



SUNCOAST SEMINAR

Presented by the
**Pinellas Optometric
Association**

Course Syllabus

Suncoast Seminar 2024


Schedule of Events

Saturday, April 27, 2024

- 7:45 am – 8:15 am **Registration**
Continental Breakfast - sponsored by Eye Institute of West Florida
Exhibit Hall open
- 8:15 am – 9:55 am **Co-Managing the Light Adjustable Lens (90938-PO)**
T. Hunter Newsom, M.D., Brian Szabo, D.O., and Eric Fazio, O.D.
- 9:55 am – 10:40 am **Break** - sponsored by Updegraff Vision
Exhibit Hall open
- 10:40 am – 12:20 pm **Emerging Trends in Macular Disease (TQ) (90790-TD)**
Sherrol A. Reynolds, O.D.
- 12:20 pm – 1:10 pm **Lunch** - sponsored by St. Luke's Cataract & Laser Institute
Exhibit Hall open
- 1:10 pm – 1:20 pm **Lighthouse of Pinellas Update**
- 1:20 pm – 1:30 pm **F.O.A. Update**
- 1:30 pm – 3:10 pm **Eye on Systemic Disease (TQ) (90791-SD)**
Sherrol A. Reynolds, O.D.
- 3:10 pm – 3:30 pm **Break** - sponsored by Sight360
- 3:30 pm – 5:10 pm **The ODs Role in Diabetes (TQ) (86739-TD)**
Sherrol A. Reynolds, O.D.

Sunday, April 28, 2024


- 7:30 am – 8:00 am **Registration**
Continental Breakfast - sponsored by Next Vision Instruments
- 8:00 am – 9:40 am **Neural Pearls (TQ) (89379-NO)**
Joe Sowka, O.D.
- 9:40 am – 10:00 am **Break** – sponsored by Suncoast Seminar
- 10:00am – 11:40 am **Prevention of Medical Errors (89825-EJ)**
Joe Sowka, O.D.
- 11:40 am – 12:00 pm **Break** – sponsored by Suncoast Seminar
- 12:00 pm – 1:40 pm **Florida Jurisprudence (89275-EJ)**
Joe Sowka, O.D.



Eye on Systemic Diseases

Sherrol A. Reynolds OD, FAAO, FNAF, FORS
 Professor of Optometry
 Nova Southeastern University (NSU)
 College of Optometry

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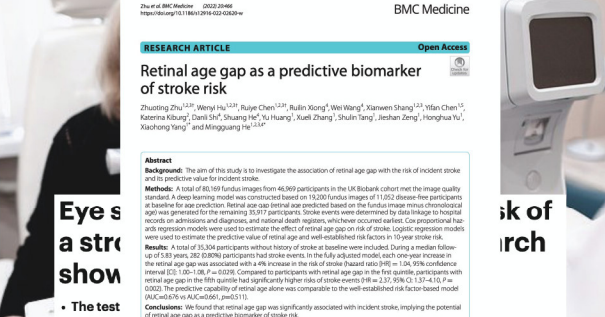
COPE Disclosure

Sherrol A. Reynolds OD, FAAO, FNAF, FORS

Serve on the speaker bureau, advisory or contributed to the board of:

Vision Service Plan (VSP), American Diabetes Association (ADA), Allergan (AbbVie Company)

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RESEARCH ARTICLE Open Access

Retinal age gap as a predictive biomarker of stroke risk

Zhuang Zhu^{1,2*}, Wenyi Hu^{1,2*}, Ruiyi Chen^{1,2*}, Rutin Xiong¹, Wei Wang¹, Xianwen Shang^{1,2}, Yan Chen¹, Kezhen Kong¹, Dawei Shi¹, Shuang He¹, Yu Huang¹, Xuei Zhang¹, Shulin Tang¹, Jianhui Zeng¹, Honghua Yu¹, Xiaochong Yang¹ and Mingqiang He^{1,3,4*}

Abstract
 Background: The aim of this study is to investigate the association of retinal age gap with the risk of incident stroke and its predictive value for incident stroke.
 Methods: A total of 40,169 fundus images from 46,969 participants in the UK Biobank cohort met the image quality standard. A deep learning model was constructed based on 19,000 fundus images of 13,602 disease-free participants at baseline for age prediction. Retinal age gap (retinal age predicted based on the fundus image minus chronological age) was generated for the remaining 30,777 participants. Stroke events were determined by data linkage to hospital records on admissions and diagnoses, and national death registers, whichever occurred earlier. Cox proportional hazards regression models were used to estimate the effect of retinal age gap on risk of stroke. Logistic regression models were used to estimate the predictive value of retinal age and well-established risk factors in 10-year stroke risk.
 Results: A total of 15,244 participants without history of stroke at baseline were included. During a median follow-up of 7.83 years, 282 (2.06%) participants had stroke events. In the fully adjusted model, each one-year increase in the retinal age gap was associated with a 4% increase in the risk of stroke (hazard ratio [HR] = 1.04, 95% confidence interval [CI]: 1.00–1.08, P = 0.029). Compared to participants with retinal age gap in the first quintile, participants with retinal age gap in the fifth quintile had significantly higher risk of stroke events (HR = 2.37, 95% CI: 1.31–4.12, P = 0.002). The predictive capability of retinal age alone was comparable to the well-established risk factor-based model (ROC-AUC 0.64 vs 0.64, P = 0.11).
 Conclusions: We found that retinal age gap was significantly associated with incident stroke, implying the potential of retinal age gap as a predictive biomarker of stroke risk.
 Keywords: Retinal age, Stroke, Prediction, Biomarker

**Eye s
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- The test
- Research

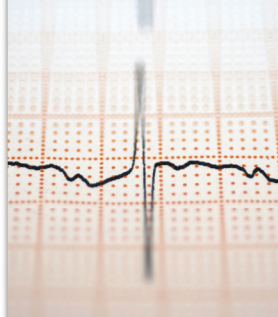
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Course Agenda

- Describe the latest data (increasing prevalence) of common systemic conditions.
- Know the current guidelines in the diagnosis and management.
- Appreciate advance technologies and methodologies to analyze ocular findings including multi-modal imaging with SD-OCT, SD-OCTA, SD-EDI, fluorescein angiography, fundus autofluorescence (FAF), and wide-field imaging.
- Recognize the importance of the OD role in the interdisciplinary management of systemic diseases.

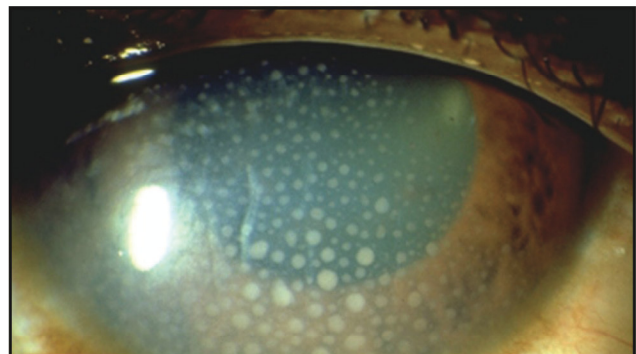


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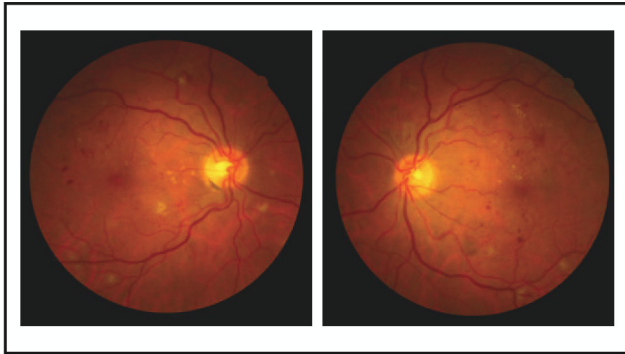
Case 1

- 54 year-old BF c/o painful, red, watery, and photophobic OD X 4 days
- POHX: Unremarkable
- PMHX: + Type 2 Diabetes, +HTN, + Hypercholesterolemia
- Medications: Metformin 1000mg BID, Lotrel 10/40, and Lipitor 20mg
- BCVA: OD 20/ 25 and OS 20/30
- Pupils: - APD
- SLE & DFE.....

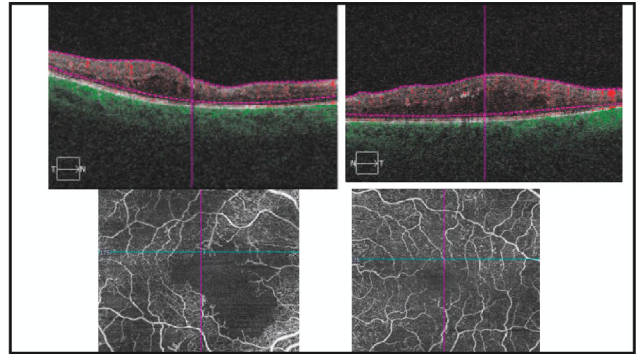
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Assessment & Plan

- Very Severe NPDR with CI- DME OU
- Stage 3 HTN Retinopathy OU
- Granulomatous Uveitis OD
 - Pred Forte q1hr OD
 - RTC X 1 day for f/u evaluation
- Set-up appointment with PCP for physical further evaluation and CBC w/ differential
 - Summary report included
- Referred to retinal specialist

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Prevalence of Diabetic Retinopathy in the US in 2021

Elizabeth A. Lundeen, PhD¹; Zeb Burke-Conte, BS²; David B. Rein, PhD, MPA¹; et al
> Author Affiliations

2060 approximately 60.6 million US adults, or 17.9% of the adult population will have diabetes

Findings The study team estimated that 9.60 million people in the US (26.43% of those with diabetes) had diabetic retinopathy and 1.84 million people (5.06% of those with diabetes) had vision-threatening diabetic retinopathy in 2021. There was marked variation in prevalence across states and the number of people living with diabetes-related eye disease grew substantially since prevalence was last estimated in 2004.

Meaning The US prevalence of diabetes-related eye disease remains high and may grow in the coming decades due to the increasing burden of diabetes among youth and adults.

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Diabetic Retinopathy is the 1st cause of Vision Loss in Adults Aged 20–74 yr

Diabetes in the United States

38.4 million

Diagnosed: 29.7 million

Undiagnosed: 8.7 million

Prediabetes: 96 million

537 million adults have diabetes

1.31 Billion people could be living with diabetes by 2050

...these numbers are expected to rise as the prevalence of diabetes increases

Centers for Disease Control and Prevention. National Diabetes Statistics Report website. <https://www.cdc.gov/diabetes/data/statisticsreport/index.html> Accessed March, 2024 2 American Diabetes Association. Diabetes Care 2023;46(Supplement_1):S203–S215 International Diabetes Federation Atlas 10TH edition. Available from <https://www.idf.org/about-diabetes/what-is-diabetes/facts-figures.html>; Accessed 9 October 2023

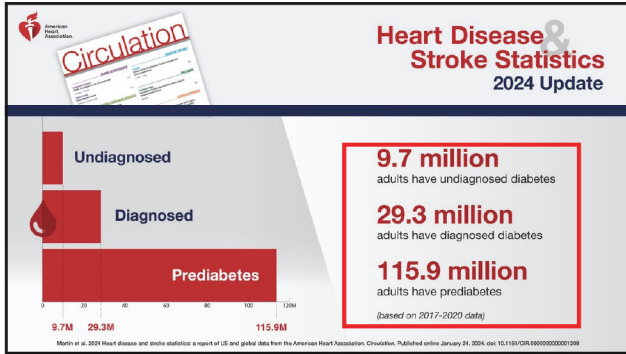
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Diabetes Health Impact

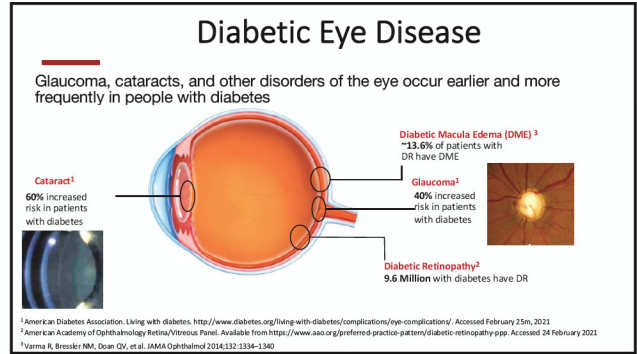
- Leading cause of blindness in working age adults (20-74 year of age.) 9.6 Million Americans
- Diabetic retinopathy
- Stroke
- 2-fold to 4-fold increase in cardiovascular mortality and stroke
- Cardiovascular Disease
- Diabetic Nephropathy
- Leading cause of end-stage renal disease
- Diabetic Neuropathy
- Leading cause of non-traumatic lower extremity amputations

National Diabetes Information Clearinghouse. Available from <http://diabetes.niddk.nih.gov>. Accessed 9 February 2022
 Centers for Disease Control and Prevention. Available from <https://www.cdc.gov/diabetes/data/statisticsreport/index.html#diabetic-complications>; Accessed 8 February 2022

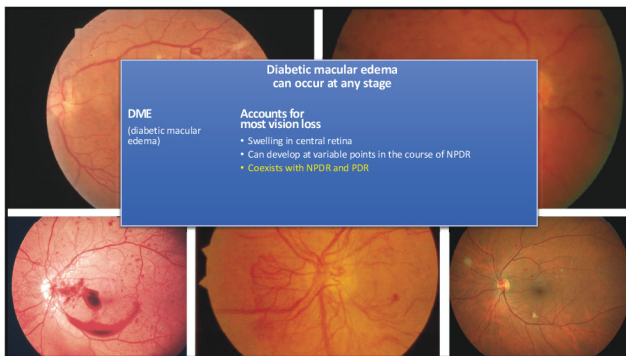
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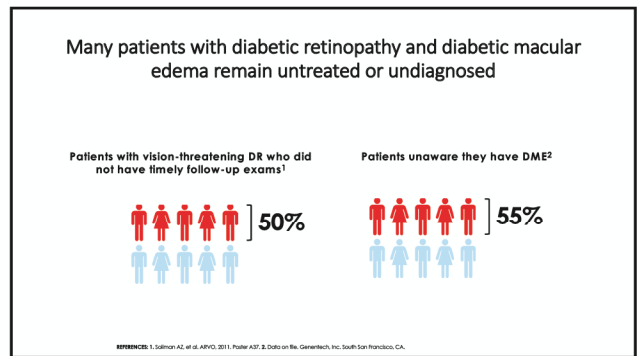
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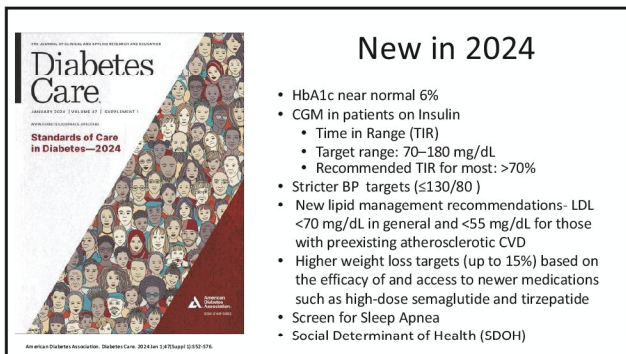
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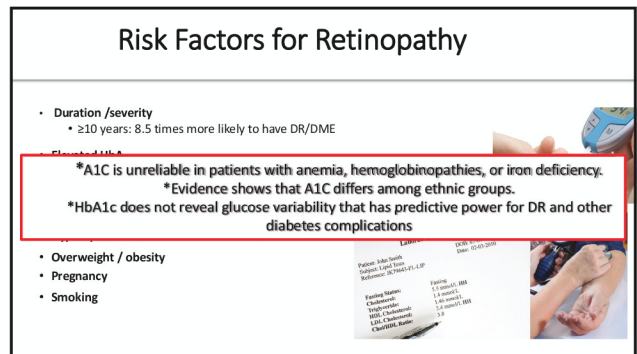
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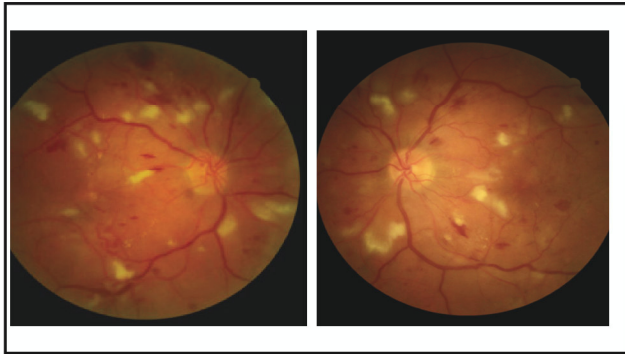
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Time in Range (TIR)

- A new parameter to evaluate blood glucose control
- Indicates the percentage time a person's glucose value was within the target range during a defined period
- Target range: **70-180 mg/dL**
- Recommended TIR for most: **>70%**
- **The higher the TIR range percentage- the lower the risk of developing complications**
- **The lower the TIR range percentage, the higher the risk of developing complications**

AGP Report

Diabetes Management Report (DMR) 2023-2024

Target Range: 70-180 mg/dL

Time in Range (TIR): 78.2%

Time Below Range (TBR): 18.5%

Time Above Range (TAR): 3.3%

Time in Hypoglycemia (TIR-H): 1.2%

Time in Hyperglycemia (TIR-H): 2.1%

Time in Very High (TIR-VH): 0.5%

Time in Very Low (TIR-VL): 0.3%

Time in Normal (TIR-N): 78.2%

Time in Borderline (TIR-B): 1.5%

Time in Severe (TIR-S): 0.2%

Time in Critical (TIR-C): 0.1%

Time in Extreme (TIR-E): 0.1%

Time in Unstable (TIR-U): 0.1%

Time in Stable (TIR-S): 0.1%

Time in Normal (TIR-N): 78.2%

Time in Borderline (TIR-B): 1.5%

Time in Severe (TIR-S): 0.2%

Time in Critical (TIR-C): 0.1%

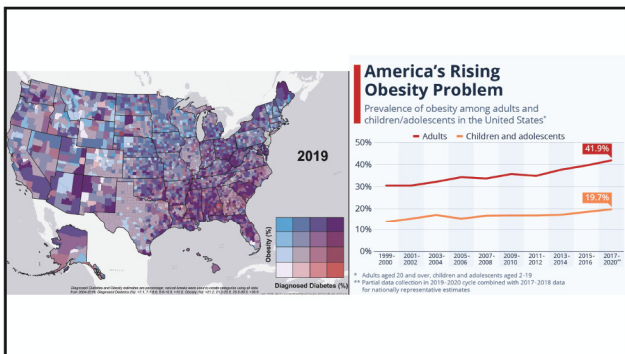
Time in Extreme (TIR-E): 0.1%

Time in Unstable (TIR-U): 0.1%

Time in Stable (TIR-S): 0.1%

American Diabetes Association. Diabetes Care 2023;46(Supplement_1):S203-S215
American Diabetes Association. Diabetes Care. 2024 Jan 1;47(Suppl 1):S52-S76.

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SKINNY SHOT

Ozempic (semaglutide) injection (For Adults With Type 2 Diabetes)

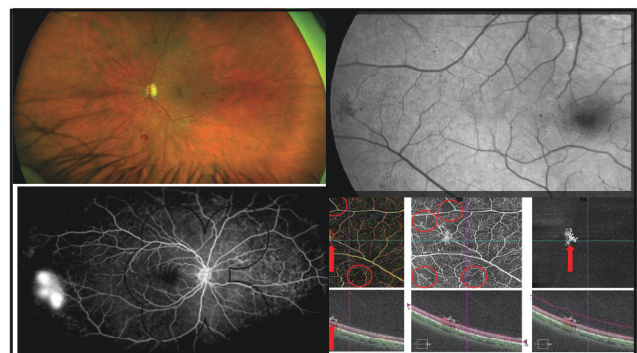
Larger weight loss substantially reduces A1C and fasting glucose and has been shown to promote sustained diabetes remission through at least two years

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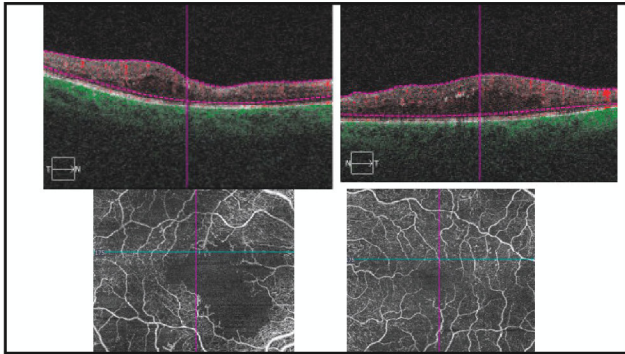
Complications

- Pancreatitis- Inflammation of the pancreas
- Low blood sugar (hypoglycemia)
- Serious allergic reactions
- Kidney problems (kidney failure)
- Severe stomach problems (stomach paralysis)
- Gallbladder problems

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Approved Agents for DR/DME

| |
|---|
| Ranibizumab 0.3 mg (DME) |
| Aflibercept 2.0 mg |
| Brolucizumab 6.0 mg |
| Faricimab 6.0 mg |
| Aflibercept HD (8.0 mg) |
| Steroids: |
| Dexamethasone implant (Ozurdex) |
| Fluocinolone implant (Iluvien) |
| Intravitreal Triamcinolone (Triessence) |

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| |
|--------------------------------------|
| Biosimilars |
| Ocuphire Pharma's APX3330 |
| Ocuterra Failed Phase 2 (3/2024) |

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ARTIFICIAL INTELLIGENCE for the Screening of Diabetic Retinopathy

TELEMEDICINE AND ARTIFICIAL INTELLIGENCE FOR DIABETES

The American Diabetes Association (ADA) recommends retinal telemedicine screening to identify **Diabetic Retinopathy** as a method of overcoming barriers to in-person care, such as a low provider-to-patient ratio, and prohibitive distance to reach a provider.^{1,2} That said, it's important to note that retinal photos are not a substitute for a comprehensive dilated eye exam. This is especially the case when the photos are unreliable and for follow-up if abnormalities are detected. Two automated deep-learning artificial intelligence devices are available: The IDx-DR, from Digital Diagnostics, and the EyeScreener, from EyeNuk, Inc.

- The Dx-DR sensitivity and specificity of 87.4% and 89.5%, respectively, 1 in 10 patients will have a false-positive or false-negative result.
- EyeNuk is an AI screening program that utilizes the EyeArt software which has shown positive results with over 95% sensitivity when using fundus images obtained from smartphone

1/1 Fund and Drug Administration: FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems. 2018. Accessed August 07, 2022.

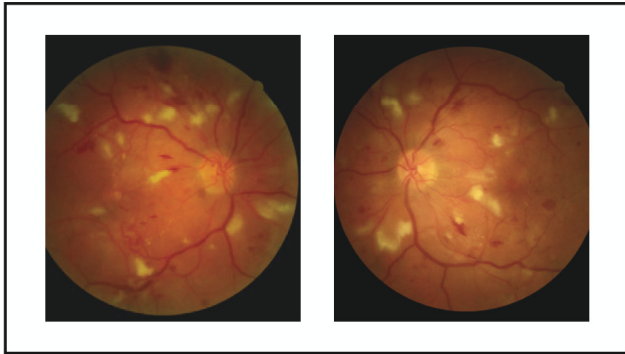
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The Multidisciplinary Diabetes Care Team

| | | |
|--|---|---|
| Physicians <ul style="list-style-type: none"> Endocrinologist Primary Care Podiatrist Other Specialists | Nurses and Certified Diabetes Care and Education Specialists | Advance Practice Providers <ul style="list-style-type: none"> Nurse Practitioner Physician Assistant |
| Exercise Physiologists | Person with Diabetes and Family | PFCD Professionals <ul style="list-style-type: none"> Pharmacist Podiatrist Optometrist Screen |
| Social Workers and Case Managers | Mental Health Professionals <ul style="list-style-type: none"> Psychologist Behavioral Therapist Manager & Family Therapist | Registered Dietitian Nutritionists |

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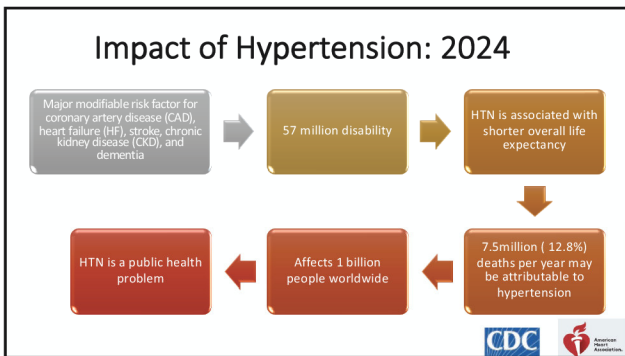
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Impact of Hypertension: 2024

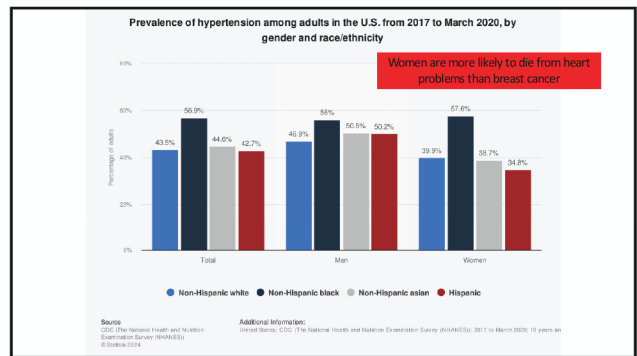
Nearly half of adults have hypertension (119.9 million)

About 1 in 4 adults with hypertension have their hypertension under control (52%)

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NEW Hypertension Guidelines

- Defined as a Blood Pressure of **≥130/80 mmHg**
 - A change from the old definition of ≥140/90
 - Complications that can occur at those lower numbers.

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Recommendations for BP Goal for Patients With Hypertension

References that support recommendations are summarized in Online Data Supplement 26 and Systematic Review Report.

| COE | LOE | Grade | Recommendation |
|-----|-----|-------|--|
| I | A | 1 | For adults with confirmed hypertension and known CVD or 10-year ASCVD event risk of 10% or higher (see Section 8.3.2), a BP target of less than 130/80 mm Hg is recommended (1-5). |

9.6. Diabetes Mellitus

Recommendations for Treatment of Hypertension in Patients With DM

References that support recommendations are summarized in Online Data Supplements 65 and 47 and Systematic Review Report.

| COE | LOE | Grade | Recommendation |
|-----|-----|-------|--|
| I | A | 1 | In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg (1-6). |

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Blood Pressure Categories

| BLOOD PRESSURE CATEGORY | SYSTOLIC mm Hg (upper number) | and | DIASTOLIC mm Hg (lower number) |
|---|-------------------------------|--------|--------------------------------|
| NORMAL | LESS THAN 120 | and | LESS THAN 80 |
| ELEVATED | 120 – 129 | and | LESS THAN 80 |
| HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1 | 130 – 139 | or | 80 – 89 |
| HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2 | 140 OR HIGHER | or | 90 OR HIGHER |
| HYPERTENSIVE CRISIS (consult your doctor immediately) | HIGHER THAN 180 | and/or | HIGHER THAN 120 |

BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure).

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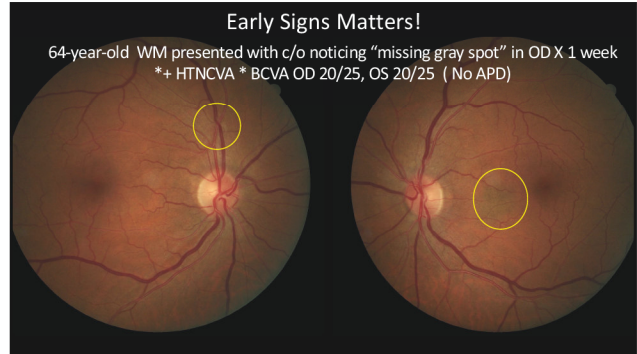
Recently published 2023 European Society of Hypertension (ESH) Guidelines for the Management of Arterial Hypertension

Table 2. Blood pressure classification (in mm Hg)

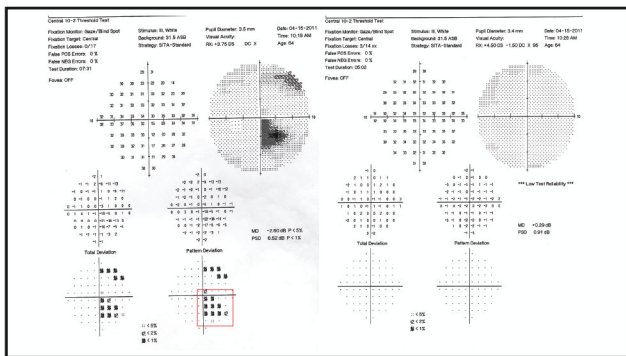
| Normal (Systolic/Diastolic) | Elevated/High Normal | Hypertension, Stage/Grade 1 | Hypertension, Stage/Grade 2 | Hypertension, Stage/Grade 3 |
|------------------------------|----------------------|-----------------------------|-----------------------------|-----------------------------|
| ACC/AHA <120/<80 | 120-129/<80 | 130-139/80-89 | ≥140/≥90 | Not defined |
| ESC/ESH 120-129/80-84 | 130-139/85-89 | 140-159/90-99 | 160-179/100-109 | ≥180/≥110 |

Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023 Dec; 14(12):1874-2071.

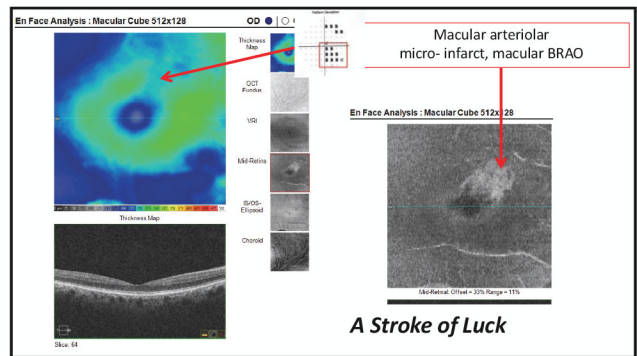
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HYPERTENSIVE RETINOPATHY (HTR)

Retinal vasculature is **AUTOREGULATED**

- The absence of sympathetic nerve supply
- Initial response to HBP = generalized vasoconstriction of the arteries
- Persistent increase in BP
- Intima layer: Thickening
- Media layer: Hyperplasia
- Arteriolar wall: Hyaline degeneration
- Eventually there is retinal-blood-barrier breakdown

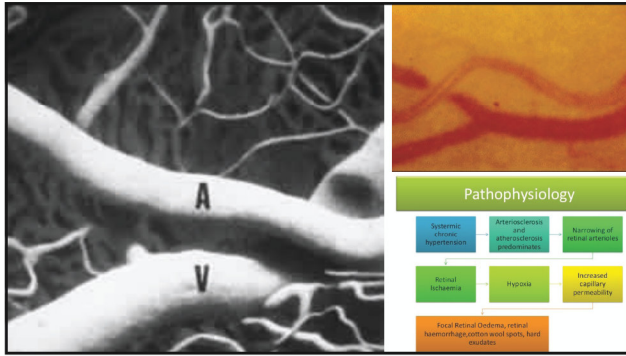
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Hypertension Ocular Complications

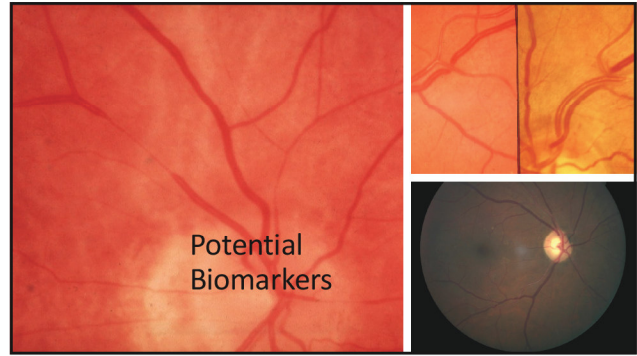
- **HYPERTENSIVE RETINOPATHY**
 - HTR is the most common ocular manifestations of HTN
- **HYPERTENSIVE OPTIC NEUROPATHY**
 - OPTIC DISC EDEMA
 - OPTIC ATROPHY
 - ISCHEMIC OPTIC NEUROPATHY
- **HYPERTENSIVE CHOROIDOPATHY**

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| Current Classification System for Hypertensive Retinopathy | | | |
|---|---|---|--|
| Keith-Wagner-Baker Classification System and Associated Clinical Features | | Wong- Mitchell Classification System Clinical Features and Associated Classification System | |
| Grade 1 | Generalized arteriolar narrowing | Mild | Generalized/focal arteriolar narrowing, arteriovenous nicking, opacity of arteriolar wall (copper wiring), or combination of these signs |
| Grade 2 | Focal narrowing and arteriovenous nicking | Moderate | Soft/hard exudates, hemorrhages (flame, dot, blot), microaneurysms, or combination of these signs |
| Grade 3 | Grade 2 plus exudates, hemorrhages, cotton wool spots (CWS) | | Malignant |
| Grade 4 | Grade 3 plus optic disc swelling | | |

Systemic Associations Proposed by Wong and Mitchell for the Wong-Mitchell

- *Modest association with risk of stroke. However, association has only specifically observed for generalized arteriolar narrowing and arteriovenous nicking.
- *Modest association with coronary heart disease. However, association has only specifically observed for focal narrowing and arteriovenous nicking.
- *Modest association with death. However, association has only specifically observed for focal/generalized arteriolar narrowing and arteriovenous nicking in middle-aged persons.
- *Strong association with the risk of stroke. However, association has only been observed for microaneurysms, soft exudates, like hemorrhages or flame-shaped hemorrhages.
- *Strong association with cognitive decline. However, association has only been specifically observed for microaneurysms, soft exudates, and retinal hemorrhages.
- *Strong association with death from cardiovascular causes. However, association has not been demonstrated with any specific parameter.
- Strong association with death. However, no studies support this conclusion.

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Early HTR Sign a predictor of CVD

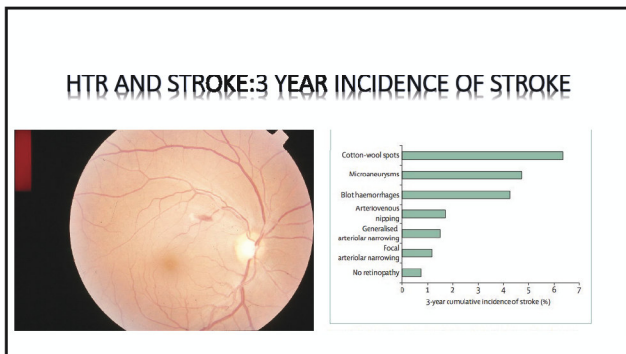
The ARIC study- the presence of AV nicking and focal retinal arteriolar narrowing was associated with an increased risk of MRI-detected silent cerebral infarcts.

Only AV nicking was associated with incident stroke in the CHS and the ARIC cohort.

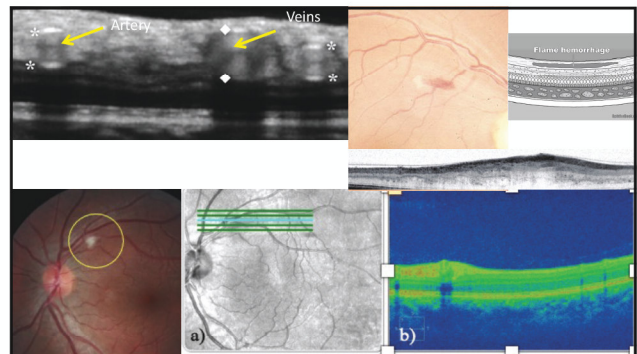
Focal retinal arteriolar narrowing and AV nicking at baseline was associated with an increased risk of incident stroke, or stroke mortality.

The atherosclerosis risk in communities study. Stroke. 2008; 37: 82-86.
The cardiovascular health study. Am J Epidemiol. 2007; 165: 76-83.
Prevalence and associations of enhanced retinal arteriolar light reflex: A new tool for early signs. Ophthalmology. 2017; 124: 113-120.

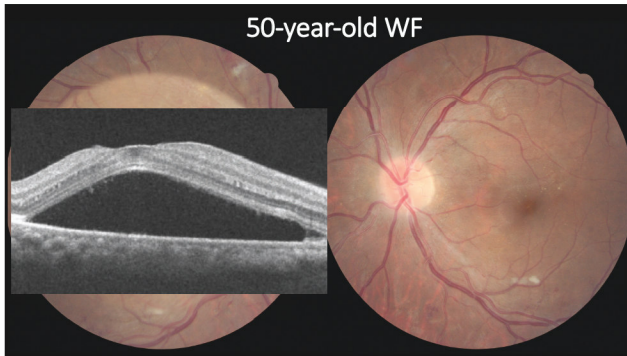
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BP in office 195/120mmHg

More Information

- What's the Dx?
- How should condition be managed?

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The myth & truth about malignant HTR

MYTHS VS FACTS

- o Myth
 - o Malignant HTR occurs in all patients with HTN
 - o BP needs to be lowered STAT
- o Truth
 - o Malignant HTR rarely occurs
 - o 1 to 2 cases per million per year
 - o BP must be lowered slowly over hours or days

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Hypertensive Crisis

- Urgency**
 - Severe Hypertension (> stage2) + NO End Organ Damage
 - Usually due to under-controlled HTN
- Emergency (911)**
 - Severe Hypertension Severely elevated BP (≥180/120mmHg) + End Organ Damage

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Hypertensive Urgency

Goal: Reduce BP over several hours to day

- Elderly at high risk of ischemia from rapid reduction of BP, therefore slower reduction in BP in this patient population

Treatment

- Initiate medication
- Increase dose of existing medication or add another medication
- Re-institute medication(s) in non-compliant patients

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Hypertensive Emergency

Goal: Lower Diastolic BP to approximately 100-105 over 2-6 hours

- Anti-hypertensive agents (IV drip) for and admission to ICU
- Maximum initial fall not to exceed 25%
- More aggressive decrease (abrupt drop in BP) can lead insufficient perfusion pressures and organ damage
 - Ischemic stroke and myocardial ischemia

Treatment

- If focal neurological symptoms present, obtain MRI to r/o acute stroke (rapid BP correction contraindicated)
- **The mortality rate is 50% at 2 months and 90% at one year if untreated**

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Signs and Symptoms/ End-Organ Damage

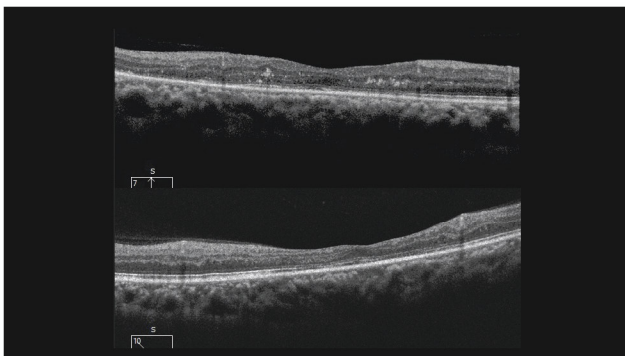
- Headaches
- Nausea/ vomiting
 - Cerebral edema
- Epistaxis
- Chest Pain
- Shortness of Breath (SOB)
- Confusion
- Loss of consciousness
- Dizziness
- TIA/AF
- Diplopia
- Other neurological signs and symptoms

- Hypertensive Encephalopathy
- Intracerebral Hemorrhage
- Acute MI
- LV failure with pulmonary edema
- Acute Coronary Syndrome(ACS)
- Dissecting aortic aneurysm
- Eclampsia/ Pre-eclampsia

55

32 year old female with a history of hypertensive emergency, presenting with a left inferior visual field defect OS. BCVA OD 20/20 and OS CF@2 FT with

56



57

Hypertensive Choroidopathy

The choriocapillaries are vulnerable to acute severe HBP rise

Vasculature alteration causes choroidal vasculature infraction

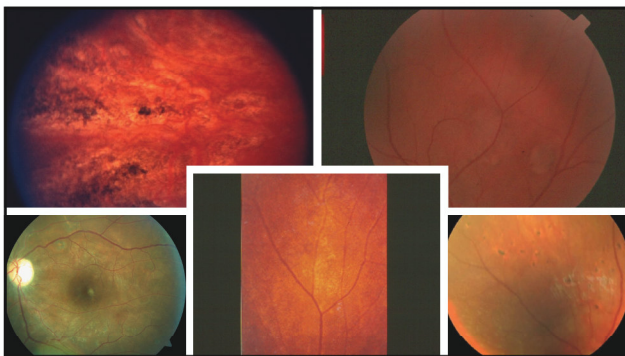
HTR is typically observed with chronic slow progressive HBP

HTN choroidopathy is more common in YOUNG patients with acute severe HBP

They do not autoregulate

Overlying RPE damage

58

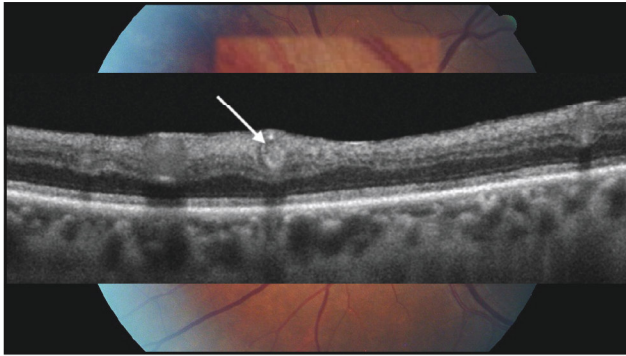


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Hypertensive Choroidopathy Management

- The lesions are NOT the problem
- Because of the association with ACUTE onset of HTN
- URGENT REFERRAL

60



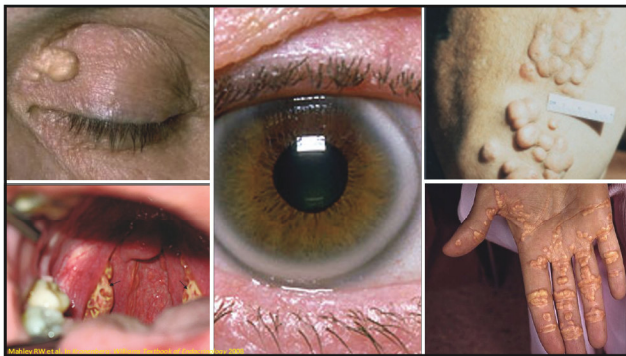
61

Impact of Hypercholesterolemia 2024

- 86 million U.S. adults have total cholesterol levels above 200 mg/dL.
- Nearly 25 million adults in the United States have total cholesterol levels above 240 mg/dL.
- High cholesterol raises the risk for heart disease, the leading cause of death, and for stroke, the fifth leading cause of death.

| | |
|--|--|
| Cholesterol <ul style="list-style-type: none"> Desirable <200 Borderline High 200-339 High ≥240 | Triglycerides <ul style="list-style-type: none"> Desirable <150 Borderline 175-199 High 200-499 Very High ≥500 |
| HDL <ul style="list-style-type: none"> Low <40 High ≥60 | LDL <ul style="list-style-type: none"> Desirable < 100 (70) Borderline 100-159 High 160-189 Very High ≥190 |

62



63

Emboli

- Cholesterol (75%)
 - Most commonly originating from the ipsilateral carotid artery
- Platelet/fibrin (25%)
- Calcific (10%)
- Infectious
 - Both Spot hemorrhage
- Medications
 - Serotonin

64

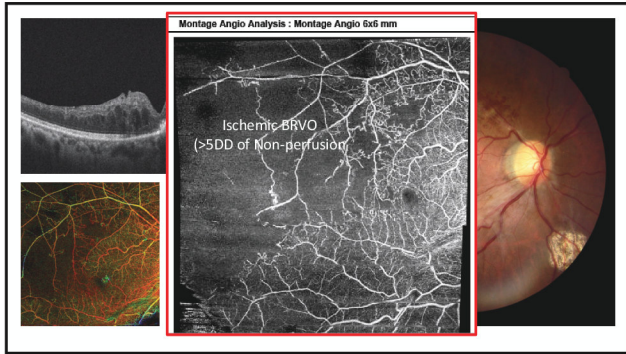
RVO 16.4 million

Global epidemiology of retinal vein occlusion: a systematic review and meta-analysis of prevalence, incidence, and risk factors. J Glob Health. 2018;9(2):12042.

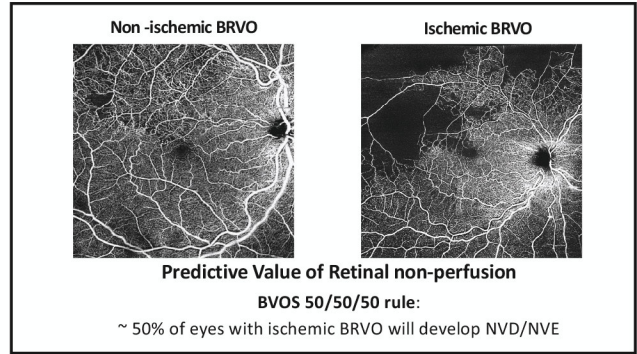
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55 year-old male: BCVA 20/20 OD and OS

66



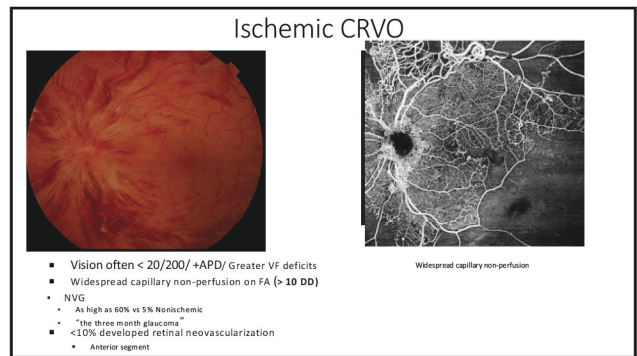
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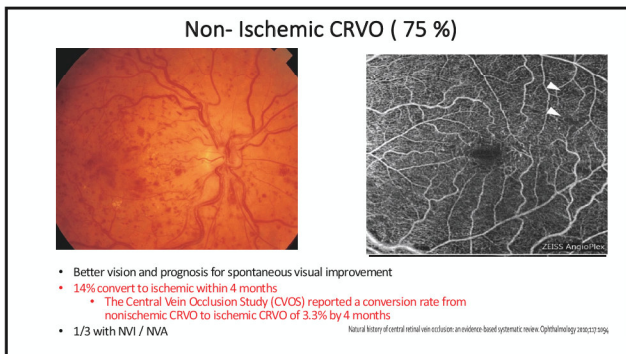
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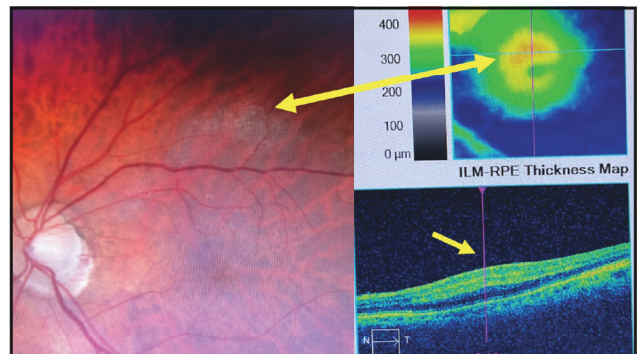
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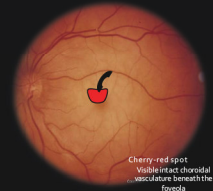


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- Characteristics
 - Sudden severe visual loss
 - Painless
 - Retinal appearance
 - Opaque and edematous
 - Most prominent in posterior pole
 - Thickest ganglion cell layer



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Retinal Artery Occlusion Emergent Stroke Evaluation

CRAO, BRAO, & TIAs = a stroke & needs to be recognized as an EMERGENCY!

- Silent POSITIVE DWI-MRI strokes are seen in:
 - >55% of CRAO
 - ~31% of BRAO
 - ~18% OF TVO
- Pts with (+) DWI-MRI silent strokes have a High risk for MAJOR stroke
- Especially during the next week to month
- Rate for stroke peaks (~60%) within 1 week s/p CRAO onset
- Urgent referral to ER (with stroke center) is CRUCIAL
- Management requires identifying and treating risk factors + neuro consult + cardiology evaluation

Update on the Management of Central Retinal Artery Occlusion

Michael D'Amico, MD, MPH¹, Valerie Boucsei, MD^{2,3,4}, Nancy J. Newman, MD^{5,6,7}

KEYWORDS
 • Central retinal artery occlusion • Branch retinal artery occlusion • Stroke • Ischemia • Management • Treatment • Prognosis

KEY POINTS

- Acute central retinal artery occlusion (CRAO) and branch retinal artery occlusion (BRAO) are the most common types of retinal artery occlusion (RAO).
- The risk factors for a CRAO or BRAO are similar and include cardiovascular risk factors and a retinal vascular anomaly.
- Up to 24% of patients with acute RAO have concomitant cerebral infarctions or TIA within 90 days.
- Prompt and correct identification and treatment of RAO is critical to optimize visual outcomes.
- Management of RAO should be focused on secondary prevention of stroke events, such as cerebral ischemia, myocardial infarction, and cardiovascular death.

Retinal and ophthalmic artery occlusions preferred practice pattern [published correction appears in Ophthalmology. 2020;127(9):1280]. Ophthalmology. 2020;127(9):P259-P287. Bulawa RA, Mendelson SJ, Brinson JR. Acute secondary prevention of ischemic stroke: overlooked no longer. *Expert Rev Neurother*. 2014;14(2):169.

75

A 58-YEAR-OLD BLACK MALE + SICKLE CELL TRAIT

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Sickle cell Maculopathy (SCM)

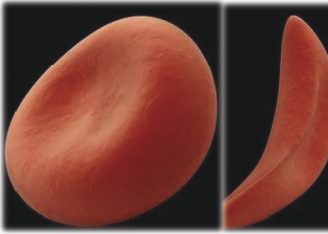
Capillary non-perfusion in the perimacular area. *Arch Ophthalmol*. 2011;129(7):947-949

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Genetics of Sickle Cell Disease (SCD)

- Autosomal recessive genetic disorder
- The most prevalent genetic disorders in US:
 - 10-14% of African-Americans/Mediterranean ancestry
- A genetic disorder caused by a mutation in both copies of a person's *HBB* gene
 - Hypoxia, acidosis, and ischemia.
 - Results in hemolysis and vaso-occlusive events that produces tissue and organ damage

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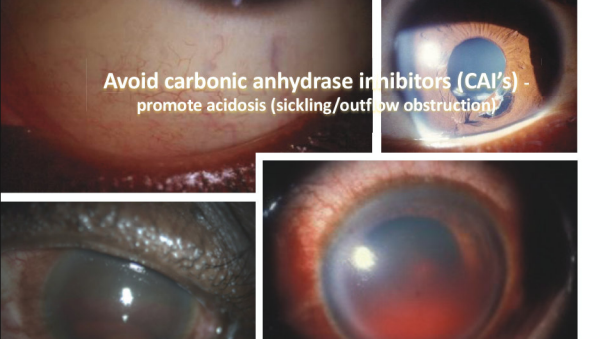


Normal RBC lives 90-120 days | Live 10-20 days

Risk factors for Sickling

| | |
|--|---|
| Altitude • Low oxygen tension | Heat stress • Dehydration • Acidosis |
| Extreme physical exercise | Sustained maximal exertion |
| Concomitant diseases (DM, HTN, CVD) | Pregnancy |

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Avoid carbonic anhydrase inhibitors (CAI's)
 promote acidosis (sickling/outflow obstruction)

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| Name | Genetics | Systemic manifestations | PSR prevalence (Fekrat and Goldberg [7]) | PSR prevalence (Dembélé et al. [8]) | PSR prevalence (Bonanomi et al. [9]) | PSR prevalence (Levezuel et al. [10]) | PSR prevalence (Downes et al. [11]) | |
|------------------|---|---|--|-------------------------------------|--|---------------------------------------|-------------------------------------|-----|
| HbSS | Sickle cell anemia | Sickle cell homozygote | Most severe systemically | 3% | 5.2% | 14.64% | 18.1% | 14% |
| HbSC | Sickle cell "C" trait | Sickle cell heterozygote, with another abnormal HbC allele | Mild systemically | 33% | 12.4% | 54.54% | 54.6% | 43% |
| HbSthal | β-Thalassemia anemia | Sickle cell heterozygote, with another β-thalassemia allele | Severe form systemically (β ⁰) Milder form systemically (β ⁺) | 14% | 9.4% (SS ⁰ -thalassaemia) 9.3% (SS ⁺ -thalassaemia) | - | - | - |
| HbSD, HbSE, HbSO | Sickle cell heterozygote, with another abnormal Hb allele | Varies systemically | - | - | - | - | - | |
| HbAS | Sickle cell trait | Sickle cell heterozygote, with 1 normal Hb allele | Mild systemically | - | - | - | - | |

© BMJ 2019; first published as 10.1136/bmj-2018-025719 on 11 September 2019. Please cite as follows: Br J Haematol 2019; 184:1355-1364

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SCD Genomic Update

Bone Marrow/ Stem Cell Transplant for SCD

Excellent outcome of stem cell transplantation for sickle cell disease

Tanya Miller, Emma Schmitt, Lisa Gilchrist, Heather Baines, Jutta Ahrens, Tobias Fuschberger, Christoph Klein, Vincent D. Garman, Michael K. Albert

Received 11 June 2023 | Accepted 7 September 2023 | Published online 10 September 2023

Abstract
 Many sickle cell disease (SCD) patients lack matched family donors (MFD) or matched unrelated donors (MUD), limiting high-dose therapy (HDT) as a curative disease option. We used a related history protocol for all donor types. We included 11 patients (5-22 years) with MFD (n=10), MUD (n=1), or MUD (n=1) and nontransfused with abnormal hemoglobin (Hb) variants, including HbS, HbC, and HbE, and genotyping cytochrome b45 (CYP2C8). After the initial six patients, transfusion was replaced by targeted transfusion (AUC 65-75 g/dL). After a median follow-up of 20 months (n=13), all patients are alive and transfusion-free. Two (18%) patients received a matched unrelated donor graft. After the first recipient of SCD, HbA after successful conditioning. Neither acute GVHD, nor late non-relapse related GVHD was observed. The duration of acute GVHD-free survival was 100%, 100%, and 100% in the MFD, MUD, and MUD groups, respectively (p=0.146). There was a higher rate of virus reactivation in MUD (100%) and MUD (80%) compared to MFD (40%, p=0.008). In our study, we found that HbS patients (n=10) or HbE (n=1) who had transfusion-free conditioning, rate of virus reactivation post-transplant (10%), compared to 40% (80%) after transfusion-based conditioning (p=0.002). Donor stem cell engraftment was 100% in all patients (100%) in our follow-up. Related toxicity, hepatotoxicity conditioning treated unrelated donor survival, negative GVHD, and low toxicity among all donor groups in pediatric and young adult patients with SCD.

Keywords: Sickle cell disease - Stem cell transplantation - High-dose therapy - Hematology - Bloodless

Front Med February 2023; 9: 1023. Hematology Volume 10 - 2023
 Valles, T., Schmitt, E., Gilchrist, L., et al. Excellent outcome of stem cell transplantation for sickle cell disease. Ann Hematol 102, 3217-3227 (2023)

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First Gene Therapies to Treat Patients with Sickle Cell Disease



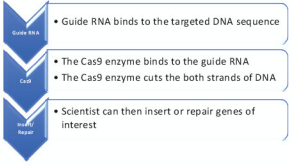
The First BRIGHT Drop: Vertex Pharmaceuticals' Casgevy Wins U.K. Approval for Sickle Cell Disease

- Approve December 2023
- The first cell-based gene therapies for the treatment of sickle cell disease (SCD) in patients 12 years and older.
- **Casgevy** is the first FDA-approved therapy utilizing CRISPR/Cas9, a type of genome editing technology.
 - Crispr –cas9 (clusters of regularly interspaced short palindromic repeats)
- **Lyfgenia** uses a lentiviral vector (gene delivery vehicle) for genetic modification

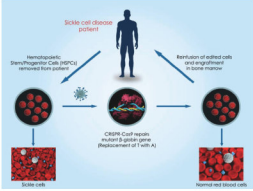
FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease. FDA New Release, December 08, 2023. Accessed January 20, 2024.
 1. Duroy et al. CRISPR-Cas9 to Induce Hemoglobin for the Treatment of Sickle Cell Disease. *N Engl J Med*. Dec. 2023; 33(50): 276-285.
 Casgevy and Lyfgenia: Two gene therapies for sickle cell disease. *N Engl J Med*. 2024 Jan 23;390(3):301-310.

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Crispr –cas9 (clusters of regularly interspaced short palindromic repeats)



- Guide RNA binds to the targeted DNA sequence
- The Cas9 enzyme binds to the guide RNA
- The Cas9 enzyme cuts both strands of DNA
- Scientist can then insert or repair genes of interest



Sickle cell disease patients

Hematopoietic Stem/Progenitor Cells (HSCs) removed from patient

CRISPR-Cas9 system (Cas9 + guide RNA) (Replacement of beta-globin)

Replacement of mutated cells with engineered normal red blood cells

Sickle cells

Normal red blood cells

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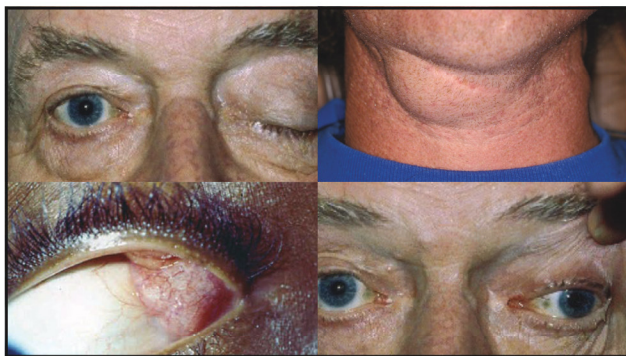
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Leukemia

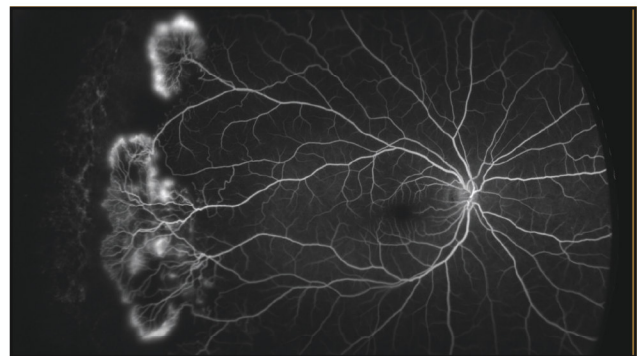
- Type of Leukemia
 - Type of white blood cell affected
 - Myeloid cells
 - Lymphoid (Lymphatic system)
- Acute or Chronic
 - **Acute**
 - Rapid/progressive course that ends in death within months
 - Without treatment: average survival rate is 4 months.
 - **Chronic**
 - Insidious onset and symptoms
 - Longer survival
 - Respond to treatment

- Acute myelogenous leukemia-AML
 - **common adult leukemia**
- Acute lymphocytic leukemia-ALL
 - **common in young children**
- Chronic myelogenous leukemia-CML
 - Philadelphia chromosome (+) is >90% of cases
- Chronic lymphocytic leukemia-CLL

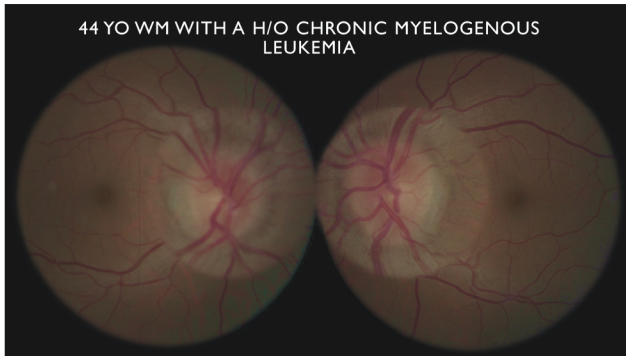
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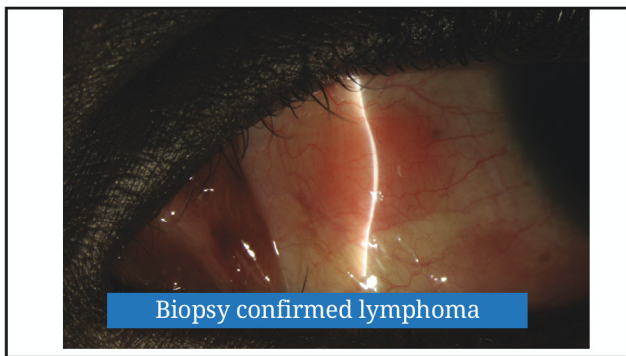
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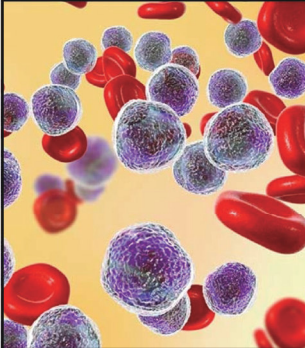
Management

- Leukemic Retinopathy
 - More common in Acute Leukemias
 - *Is an Ocular Emergency until proven otherwise*
- Systemic chemotherapy or direct radiation
- Injection of subconjunctival chemotherapeutic agents
- Bone marrow transplant

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Lymphomas

- Classification:
 - Hodgkin Lymphoma
 - Multinucleated, giant cells called Reed-Sternberg cells
 - Non-Hodgkin Lymphoma (B-cells or T-cells)
 - More common
 - Most prevalent hematological malignancy
 - Approximately 3% to 4% of all cancer diagnosed annually

Shetty M.L, Coupland S, Loeffler KU. High-grade malignant B-cell lymphoma of the retina in a patient with concomitant gastric MALT lymphoma. Graefes Arch Clin Exp Ophthalmol 2007; Mar;245(3):448-50.

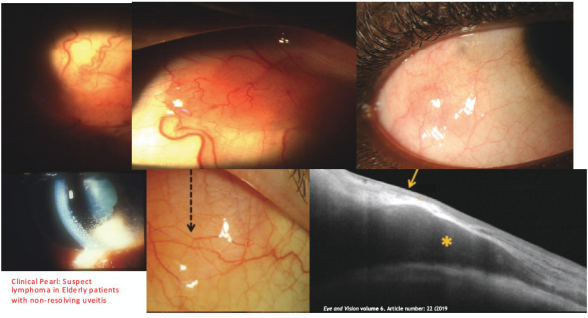
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Ocular Lymphoma

- Hodgkin Lymphoma
 - Rarely causes ocular disease
- Non-Hodgkin Lymphoma (NHL)
 - Most common type of ocular lymphoma
- Lymphoma has been described as the most common malignant orbital tumor
 - 55% of cases in adults

Volosin GJ, Sakini D, Moller M, Brown NS, Paterson A. Imaging of orbital lymphoproliferative disorders. Austral J Ophthalmol. Jan 1999;37(1):119-30.

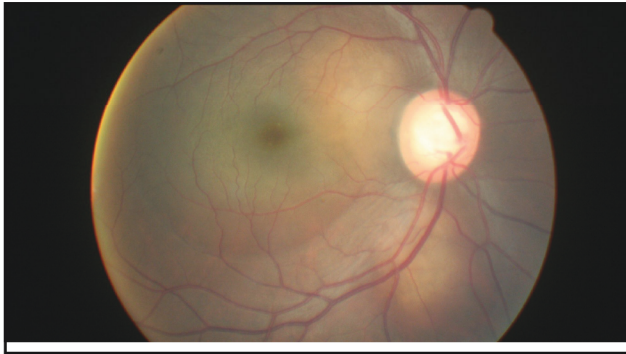
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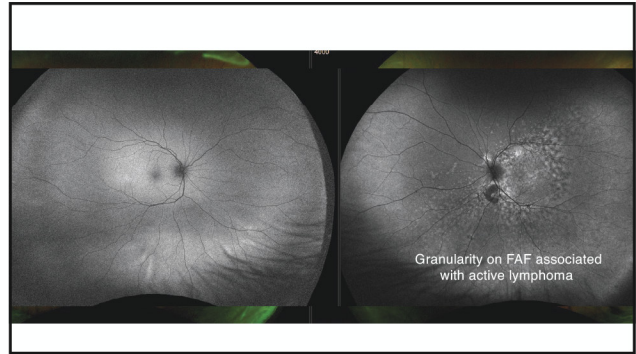
Clinical Pearl: Suspect lymphoma in elderly patients with non-resolving uveitis

Ear and Vision volume 6, Article number: 22 (2019)

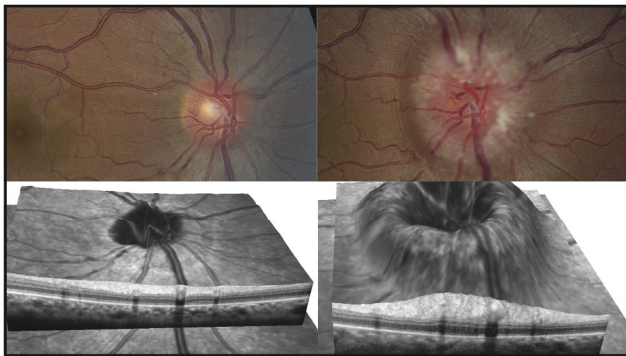
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Lymphomas

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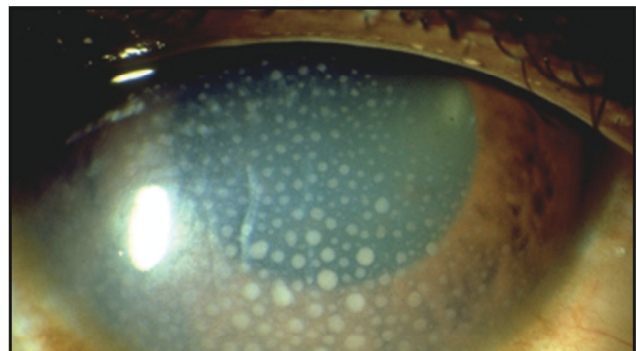
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| Table 1. Features of Various Types of Intraocular Lymphoma | | | | | | |
|--|--------------------|-------------------------|------------------------------------|---|---------------------------|--|
| Lymphoma | Epidemiology | Laterality | Symptoms | Clinical Features | Subtype | Morphology |
| Primary Vitreoretinal Lymphoma | 50-70 years | Frequently bilateral | Decreased vision Floaters | Vitreous cells Retinal/choroidal infiltrates CNS involvement | DLBCL | Large cells Minimal cytoplasm Prominent nucleoli |
| Primary Uveal Lymphoma | M>F 50-70 years | Usually unilateral | Decreased vision Metamorphopsia | Clear vitreous Diffuse choroidal thickening Exudative retinal detachment | EMZL | Small centrocyte-like cells with variable plasmacellular differentiation |
| Secondary Intraocular Lymphoma | Variable | Unilateral or bilateral | Decreased vision | Variable: Choroidal thickening Iris infiltrates Pseudohypopyon Vitreous cells | Dependent on systemic NHL | Similar to systemic NHL |

M: males, F: females, DLBCL: diffuse large B-cell lymphoma, EMZL: extranodal marginal zone lymphoma, NHL: non-Hodgkin's lymphoma

Primary lymphoma of the central nervous system. Ophthalmol Clin North Am 2006;18:100-207.

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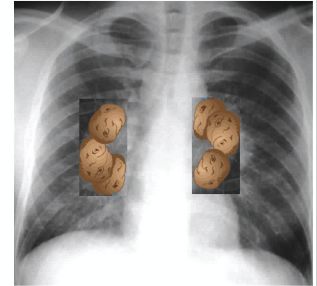
Sarcoidosis

- A multisystem granulomatous inflammatory disease
 - Noncaseating Granulomas (NCG)- are comprised of epithelioid cells and giant cells
 - Delayed hypersensitivity and heightened Th1 immune response in affected organs
- 16X more common in Black females
 - The disease is usually more serious
- Predominantly in the lungs and lymph nodes
- Arthritis/ Bone and joint involvement

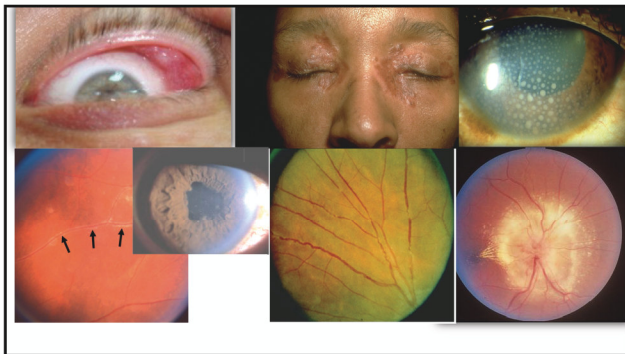
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Clinical features

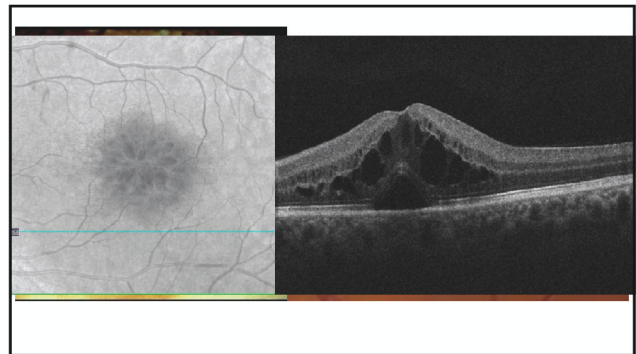
- Bilateral hilar lymphadenopathy AKA "Potato nodes"
- Pulmonary infiltration
- Arthritis/Bone and joint involvement
- Neurological involvement
- Cardiac involvement



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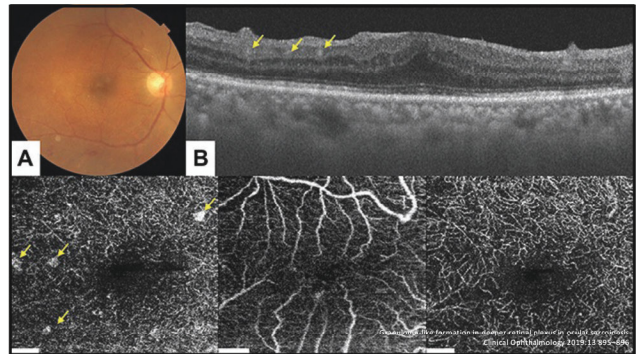


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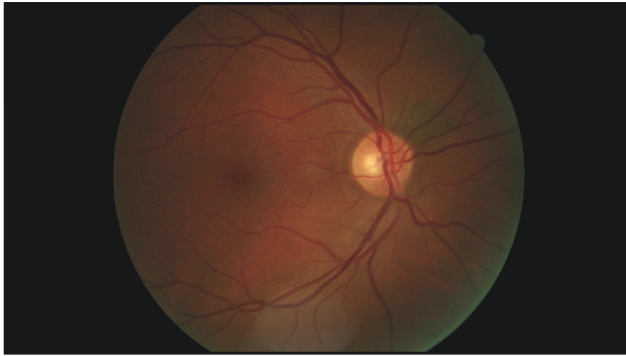
Laboratory Findings

| | | |
|---|---------------|--|
| (+) Angiotensin-converting enzyme (ACE) | (+) PPD | Chest X-ray • Hilar lymphadenopathy |
| Pulmonary function test | Tissue Biopsy | |

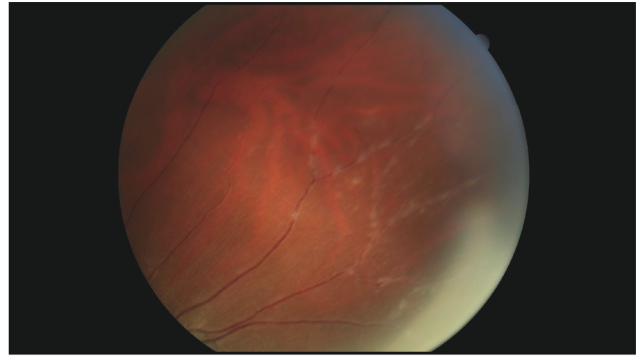
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Rheumatoid Arthritis (RA)

- Inflammation of the synovial membrane of the joints and/or other internal organs
- Prevalence: 1-2%
- Occurrence:
 - Any age
 - 3:1 Females
 - Unknown etiology
 - Interplay between genetic (HLA-DRB1) predisposition and environmental triggers.

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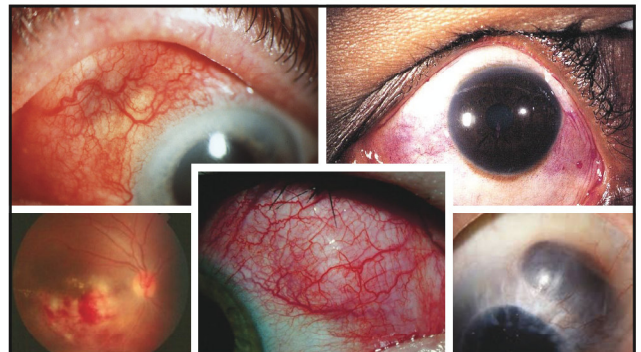
Rheumatoid Arthritis (RA)

- Swelling of synovial lining
 - Angiogenesis
- Rapid division/growth of cells=Pannus
 - Synovial thickening/hyperplasia
 - Inflammatory vascularized tissue
 - Generation of metalloproteinases
- Cytokine release
 - Infiltration of leukocytes
- Changes in cell-surface adhesion molecules & cytokines
 - Destruction of bone & cartilage

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TREATMENT OVERVIEW

- Non-pharmacologic therapy
- Pharmacologic therapy
 - Non-disease modifying drugs
 - NSAIDs
 - Corticosteroids
 - Prednisone < 10mg PO daily
 - Disease-modifying antirheumatic drugs (DMARDs)
 - Non-biologics
 - Biologics

| DRUG | DOSE | MONITORING |
|--------------------|---|--|
| Methotrexate | PO/IM: 7.5-15mg weekly | <ul style="list-style-type: none"> • Baseline LFTs, CBC, Cr/BUN, hepatitis panel • CBC, AST/ALT, albumin q1-2 months |
| Leflunomide | PO: 100mg daily x 3 days, then 10-20 daily Q8-10-20 mg daily w/o LD | <ul style="list-style-type: none"> • Baseline LFTs, CBC • CBC, AST/ALT monthly, then q6-8 weeks |
| Hydroxychloroquine | PO: 200-300mg BID x 1-2 months, then can ↓ to 200mg daily or BID | <ul style="list-style-type: none"> • Baseline eye exam • Ophthalmoscopy q9-12 months |
| Sulfasalazine | PO: 500mg BID, then ↑ to 1000mg BID | <ul style="list-style-type: none"> • Baseline CBC • CBC weekly x 1 month, then q1-2 months |
| Minocycline | PO: 100-200mg daily | <ul style="list-style-type: none"> • LFTs, BUN/Scr with long-term treatment |

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Biologics

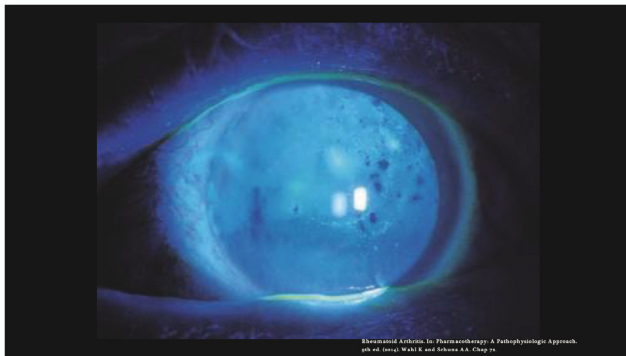


- Infliximab (Remicade)
- Etanercept (Enbrel)
- Adalimumab (Humira)
- Golimumab (Simpani)
- Certolizumab (Cimzia)
- Ixekizumab (Taltz)
- Anakinra (Kin)
- Abatacept (Orencia)
- Rituximab (Rituxan)
- Tocilizumab (Acetemra)
- Tofacitinib (Xeljanz)

Drug Targets:

- TNF α
- IL-1
- IL-6
- B cells
- JAK

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Sjögren's Syndrome

- Systemic chronic inflammatory disorder characterized by lymphocytic infiltrates in exocrine organs
 - Lacrimal, salivary, and sweat glands
- Occurrence:
 - 4/5/6th decade
 - 9:1 Females
 - Autoimmune- HLA- B8/ DR3
 - Antibodies to the Ro antigen

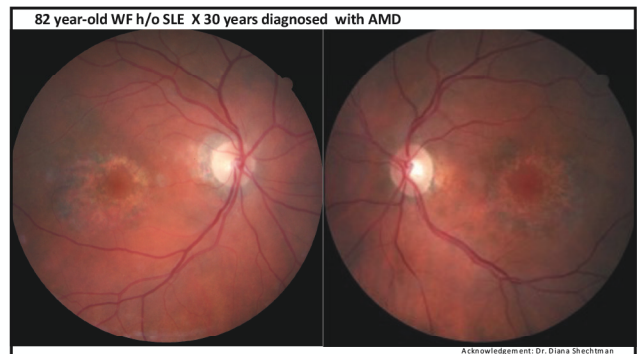
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Sjögren's Syndrome

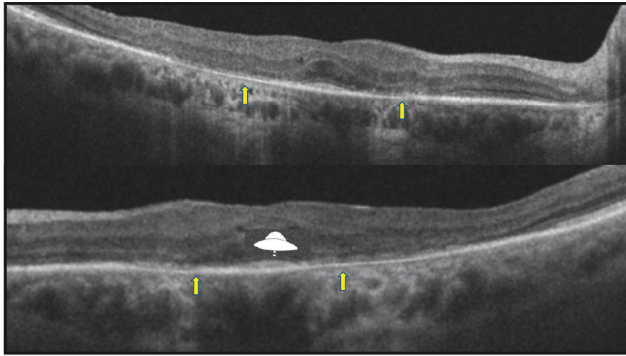
- Primary**
 - Sjogren's syndrome that occurs alone
- Secondary**
 - Rheumatoid Arthritis
 - Systematic Lupus Erythematosus
 - Scleroderma
 - About 50% of patients have secondary Sjogren's
- Sicca Syndrome**
 - Xerophthalmia (dry eyes)
 - Xerostomia (dry mouth)
 - Xeroderma (dry skin)
 - Parotid gland enlargement



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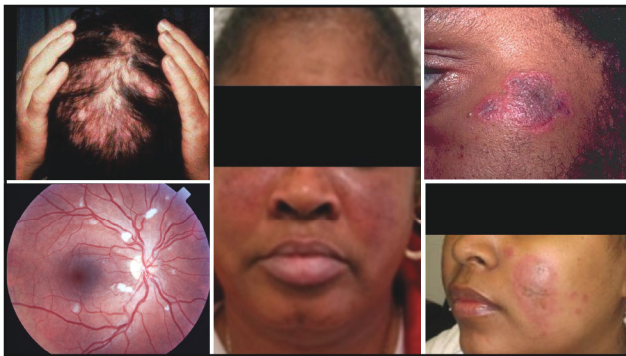


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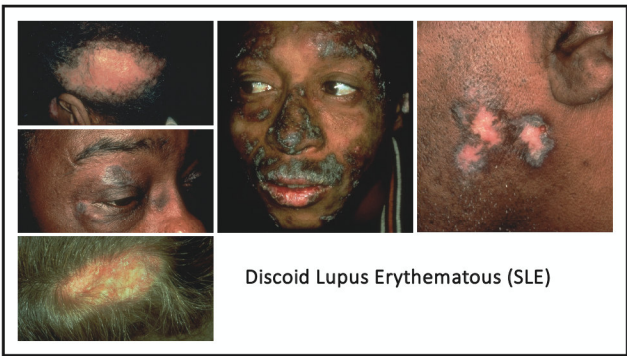
Systemic Lupus Erythematosus (SLE)

- An inflammatory, multisystem, autoimmune disease of unknown etiology with protean clinical and laboratory manifestations and a variable course and prognosis
- Occurrence:
 - Women in their reproductive years
 - **10:1 Females**
 - Variation in race/ethnicity:
 - More common in Black (3–6x)
 - Hispanic and Native American (2–3x)
 - Asian (2x) populations

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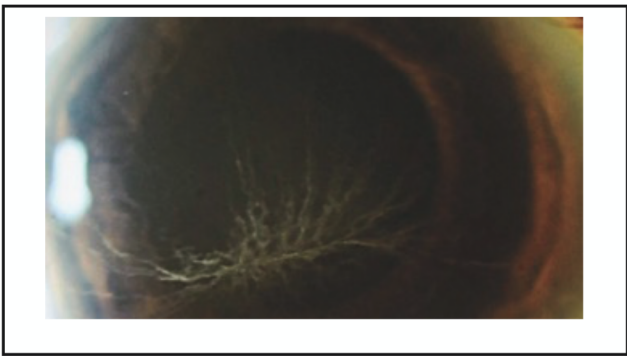
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Sildenafil in the Treatment of Raynaud's Phenomenon Resistant to Vasodilatory Therapy
Revised Print, Karen Shorrock, Hester Lee van Wieringen and Michael Kahn
 Abstract published by SAGE Publications in JOURNAL OF CUTANEOUS MEDICINE AND SURGERY, 2003; 9: 389-393

Abstract
Background: Vasodilatory therapy of Raynaud's phenomenon represents a difficult clinical problem because treatment often remains inefficient and may be not tolerated because of side effects.
Methods and Results: To investigate the effects of sildenafil on symptoms and capillary perfusion in patients with Raynaud's phenomenon, we performed a double-blind, placebo-controlled, fixed-dose, crossover study in 18 patients with idiopathic, idiopathic Raynaud's phenomenon resistant to vasodilatory therapy. Patients were treated with 50 mg sildenafil or placebo twice daily for 4 weeks. Symptoms were assessed by diary sheets including a 70-point Raynaud's Correlation Score. Capillary flow velocity was measured by digital perfused capillaries by a 70-point Doppler anemometer. While taking sildenafil, the mean frequency of Raynaud attacks was significantly lower (85±14 attacks/3.6 vs 108±26). The cumulative attack duration was significantly shorter (95±15 versus 108±26 minutes, P=0.038), and the mean Raynaud's Correlation Score was significantly lower (2.5±0.4 versus 3.0±0.6, P=0.038). Capillary blood flow velocity increased in each individual patient, and the mean capillary flow velocity of all patients more than quadrupled after treatment with sildenafil (2.0±0.3 versus 8.1±0.5 mL/min, P<0.0001). All patients reported side effects leading to discontinuation of the study drug.

- Occurs in 20-30% of patients with SLE
- Episodic vasospasm of small peripheral arteries
- Blue discoloration of hands and feet

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

| | |
|-------------------------------|---|
| Daily dose | > 5.0 mg/kg (real weight) for Hydroxychloroquine > 2.3 mg/kg (real weight) for Chloroquine |
| Drug use time | More than 5 years |
| Renal disease | Abnormal glomerular filtration rate |
| Concomitant drugs used | Tamoxifen use |
| Macular disease | Can affect the evaluation and susceptibility to chloroquine and hydroxychloroquine |

Adapted from: Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. American Academy of Ophthalmology. Ophthalmology. 2016 Jun; 123(6):1386-94.

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"Safe" Daily Dosage Calcs

Weight: 120 lbs (120 lbs = 54.4 Kg)

200 mg taken BID for 1 years (146g)

calculate idea weight from height

Result
5.0 mg / kg x 54.4 kg = **272 mg/day**

This dosage (and less) would be regarded lower risk daily dose. Dosages greater than this amount will increase risk of retinotoxicity.

Taking the typical Plaquenil dosage (two 200 mg tablets or 400 mg/day), may place your patient at higher risk for retinotoxicity.

<https://www.eyedock.com/calcs/plaquenil-calcs>

Cumulative Dosage Calcs

Cumulative Dosage: 146g

The majority of cases of retinotoxicity have occurred in patients that have had a cumulative dose exceeding 1000g of hydroxychloroquine (Plaquenil).

This level is reached in about 7 years with the most common daily dose of Plaquenil, 400 mg/day (200 bid).

HCQ is typically dose: 200mg BID. The maximum safe dose is 5.0 mg/kg
The threshold dose would be 400 mg/day for a patient weighing 175 lbs or 300mg for a patient weighing 135lbs

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Lesser Risk Factors

- Age**
 - Elderly patients might seem to be at higher risk
 - A recent demographic study found no significant association between age and risk of toxicity
- Liver disease**
 - No clear association between liver disease and toxicity has been demonstrated
- Genetic factors**
 - There have been suggestions that some patients have a genetic predisposition to HCQ toxicity
 - More research necessary

Ask about common side effects of CQ/HCQ therapy

- Pruritus, headaches, dizziness and gastrointestinal upset to detect those that are non-compliant and those that are receiving a dose that is too high.
- Less frequent side effects include discoloration of the oral cavity, nails, skin and hair and rash

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Table 3. Clinical Examination Techniques

Recommended Screening Tests
Primary tests: ideally do both
Automated visual fields (appropriate to race)
SD OCT
Other objective tests (as needed or available):
mERG
FAF
Newer tests of possible value in future
Microperimetry
Adaptive optics retinal imaging

Not Recommended for Screening
Fundus examination
Time-domain OCT
Fluorescein angiography
Full-field ERG
Amsler grid
Color testing
EOG

EOG = electro-oculogram; ERG = electroretinogram; FAF = fundus autofluorescence; mERG = multifocal electroretinogram; SD OCT = spectral-domain optical coherence tomography.

White 10-2: White Stimulus/ 24-2 or 30-2 VF for Asian Patients

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Preservation of the outer retinal layers subfoveally with perifoveal loss of the ILM on both sides of the fovea.

Displacement of the inner retinal structures toward the retinal RPE with variable loss of the foveal contour

Flying Saucer and Sinkhole Sign

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Localized paracentral ERG depression

HCQ Ophthalmol Vol. 15 No. 1

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SEQUENTIAL CHANGES IN HYDROXYCHLOROQUINE RETINOPATHY UP TO 20 YEARS AFTER STOPPING THE DRUG
Implications for Mild Versus Severe Toxicity

Results

- Early and moderate cases stabilized in FAF appearance, foveal thickness, ellipsoid zone line length, and visual acuity for up to **9 years after stopping HCCQ**.
- By contrast, severe cases demonstrated a **continual loss of these parameters for up to 20 years off the drug**.
- Presence of RPE damage at initial examination predicted progressive retinopathy over many years.

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23-year-old African-American female presented complaining of a "spot" on the retina of her left eye one-week prior by a previous eye doctor. She denied symptoms of pain, floaters, flashes of light, trauma, systemic disease, medication use or smoking.

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HIV Infection

Human Immunodeficiency Virus (HIV) – retro-virus

- Results in immuno-compromised patient
- Different types and strains
 - HIV-1 and HIV-2 are two main types of HIV
 - HIV-1 = more prevalent & more pathogenic (over 60 strains of HIV-1)
 - Finding new strains of HIV-1 all the time
 - The HIV-1 B strain most common in US.
 - HIV-1 C strain most common Worldwide
 - HIV-2 found principally in western Africa

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CMV Retinitis

- Slow progression
- Starts in periphery
- Spreads along retinal vasculature towards posterior pole
- Dense white/granular opacification (full-retinal thickness)
- Hemorrhage
- Mild vitritis
- The ocular symptoms of CMV retinitis include the four "F's"
 - Failing vision
 - Floaters
 - Flashes
 - Field deficits

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Conclusion

Early detection and treatment are crucial in preventing and reducing visual impairment from these conditions.

Optometry is on the forefront of early detection of the silent killers.

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