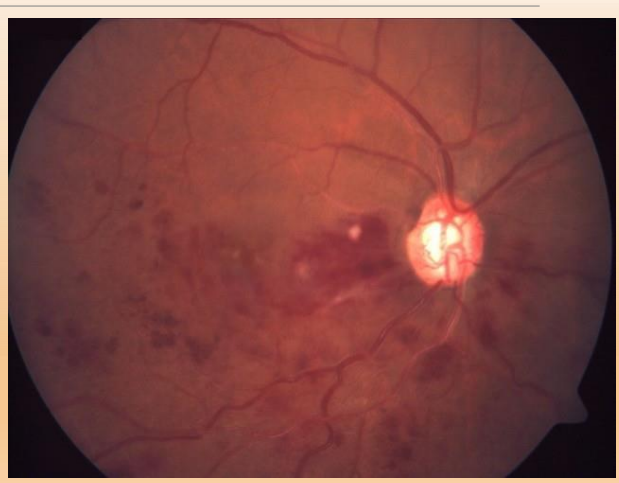
- Occlusion occurring at the disc involving half of neurosensory retinal drainage (S or I hemifield)

https://www.researchgate.net/figure/Anatomy-of-ocular-circulation-a-artery-b-vein-n-nerve-A-Cut-away-drawing-along-the_fig17_224949360

19

Evaluation of HRVO

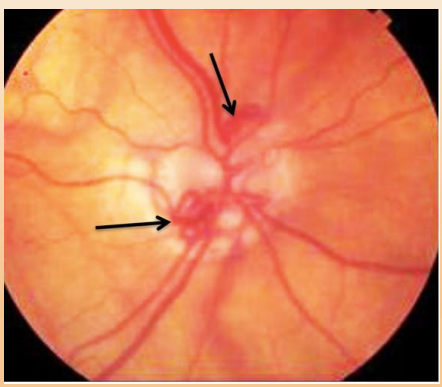
- Early clinical findings:
  - Vascular tortuosity and dilation
  - Retinal and macular edema
  - Retinal hemorrhages (2 Quadrants)
    - N and T
  - CWS



20

Evaluation of HRVO

- Later clinical findings:
  - Collaterals
    - CRVO/HRVO: Between retinal venules and choroidal circulation at the disc
  - Optic Disc Edema

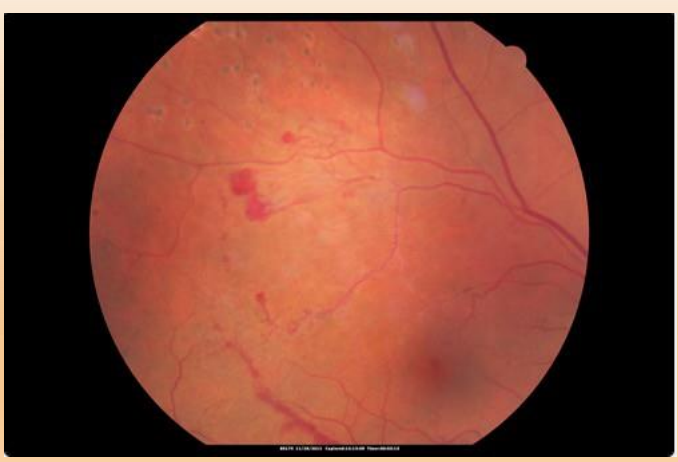


http://www.retinareference.com/diseases/28f9641cc2c160e4/images/0a84f11b51

21

Evaluation of HRVO

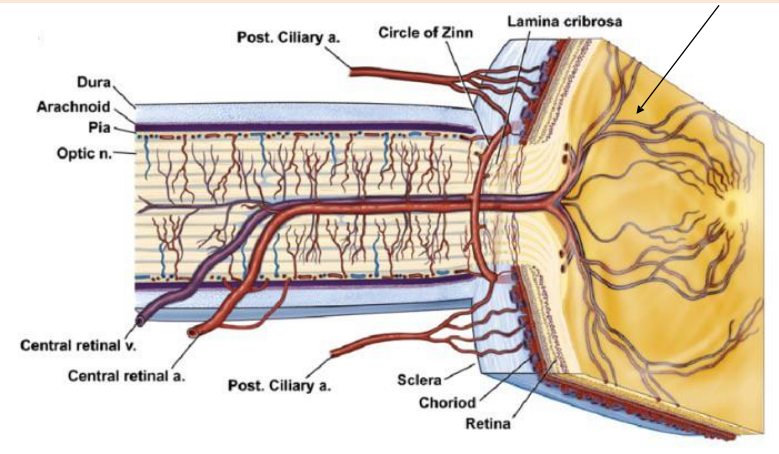
- Later clinical findings:
  - Neovascularization
    - Retinal>iris
  - Vitreous hemorrhage
  - Neovascular glaucoma



https://retinagallery.com/displayimage.php?album=953&pid=7716#top_display_media

22

Let's Review the Anatomy; BRVO

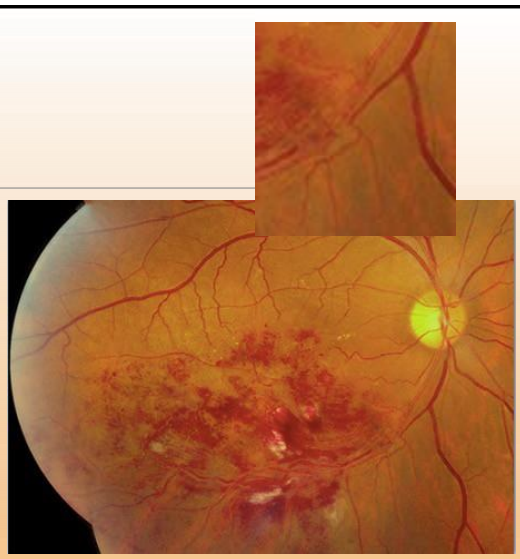


- Complete or partial obstruction at a branch of the central retinal vein

https://www.researchgate.net/figure/Anatomy-of-ocular-circulation-a-artery-b-vein-n-nerve-A-Cut-away-drawing-along-the_fig17_224949360

23

Evaluation of BRVO

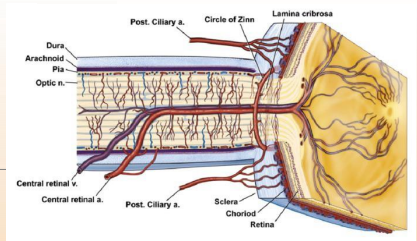


- Clinical findings:
  - Superficial hemorrhages in a sector of the retina along a retinal vein (do not cross the midline)
  - CWS
  - Retinal Edema
  - A dilated and tortuous retinal vein
  - Narrowing and sheathing of adjacent artery

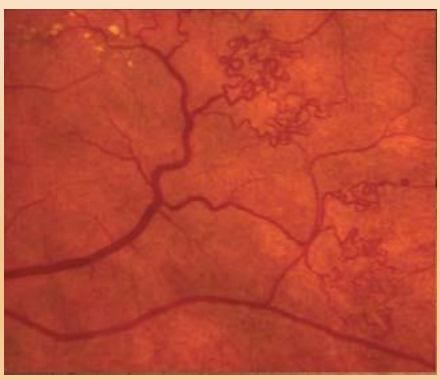
https://www.reviewofophthalmology.com/article/evaluation-and-management-of-retinal-vein-occlusion

24

Evaluation of BRVO



- Later clinical findings:
  - Collaterals
    - BRVO: Between superior and inferior retinal veins



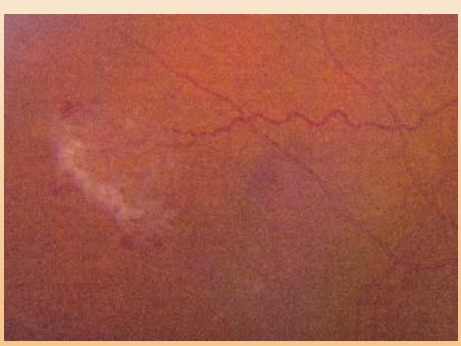
Venous-venous collateralization. Collaterals bridge the obstructed site or connect to adjacent veins in the periphery

https://www.meduweb.com/forumdisplay.php/158-Ophthalmology-Atlas(Photos-of-cases)

25

Evaluation of BRVO: SEVERE ischemia….

- Later clinical findings:
  - Neovascularization
    - Due to ischemia
    - Formed as compensatory mechanism



https://www.reviewofophthalmology.com/article/evaluation-and-management-of-retinal-vein-occlusion

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Evaluation of RVO

STEP-BY-STEP GUIDE

27

Evaluation of RVO

- *Three main components:*
  - Medical History
  - Ocular Exam
  - Retinal imaging

28

Evaluation of RVO: Medical History

- Atherosclerotic risk factors?
  - HTN, hyperlipidemia, diabetes
  - Smoking, obesity
  - Family history of coronary artery disease
- Hypercoagulability risk factors?
- Vasculitis? Prior systemic disease?

https://www.allaboutvision.com/conditions/eye-occlusions.htm

29

Evaluation of RVO: Ocular History

- Ocular History?
  - Glaucoma, Ocular Hypertension

https://www.allaboutvision.com/conditions/eye-occlusions.htm

30

Evaluation of RVO

- *Three main components:*
  - Medical History
  - Ocular Exam
  - Retinal imaging

31

Evaluation of RVO: Ocular Exam

- Visual Acuity
- Pupil exam; ?APD
- Biomicroscopy; ?iris neovascularization, IOP
- Gonioscopy; ?angle neovascularization
- Dilated fundus examination; including vitreous and periphery; macular edema; ONH cupping?

32

Evaluation of RVO

- *Three main components:*
  - Medical History
  - Ocular Exam
  - Retinal imaging

33

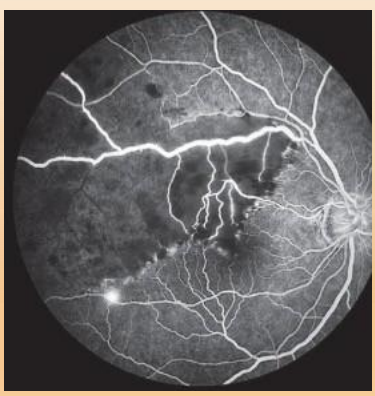
Retinal Imaging

- *Fluorescein Angiography*
  - Essential first step: Detect nonperfused capillary areas and extent of macular ischemia
- *Optical Coherence Tomography*
  - Quantify presence and extent of macular edema
- *Optical Coherence Tomography Angiography*
  - Accurately evaluates change in microvasculature (vessel density, size of FAZ)

34

Evaluation of RVO: Imaging

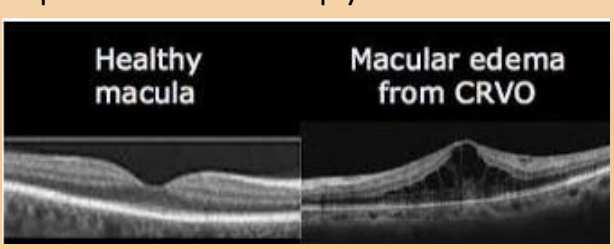
- FA
  - Identify site of damaged A/V crossing
  - Degree of non-perfusion



35

Evaluation of RVO: Imaging

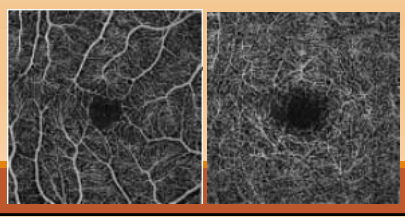
- OCT
  - Detect presence and extent of macular edema; monitor response to therapy

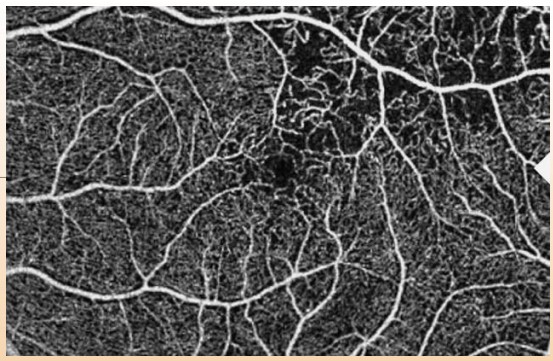


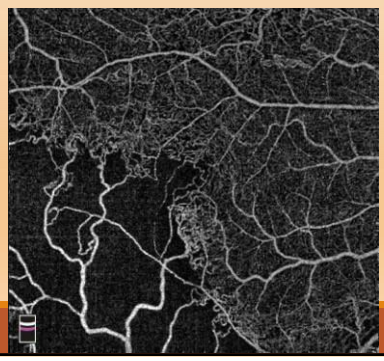
36

Evaluation of RVO: Imaging

- OCTA
  - Assess degree of capillary non-perfusion
  - Measure size of FAZ







37

Management: RVO

- Treat and evaluate for underlying medical disorders

Lab work:

Complete blood cell (CBC) count
Glucose tolerance test
Lipid profile
Serum protein electrophoresis
Syphilis serology
Thrombophilic screening, activated protein C resistance, lupus anticoagulant, anticardiolipin antibodies, protein C, protein S, and antithrombin III may be completed.

- Reduce IOP

38

Treatment: Ocular

- Macular Edema
  - Anti-VEGF- 1st line of treatment (Lucentis, Eylea)
  - Intravitreal corticosteroids (s/e) (Ozurdex)
  - Laser photocoagulation
- Iris or Retinal Neovascularization
  - PRP (adjunct use of Anti-VEGF)

BRAVO and CRUISE: Early anti-VEGF treatment leads to better visual outcomes

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Clinical Pearl

Treatment of systemic conditions, such as unknown diabetes or hypertension, is mandatory to prevent future non-ocular life-threatening events. Furthermore, it is the only way to reduce risk for involvement of the contralateral eye.

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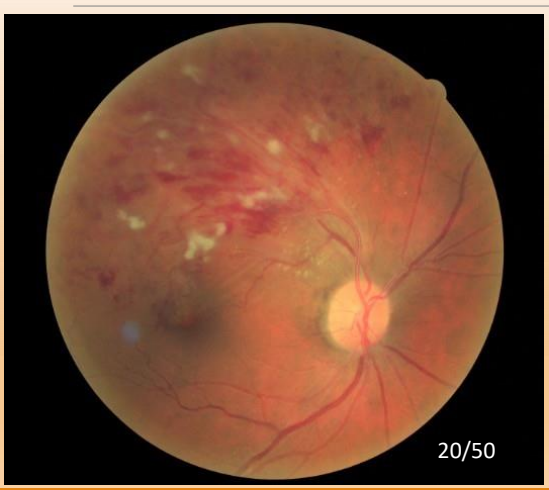
Case Examples

RETINAL VEIN OCCLUSION

41

60-year-old Black female



Reports "curtain over her vision" in the right eye x 2 months… was hoping it would go away.

42

Evaluation of RVO

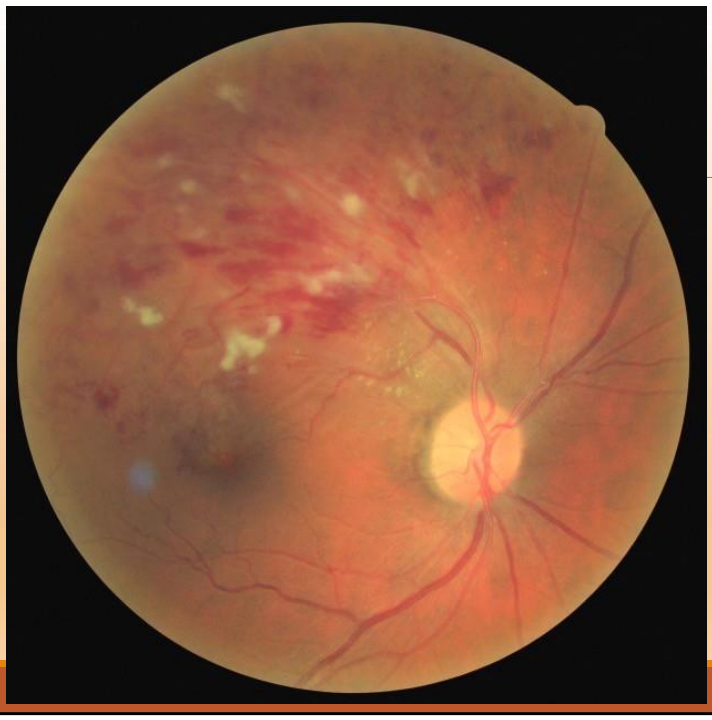
- *Three main components:*
  - Medical History: (+)Hypertension, Hypercholesterolemia
    - BP elevated in office, h/o poor cholesterol control
  - Ocular Exam
  - Retinal imaging

43

Evaluation of RVO

- *Three main components:*
  - Medical History
  - Ocular Exam…VA/?APD, ?Iris/Angle neovascularization,?IOP
  - Retinal imaging

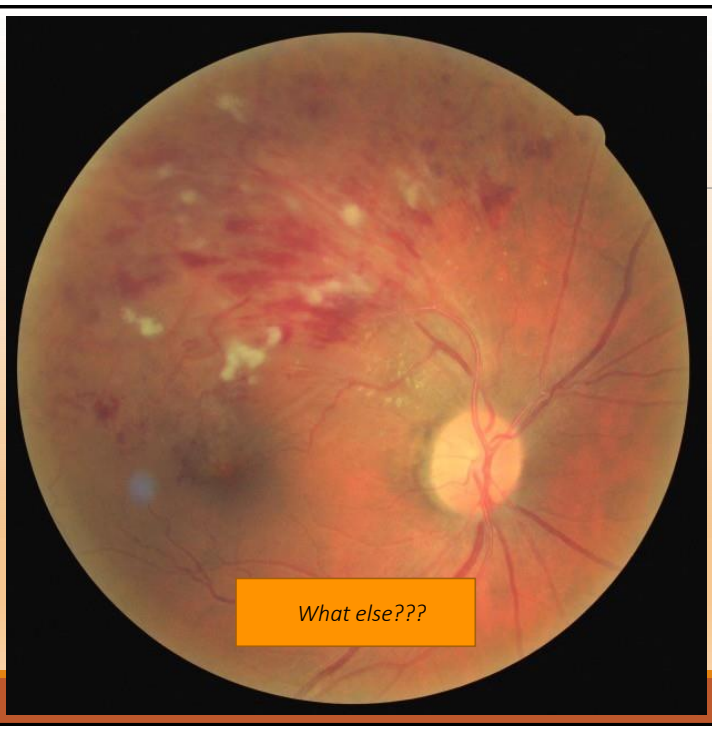
44



What kind of RVO is this?

- Vascular tortuosity
  - Crossing changes
- Retinal edema
- Intraretinal hemorrhages
- Superficial hemorrhages
- CWS

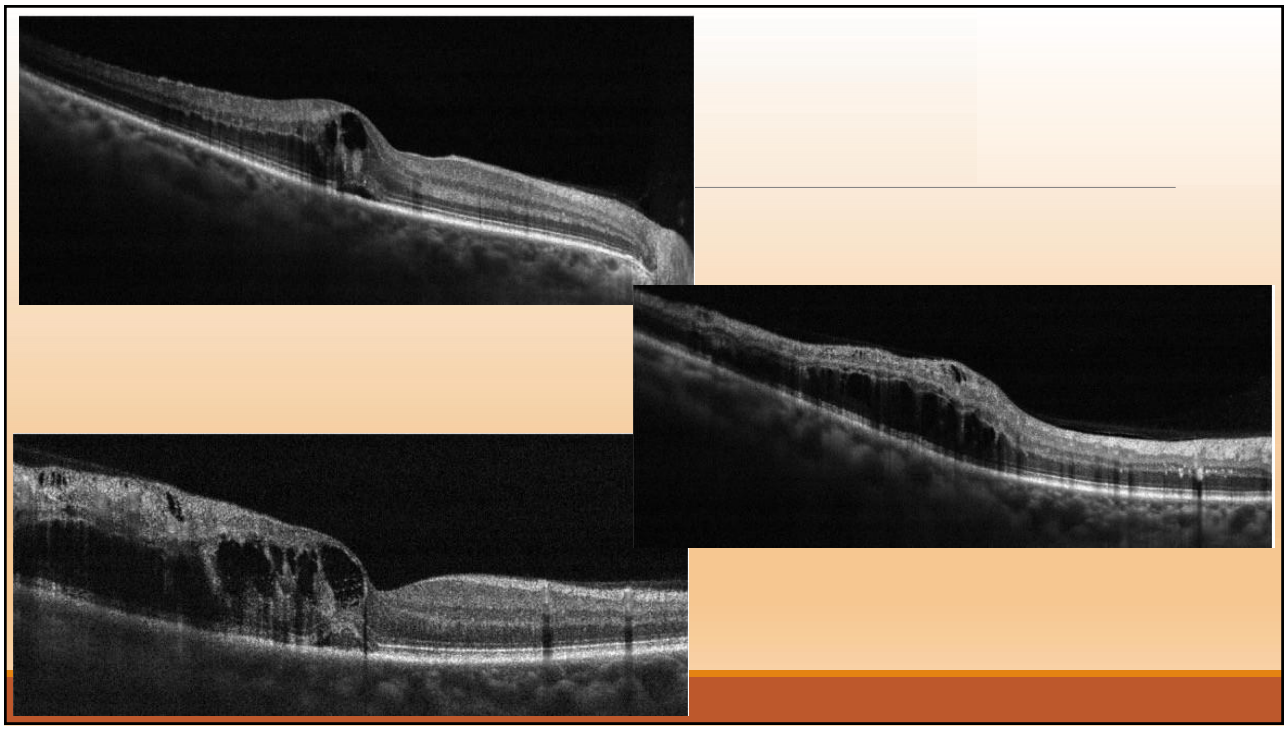
45



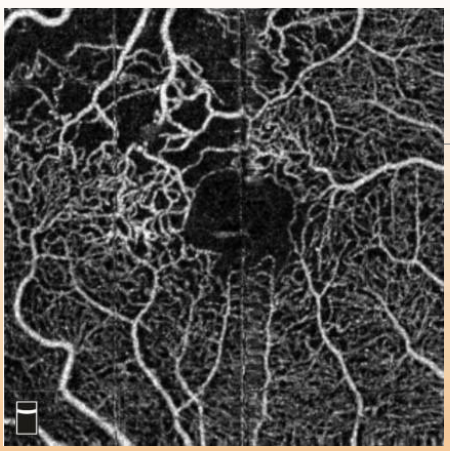
What else???

- Collaterals!!

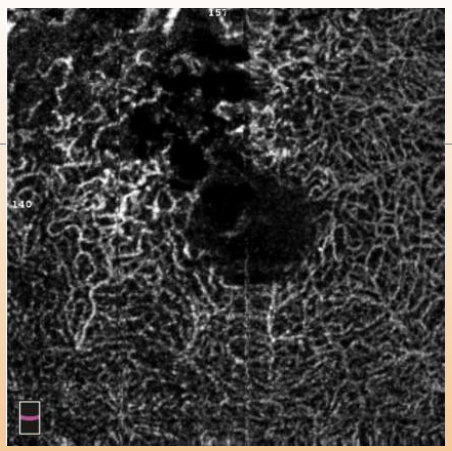
46



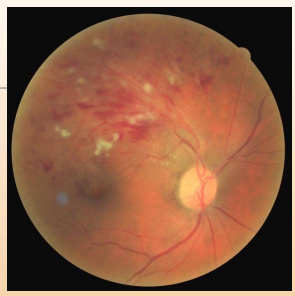
47

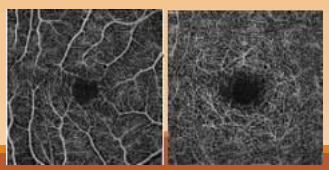


Superficial Capillary Plexus

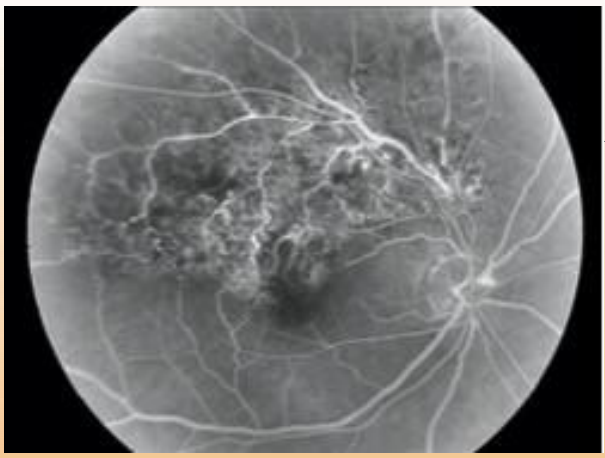


Deep Capillary Plexus





48



FA of BRVO:

- Delayed filling of occluded retinal vein
- Varying degrees of capillary nonperfusion

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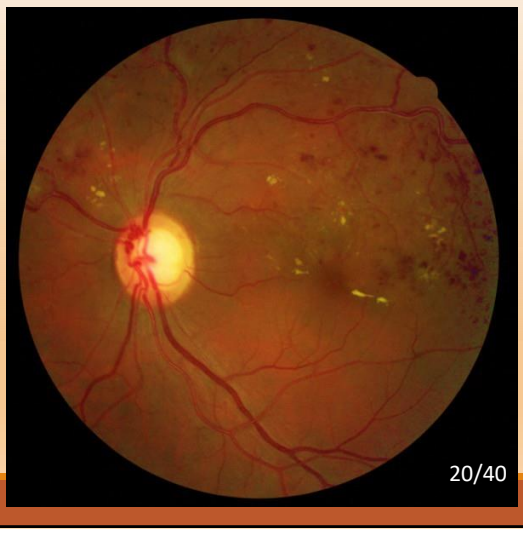
Treatment/Management

- *Co-Manage with Internist*
  - Optimizing control of systemic arterial HTN and serum lipid levels
- *Macular Edema*
  - Refer to retinal specialist; Anti-VEGF

50

57-year-old Diabetic male



- Decreased vision OS
- History of newly diagnosed DM and HTN (1 year)

He candidly reports that he has been having trouble regulating his blood sugar levels….

51

Evaluation of RVO

- *Three main components:*
  - Medical History: (+)Hypertension, Diabetes
    - A1C 9.0, unknown BS, BP elevated in office
  - Ocular Exam
  - Retinal imaging

52

Evaluation of RVO

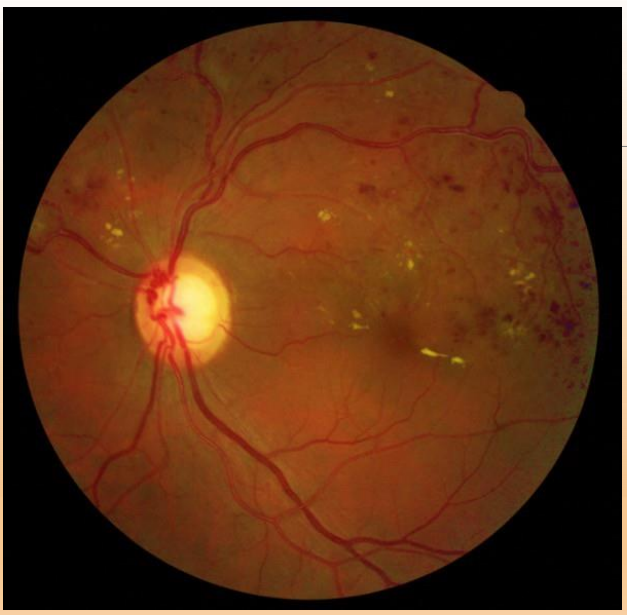
- *Three main components:*
  - Medical History
  - Ocular Exam…VA/?APD, ?Iris/Angle neovascularization, ?IOP
  - Retinal imaging

53

Evaluation of RVO

- *Three main components:*
  - Medical History
  - Ocular Exam
  - Retinal imaging

54



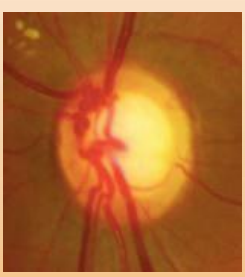
- Vascular tortuosity
  - Crossing changes
- Exudates
- Intraretinal hemorrhages

What kind of RVO?

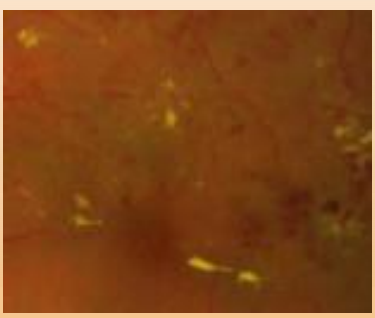
55

WHAT ELSE??

- ONH Collaterals

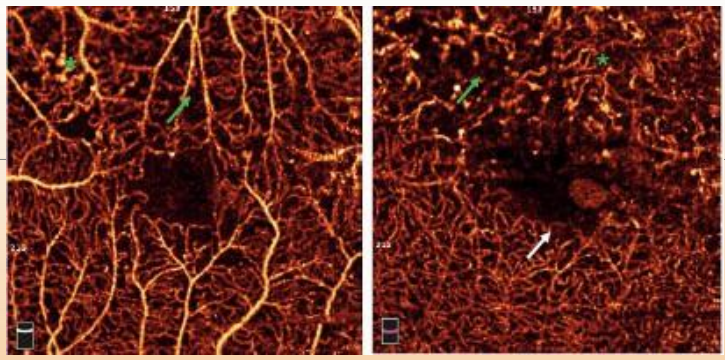


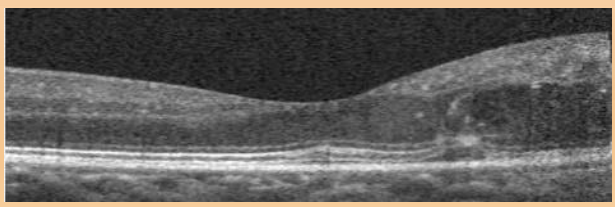
- Between retinal venules and choroidal circulation at the disc



- Retinal Collaterals

56





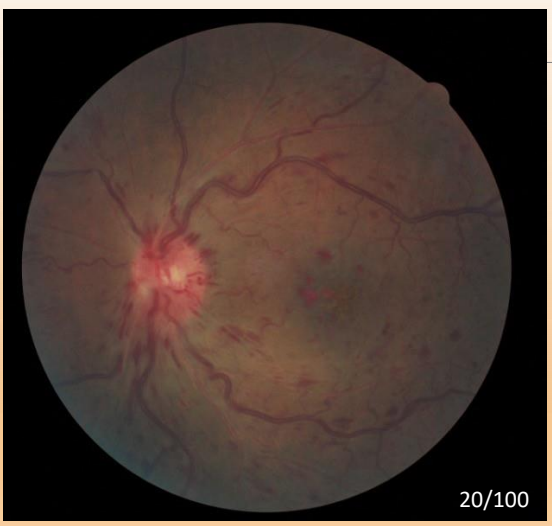
57

Treatment/Management

- *Co-Manage with Internist*
  - Optimizing control of systemic arterial HTN, Diabetes
- *Refer*
  - Macular edema!!

58

48-year-old Female



"Three months ago the vision in my left eye went bad and I have been seeing strange lights as well."

59

Evaluation of RVO

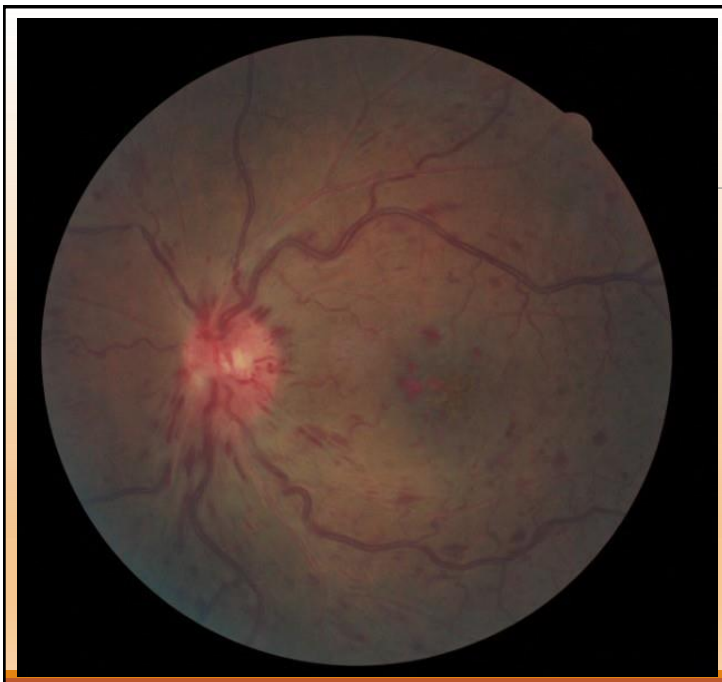
- *Three main components:*
  - Medical History: (+)H/O 2 miscarriages
  - Ocular Exam
  - Retinal imaging

60

Evaluation of RVO

- *Three main components:*
  - Medical History
  - Ocular Exam…VA/?APD, ?Iris/Angle neovascularization, ?IOP
  - Retinal imaging

61



What kind of RVO?

- Flame shaped hemorrhages in all 4 quadrants
- Intraretinal hemorrhages
- Papilloretinal edema
- Engorgement and tortuosity of major retinal veins

62

Evaluation of RVO

- *Three main components:*
  - Medical History
  - Ocular Exam
  - Retinal imaging

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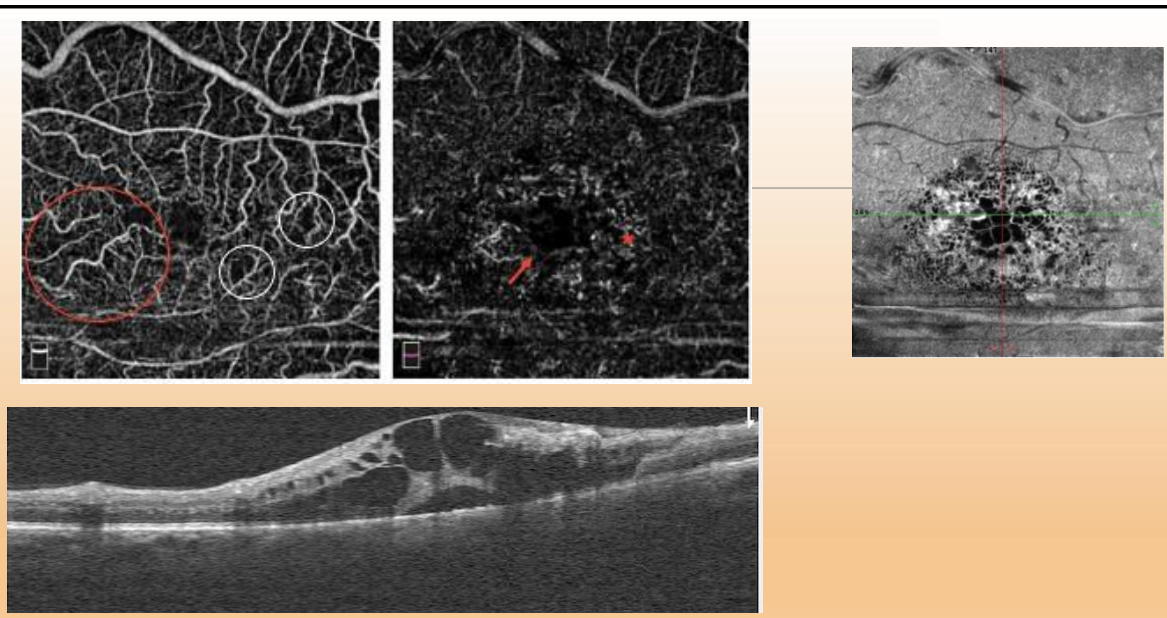

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What kind of RVO?

- *Suspected Non-Ischemic CRVO… Why??*
  - VA 20/100… with continued improvement
  - Absence of APD
  - Milder degree of hemorrhages
  - No CWS
  - Normal VF

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RECALL:: Systemic Etiology: CRVO

- Hypertension (most common systemic)
- Diabetes
- Hyperlipidemia
- Cardiovascular Disease
- Hyperviscosity Syndromes
- Vasculitis: Sarcoid, Syphilis, SLE

- Miscellaneous:
  - Drugs (Oral Contraceptives, diuretics)
  - Migraine

More detailed evaluations for bilateral cases or in patients who are <50 years.

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Evaluation of RVO: Medical History

- Atherosclerotic risk factors?
- Hypercoagulability risk factors?
  - Younger patients

Lab work:

Complete blood cell (CBC) count
Glucose tolerance test
Lipid profile
Serum protein electrophoresis
Chemistry profile
Hematologic tests
Syphilis serology
Thrombophilic screening, activated protein C resistance, lupus anticoagulant, anticardiolipin antibodies, protein C, protein S, and antithrombin III may be completed.

https://www.allaboutvision.com/conditions/eye-occlusions.htm

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Diagnosis: Hyperviscosity Disorder

- *Pt history was crucial in diagnosis*
  - *Co-Manage with hematologist; communication is a MUST*
- *Refer!! (macular edema)*
  - Anti-VEGF

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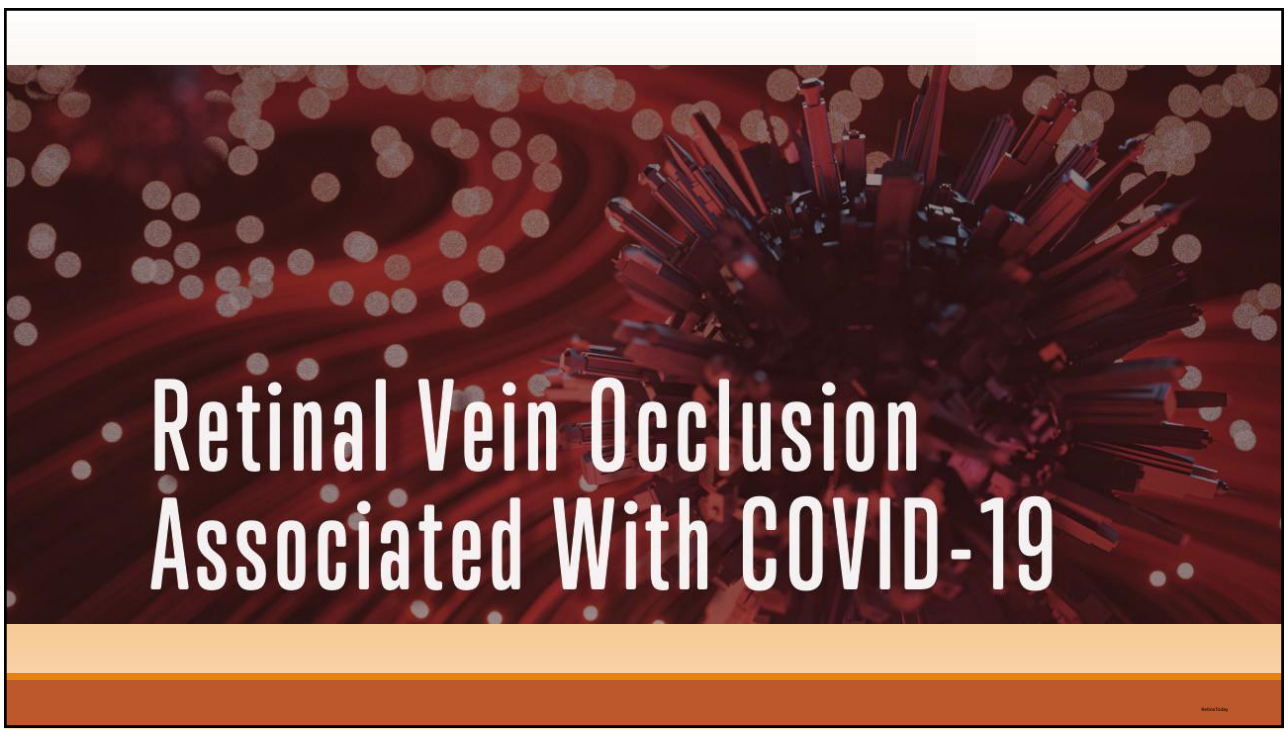

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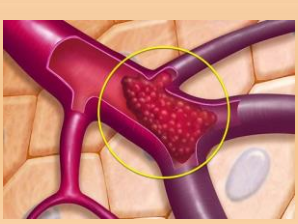
What we know about SARS-CoV-2:

(the virus that causes COVID 19)

- *The virus was initially considered primarily a respiratory illness*
- *NEW DATA: COVID-19 results in a uniquely profound pro-thrombothic cascade leading to both arterial and venous thrombosis*



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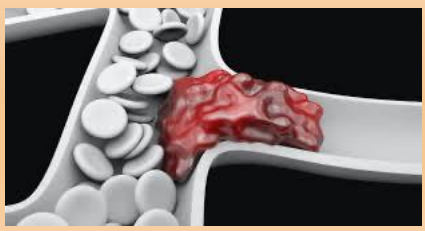
Pathophysiology behind hypercoagulable state:

- Severe inflammatory response originates in the alveoli leading to thrombosis of pulmonary vasculature
- Leads to a state of local coagulopathy
- Followed by generalized hypercoagulable state resulting in vascular thrombosis



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What we know about SARS-CoV-2:

(the virus that causes COVID-19)

- *The hypercoagulable state induced by COVID-19 may be linked with CRVO which is also associated with hypercoagulation*

RECALL:

- **Hypertension (most common systemic)**
- Diabetes
- Hyperlipidemia
- Cardiovascular Disease
- Hyperviscosity Syndromes
- Vasculitis: Sarcoid, Syphilis, SLE

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59-year-old Male

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59-year-old Male

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Findings??

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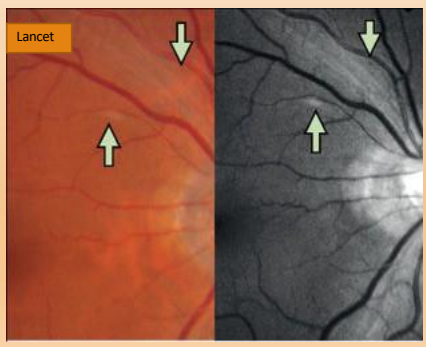
What we know about SARS-CoV-2:

(the virus that causes COVID-19)

PMH: (+) Microscopic Colitis
Meds: Aspirin 81mg/day → No association with CRVO

- *Retinal microvascular changes have been reported with COVID-19 including CWS and hemorrhages but not RVO*



https://retinatoday.com/articles/2020-sept/retinal-vein-occlusion-associated-with-covid-19

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Hypothesis:

The timing of COVID-19 infection, as documented by antibody testing in this patient, with visual symptoms and findings of a CRVO, suggest an association between the two conditions. The pathogenesis is consistent with COVID-19 inducing a hypercoagulable state, which can lead to CRVO.

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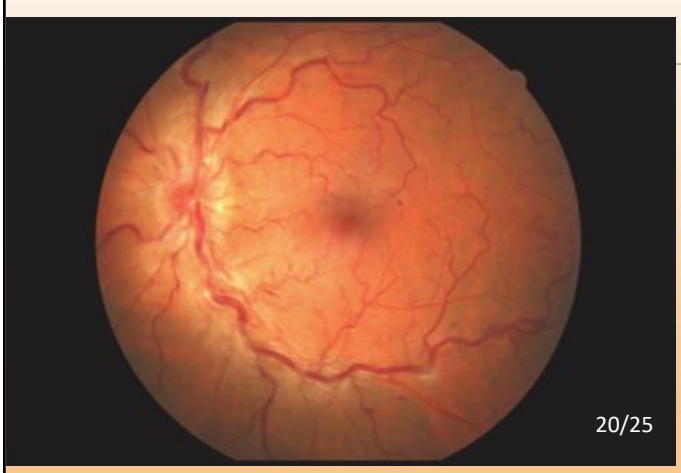
33-year-old Male



Referred to the ER due to blurred vision and flashing lights without any other neurological symptoms.

PMH: (-)HTN, sleep apnea, obesity or hypercoagulable state

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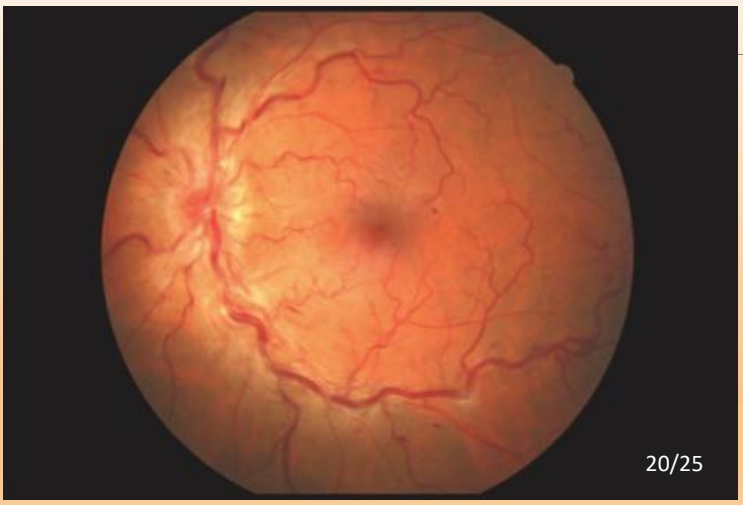
33-year-old Male…. What else?



3-week period of fatigue, dry cough, and SOB which ended two weeks prior to ocular symptoms…

PCR negative at time of admittance
IgG antibody test positive

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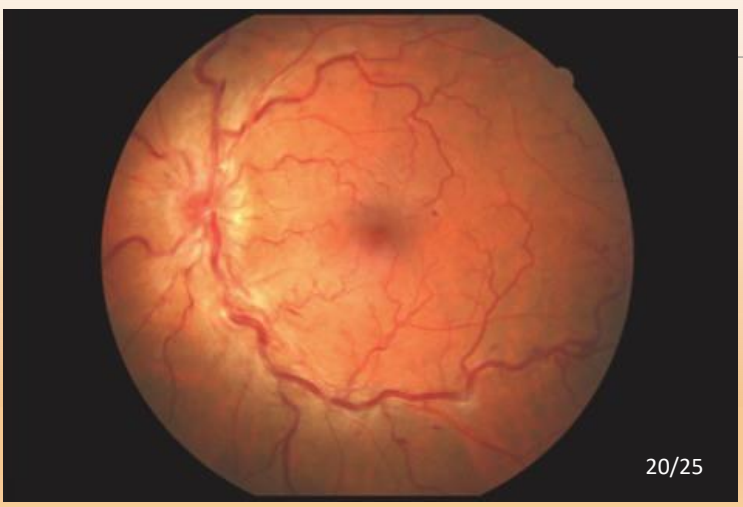
Fundoscopy



- Tortuosity and dilatation of all branches of the central retinal vein
- Dot, blot and flame-shaped hemorrhages throughout all four quadrants
- Optic disc edema

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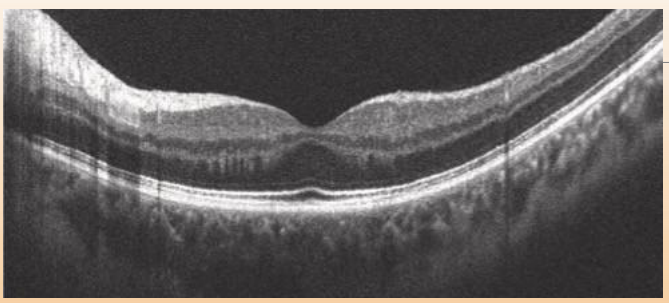
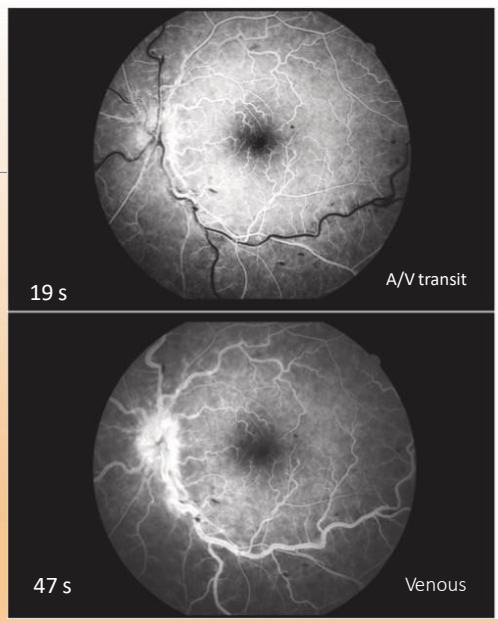
Ancillary Testing





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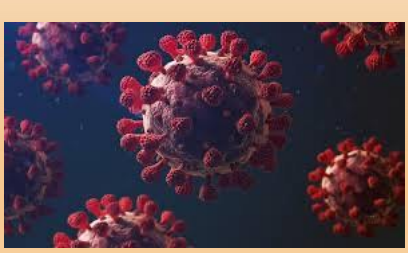
Summary:

- Eyes of patients with COVID-19 infection are at risk for vascular occlusive events and that visual symptoms may occur even with milder forms of systemic viral infection.



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SOUTHERN CALIFORNIA COLLEGE OF OPTOMETRY

CONTINUING EDUCATION COURSE SCHEDULE

2021 COURSE SCHEDULE

DATE	LOCATION	COURSE TOPIC	CE UNITS
July 10 & 11	**SCCO	MBKU** *Live Webinar*	**Ocular Disease Part II** *COPE Approval Pending*	16
September 19	**SCCO	MBKU** *Live Webinar*	**Joint SCCO I USC I VA Symposium** *COPE Approval Pending*	8
December 12	**SCCO	MBKU** *Live Webinar*	**Contemporary Topics in Optometry** *COPE Approval Pending*	8

GENERAL INFORMATION

MBKU CAMPUS LOCATIONS

SCCO I FULLERTON CAMPUS
2575 Yorba Linda Blvd. Fullerton, CA 92831

LEARN MORE & REGISTER *ketchum.edu/ce*

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Marshall B. KETCHUM UNIVERSITY
Southern California College of Optometry

Neurotrophic keratitis is a degenerative disease that warrants immediate attention[1]

oxervate® (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

OXERVATE is the first FDA-approved pharmacologic treatment that targets the root pathogenesis of neurotrophic keratitis (NK)[2]

Cenegermin-bkbj, the active ingredient in FDA-approved OXERVATE, is structurally identical to the human nerve growth factor (NGF) protein made in ocular tissues.[3]

Endogenous NGF is a protein involved in the differentiation and maintenance of neurons and is believed to support corneal integrity through three mechanisms (in preclinical models): corneal innervation, tear secretion, and epithelial cell growth.[3-5]

In clinical studies, with a single 8-week course of therapy:

- Up to **72%** of patients with NK achieved complete corneal healing*†[2]
- **80%** of patients who achieved complete corneal healing remained completely healed at 1 year (REPARO trial)[6]

OXERVATE is a recombinant human nerve growth factor indicated for the treatment of neurotrophic keratitis.

Important Safety Information

WARNINGS AND PRECAUTIONS

Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion.

ADVERSE REACTIONS

The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and increase in tears (1%-10% of patients).

Please see additional Important Safety Information on accompanying page and full Prescribing Information, including patient information, at OXERVATE.com/prescribing-information.

You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Dompé at 1-833-366-7387 or Usmedinfo@dompe.com.

TREAT NK TODAY
OXERVATE.com/HCP

*Study NGF0212 (REPARO): 52 patients per group; European patients with NK in one eye; 72% of patients completely healed; key findings were after 8 weeks of treatment; 6 times daily; vehicle response rate 33.3%.[2] Study NGF0214: 24 patients per group; US patients with NK in one or both eyes; 65.2% completely healed; vehicle response rate 16.7%[2,7]

†Complete corneal healing was defined as the absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of OXERVATE treatment.[2]

References: 1. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579. **2.** OXERVATE (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA: Dompé U.S. Inc.; 2019. **3.** Voelker R. New drug treats rare, debilitating neurotrophic keratitis. *JAMA*. 2018;320:1309. **4.** Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017;232:717-724. **5.** Muzi S, Colafrancesco V, Sornelli F, et al. Nerve growth factor in the developing and adult lacrimal glands of rat with and without inherited retinitis pigmentosa. *Cornea*. 2010;29:1163-1168. **6.** Data on file. Dompé U.S. Inc.; 2021. NGF0212. **7.** Pflugfelder SC, Massaro-Giordano M, Perez VL, Hamrah P, Deng SX, Espandar L, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy. *Ophthalmology*. 2020;127:14-26.

Dompé

US-OXE-1900180.02 02/21

oxervate™
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Brief Summary of Safety

Consult the full Prescribing Information for complete product information.

INDICATIONS AND USAGE

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

ADVERSE REACTIONS

Clinical Studies Experience Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Animal Data

In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species. In rats, hydrocephaly and ureter anomalies were each observed in one fetus at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart and aortic arch dilation were each observed in one fetus at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively. In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day. In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older [*see Clinical Studies (14)*].

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis and Mutagenesis Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD). In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

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