A course on Diabetic eye disease

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Disclosure

Has a relevant financial relationship with

Haag Streit, Genzyme, Optovue as a speaker and ZeaVision, Vector Vision, for research and consultant

The content and format of this course is presented without commercial bias and does not claim superiority and commercial product or service.

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Impact of Diabetes

34.2 million people (10.5%)

Total Cost = 327 Billion Dollars

- Direct Medical Costs
  - 237 Billion Dollars
  - (medical expenses)
- Indirect Medical Costs
  - 90 Billion Dollars
  - (disability, work loss, premature death)

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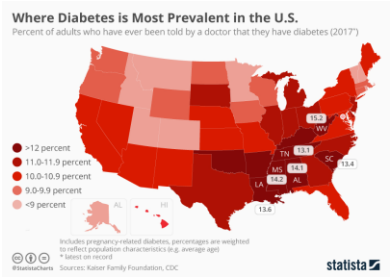

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Statistics – United States

- 34.2 million people of all ages or 10.5% of the US population have diabetes mellitus.
- 27.2% with DM (over the age of 18) do NOT know they have diabetes mellitus.
- 88.1 million Americans 18 yo or older have prediabetes
  - More men than Women
  - Prevalence of prediabetes was similar among all racial/ethnic groups and education levels
- 4.4% of the US has some level of diabetic retinopathy

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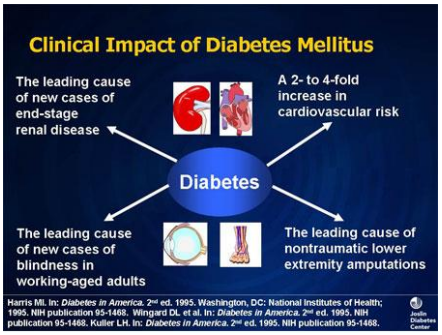

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Types of Diabetes

- Type I – bodies immune system destroys pancreatic beta cells (autoimmune condition)
- Type II – begins as insulin resistance and then gradually the pancreas loses its' ability to produce insulin.
- Gestational
  - Form of glucose intolerance during the 2nd or 3rd trimester
  - 5-10% dx'd with DM
  - 50% chance of development of DM in 5-10 years

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Role of Insulin

Helps muscle, fat, and liver cells absorb glucose from the bloodstream (inability for this to occur causes insulin resistance)

Stimulates the liver and muscle tissue to store excess glucose (as glycogen)

Insulin also lowers blood glucoses by reducing glucose production in the liver

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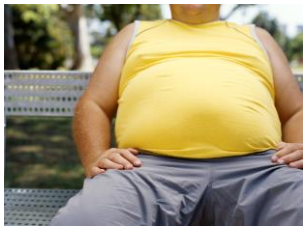
Diabetes and Obesity

- Type II DM appears to be rising parallel with global trends towards obesity.
- Weight gain of 10-15 pounds can increase the risk of DM by 50%.
  - Especially in women
  - Seeing prevalence of metabolic syndrome also rise in women.
- 65% of Americans are over-weight or obese



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Type II DM

- Associated with obesity, older age, family hx, impaired glucose metabolism, physical inactivity, and race/ethnicity
- African Americans, Hispanics, Native Americans, Asian Americans, and Pacific Islanders
- Seeing it more frequently dx'd in children

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Diagnosing DM

	A1C (%)	Fasting Plasma Glucose (mg/dl)	Oral Glucose Tolerance Test (mg/dl)
Diabetes	6.5 or above	126 or above	200mg/dl or above
Pre-diabetes	5.7 to 6.4	100 to 125	140 to 199
Normal	About 5	99 or below	139 or below

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Ocular Complications

Refractive Changes

- Due to increased glucose levels in the lens
- 21% also demonstrate transient "paralysis" of accommodation
- 40% have dry eyes

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Ocular Complications

Dry Eyes

Reduced corneal sensitivity	• Reduce reflex tearing
Goblet cell density	• Produce mucin (stability)
Affect on lacrimal gland	• Correlated to length of DM
Tear Protein Patterns	• Lactoferrin, sIgA, albumin, lipocalin and lysozyme

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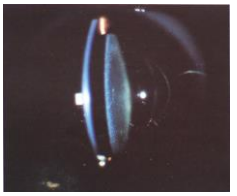
Ocular Complications

"Snowflake" cataract



- Common in uncontrolled Type I diabetic patients
- Sorbitol accumulates in the lens fibers. Water enters to correct the osmotic imbalance
- Lens fibers swell / rupture

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Ocular Complications

Posterior Subcapsular Cataract

- Earlier onset of age-related cataracts
- Due to binding of sugars to lens proteins
- Osmotic imbalance can also increase cortical changes

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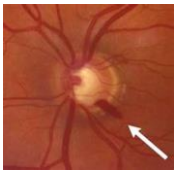
Ocular Complications

Glaucoma



- LALES found 40% higher prevalence in Type II diabetic Latino pt's
- Neovascular glc
  - VEGF-induced neovascularization of the iris and angle
- Normotensive glc

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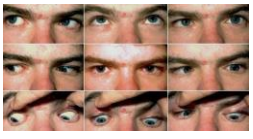
Ocular Complications

Sixth Nerve Palsy



50%

- Sudden onset
- Absence of other neurologic involvement
- Resolves in 3-6 months.

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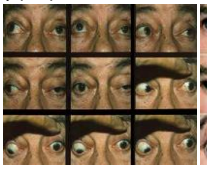
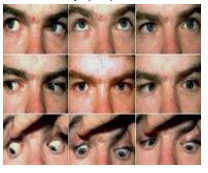
Cranial Nerve Palsies

CN III Palsy (45%)



CN IV Palsy (5%)



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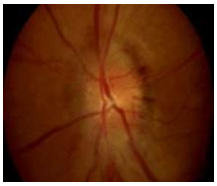
Optic Neuropathy

Diabetic Papillopathy



- Can be unilateral or bilateral
- Minimal affect on VA
- Resolved in 2-10 months
- If bilateral, need to r/o papilledema (imaging or LP)

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Chief Complaint and Patient History

- What is a "typical" chief complaint from a diabetic patient?
- Questions to ask:
  - Type of DM
  - Duration of DM
  - Blood sugars (Fasting / Post-prandial)
  - A1C
  - Medications (compliance)
  - Who do they see / How often
  - Hypertension/ BP
  - Other medical Heart, Kidney, Legs
- Does the pt smoke (increase progression)/ drink (excess = non-compliance)

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TABLE 1 Diabetic Retinopathy Disease Severity Scale and International Clinical Diabetic Retinopathy Disease Severity Scale

Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR (see Glossary)	Microaneurysms only
Moderate NPDR (see Glossary)	More than just microaneurysms but less than severe NPDR
Severe NPDR	
U.S. Definition	Any of the following (4-2-1 rule) and no signs of proliferative retinopathy: • Severe intraretinal hemorrhages and microaneurysms in each of **four** quadrants • Definite venous beading in **two** or more quadrants • Moderate IRMA in **one** or more quadrants
International Definition	Any of the following and no signs of proliferative retinopathy: • More than 20 intraretinal hemorrhages in each of **four** quadrants • Definite venous beading in **two** or more quadrants • Prominent IRMA in **one** or more quadrants
PDR	One or both of the following: • Neovascularization • Vitreous/preretinal hemorrhage

IRMA = intraretinal microvascular abnormalities; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

NOTE:

- Any patient with two or more of the characteristics of severe NPDR is considered to have very severe NPDR.

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Classifications of Diabetic Retinopathy

Non-Proliferative Diabetic Retinopathy (NPDR)

- Mild
- Moderate
- Severe
- Very Severe

Proliferative

- High risk
- Low risk

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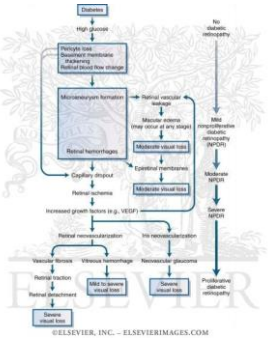

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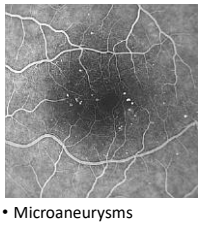
NPDR

- Pathologic progress includes the formation of capillary microaneurysms, vascular permeability and capillary closure.



- Microaneurysms

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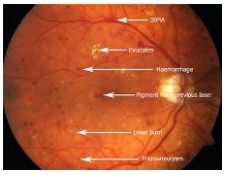
NPDR Classification

- 4 Levels of Severity
  1. Mild
  2. Moderate
  3. Severe
  4. Very Severe
- The extent of intraretinal microvascular abnormalities (IRMA), venous abnormalities, and retinal heme.s are the determining factors.



- Diabetic Retinopathy

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Mild Non-Proliferative Diabetic Retinopathy

- Microaneurysm/s: At least one but the severity is less than that depicted in ETDRS standard photograph 2A.

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Mild Non-Proliferative Diabetic Retinopathy

—

- No other diabetic retinal lesion or abnormality associated with diabetes is present.
- Follow-up: 9 months to one year
- Risk of progression to PDR = 5%

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Moderate Non-proliferative Diabetic Retinopathy

- Microaneurysms / hemorrhages
  - Greater than depicted in ETDRS standard photograph 2A in 1 – 3 retinal quadrants and/ or soft exudates, Venous beading, or IRMA definitely present.

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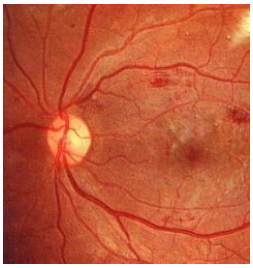
Moderate Non-proliferative Diabetic Retinopathy

- "Soft Exudates"
  - Cotton wool spots - Indicative of retinal ischemia that causes obstruction of axoplasmic flow. Subsequent swelling (ends of ruptured axons) of RNFL give their characteristic appearance.



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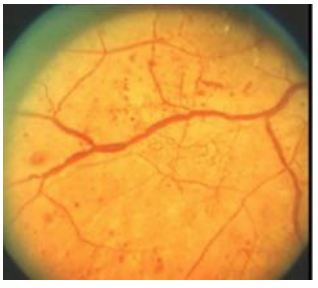
Moderate Non-proliferative Diabetic Retinopathy

- Venous beading & Intraretinal Microvascular Abnormalities (IRMA)

ETDRS Standard Photograph 6B



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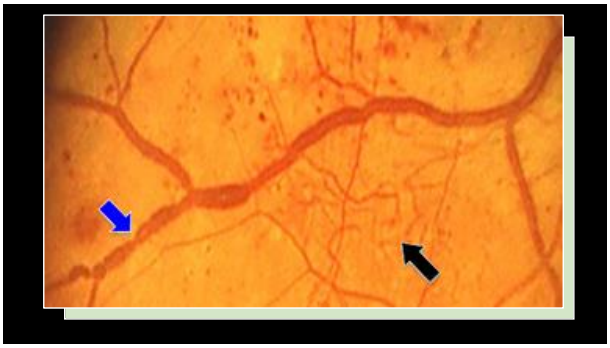

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Moderate Non-proliferative Diabetic Retinopathy

- Venous beading (less than two quadrants)
  - Occurs when the dilated venular walls have the presence of saccular microaneurysms.
- Intra-retinal microvascular abnormalities to mild degree
  - They are dilated capillaries that seem to function as collateral channels. Occur secondary to hypoxia.
  - Key ddx is neovascularization.
- Follow-up: 6 months
- Risk of progression to PDR is 12-27%

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IRMA – ETDRS Standard Photograph 8A

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Severe Non-proliferative Diabetic Retinopathy

- 4-2-1 Rule: (*at least one of the following)
  - Microaneurysms / hemorrhaging in all 4 quadrants greater than ETDRS Standard Photograph 2A in **FOUR** retinal quadrants
  - Venous beading (as seen in ETDRS Standard Photograph 6B) in 2 or more quadrants
  - Prominent IRMA (greater than ETDRS Standard Photograph 8A) in at least one quadrant

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Very/Severe Non-Proliferative Diabetic Retinopathy

- Any two criteria for severe NPDR are met, in the absence of neovascularization.
- Follow-up: <3 months or retinal consult
  - Studies show PRP may be beneficial at this stage (based on ETDRS)
  - Most retinal surgeons will hold off on PRP until PDR develops
  - 50% develop PDR within 15 months.

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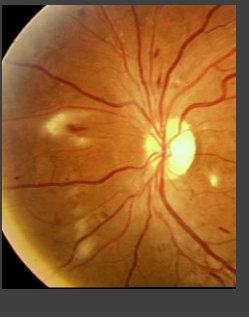
Severe Non-Proliferative Diabetic Retinopathy



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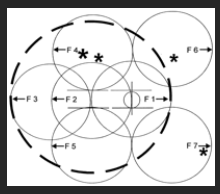
Documentation/Testing



- Baseline Fundus Photography
  - Seven Standard Diabetic Photographic Fields
    - ONH centered, Macula centered, Temporal to macula, Superotemporally, Inferotemporally Superonasally and Inferonasally (*all exclude ONH except for #1)

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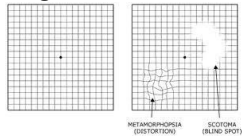
Documentation/Testing

- Amsler Grid



- OCT
- Fluorescein Angiography – assessing vascular integrity

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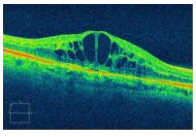
OCT



- CPT: 92133 (ONH) / 92134 (Retina)
- Requires Interpretation and Report
- Reimbursement ~ $50
- Unilateral or Bilateral
- Cannot do same day as DFE/Fundus Photos (*if billing)
- 4x's per year unless acute condition

- Diabetic Macular Edema

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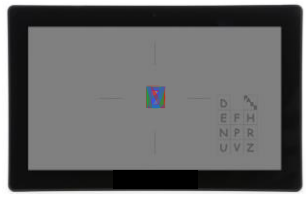
Rabin Cone Contrast Test

- Based in science
  - Co-developed between Innova Systems and US Air Force
- Combines Cone Isolation technology and Contrast Sensitivity
- Color vision technology sensitive enough to detect subtle changes from disease
- Threshold test, similar to visual field

But just faster…



- Patent No. US 9,883,794

Simulation

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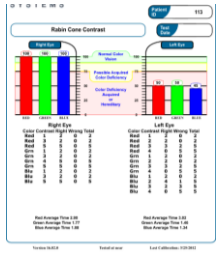
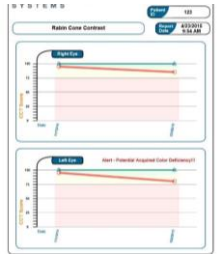
Rabin Cone Contrast Output





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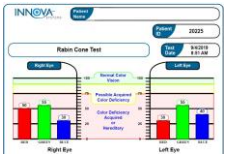
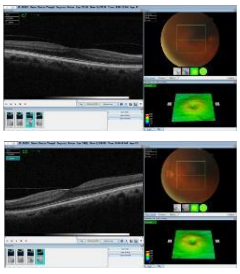
Case: Diabetes Exam- What's Your Diagnosis?

- 72 y/o Indian male
- Type 2 Diabetes
- 20/25 OU
- NS1+ Cataracts OU

Poll 2

What about now?





Case courtesy of Becky Verna, OD

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Clinical Trials Show Color Vision as Biomarker in Diabetes

Table 4 – Color vision impairment

Author(s) (year)	No. of eyes (# subjects)	Device	% Subjects with abnormal color vision (if stated, indicates the predominant affected axis)		
			No DR	NPDR	PDR
Tan et al (2017)[30]	No DR = 849 (n = 849)	Farnsworth Panel D-15	22% (Blue-yellow)		
Boynton et al (2015)[31]	CN = 15 (n = 15) PDR = 15 (n = 15) PRP = 30 (n = 30)	Farnsworth Panel D-15			26.7%
Gella et al (2015)[32]	No DR = 253 (n = 253)	Farnsworth-Munsell 100-Hue	39.5%		
Wolff et al (2015)[33]	CN = 37 (n = 37) No DR = 22 (n = 22) DR = 25 (n = 25) 9 Mild NPDR, 34 Moderate NPDR, 1 Severe NPDR, 1 PDR with 6 CSME among them	Adams Desaturated D-15	40.9% (Blue-yellow)	48.0 (Blue-yellow)	
Andrade et al (2014)[34]	CN = 64 (n = 32) DM = 49 (n = 27): 30 No DR, 13 NPDR, 6 PDR	Farnsworth-Munsell 100-Hue	86.7% (Diffused loss)	90.0% (Diffused loss)	
Feitosa-Santana et al (2010)[35]	CN for D-15 = 62 (n = 31) CN for CCT = 72 (n = 36) No DR = 61 (n = 31)	Lanthony Desaturated D-15 Test and Cambridge Color Test (CCT)	D-15: 21.3% (Blue-yellow) CCT: 27.9% (Diffused loss)		
Fong et al (1999)[36]	DM = 2701 (n = 2701), ranging from Moderate NPDR to Early PDR and/or with presence of macular edema.	Farnsworth-Munsell 100-Hue		49.4% (Blue-yellow)	
Hardy et al (1992)[37]	CN = 36 (n = 36) No DR = 38 (n = 38)	Farnsworth-Munsell 100-Hue	57.0% (Diffused loss)		
Trick et al (1988)[38]	CN 70 (n = 35) No DR = 74 (n = 37) Mild to Moderate NPDR = 40 (n = 20)	Farnsworth-Munsell 100-Hue	18.9% (Diffused loss)	25.0% (Diffused loss)	

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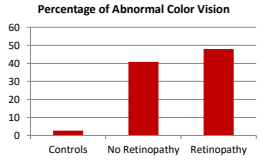
Color Vision and Neuroretinal Function in Diabetes

Wolff et al. investigates how T2DM and DR affect color vision and mfERG

84 subjects; participants included diabetics with and without retinopathy plus controls



CLINICAL STUDY RESULTS

CV Affected in patient with T2DM even without DR
Central DR increases likelihood of CV deficit

mfERG Less frequently abnormal than CV in the absence of DR

2014 *Documenta Ophthalmologica*

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Functional Retinal Outcomes: Prediabetes & T2DM

Karson et al. investigates how T2DM affect color vision and mfERG

43 subjects; 3 groups: Prediabetics, Type II diabetics, Controls

N. Karson et al. — Retinal function in prediabetes

Functional Retinal Outcomes in the Study Population

	Control (<= 5.6%)*	Prediabetes (5.7% - 6.4 %)*	Diabetes (>= 6.5%)*
No. Subjects	15	17	11
Avg HbA1c	5.3%	5.8%	7.0%
Color Vision Fail %	26.7%	70.6%	72.7%

CLINICAL STUDY RESULTS

CV Prediabetic group had measurable functional changes before diabetes
Color vision is the strongest biomarker

mfERG No change in prediabetic group

CS No change in prediabetic group

2020 *Ophthalmic & Physiological Optics*

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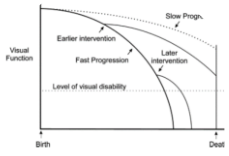
Diabetes & DR: Reduces Cone Contrast

<u>Detection of Progression</u>

- Monitor more frequently
- Health initiatives
  - ✓ Weight management
  - ✓ Exercise
  - ✓ Nutritional changes
  - ✓ Nutritional supplements
  - ✓ Medical management when needed



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Diabetic eye disease

- Retina takes a good 10-15 years of beating
- Elevated blood glucose is the culprit
- Metabolic control is a must
- Furthermore, there is a big body of literature that MPOD is depleted in diabetics

- Can we do anything with nutritional supplements without changing A1c?

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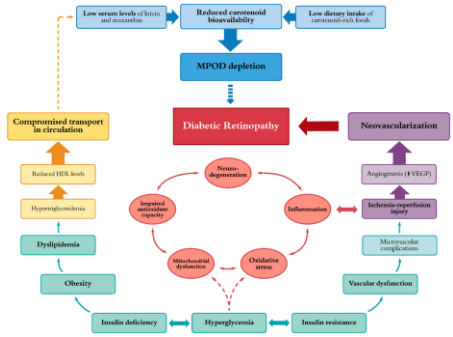

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nutrients

Review

A Systematic Review of Carotenoids in the Management of Diabetic Retinopathy

Drake W. Lem [1,†], Dennis L. Gierhart [2] and Pinakin Gunvant Davey [1,*,†]

of DR, specifically in patients with type 2 or poorly managed type 1 diabetes. Meanwhile, early interventional trials with dietary carotenoid supplementation show promise in improving their levels in serum and macular pigments concomitant with benefits in visual performance. These findings provide a strong molecular basis and a line of evidence that suggests carotenoid vitamin therapy may offer enhanced neuroprotective effects with therapeutic potential to function as an adjunct nutraceutical strategy for management of diabetic retinopathy.

Nutrients **2021**, *13*, 2441. https://doi.org/10.3390/nu13072441

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The Diabetes Visual Function Supplement Study (DiVFuSS)

The Diabetes Visual Function Supplement Study (DiVFuSS) was designed to test the effects of a novel, multi-component nutritional supplement on visual function. Participants included patients with both type 1 and type 2 diabetes.

- 2016 *British Journal of Ophthalmology*
  - six-months
  - placebo controlled

CLINICAL STUDY RESULTS WITH DVS

Randomized, placebo-controlled study demonstrated:

- **21%** improvement in color vision**
- **19%** improvement in contrast sensitivity (easier to read ink on an newspaper)**
- **12%** improvement in central and peripheral vision**

**improvements were made without significantly affecting blood glucose levels

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Diabetic Macular Edema

- Classified into focal and diffuse types.
  - Focal macular edema is caused by foci of vascular abnormalities, primarily microaneurysms
  - Diffuse macular edema is caused by dilated retinal capillaries in the retina.
  - Both are located within 2 disc diameters of the center of the macula.

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TABLE 2 INTERNATIONAL CLINICAL DIABETIC MACULAR EDEMA DISEASE SEVERITY SCALE

Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
Diabetic macular edema apparently absent	No apparent retinal thickening or hard exudates in posterior pole
Diabetic macular edema apparently present	Some apparent retinal thickening or hard exudates in posterior pole
If diabetic macular edema is present, it can be categorized as follows:	
Proposed Disease Severity Level	**Findings Observable upon Dilated Ophthalmoscopy***
Diabetic macular edema present	• Mild diabetic macular edema: some retinal thickening or hard exudates in posterior pole but distant from the center of the macula • Moderate diabetic macular edema: retinal thickening or hard exudates approaching the center of the macula but not involving the center • Severe diabetic macular edema: retinal thickening or hard exudates involving the center of the macula

Reproduced with permission from Wilkinson CP, Ferris FL III, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1680.

* Hard exudates are a sign of current or previous macular edema. Diabetic macular edema is defined as retinal thickening; this requires a three-dimensional assessment that is best performed by dilated examination using slit-lamp biomicroscopy and/or stereoscopic fundus photography. Optical coherence tomography may supplement the fundus evaluation for determining the presence of diabetic macular edema.

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Clinically Significant Macular Edema

- Retinal thickening at or within 500 microns (1/3 DD) of center of macula
- Hard exudates at or within 500 microns of the center of the macula with adjacent retinal thickening
- Retinal thickening greater than 1 DD in size which is within 1 DD from the center of the macula

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Clinically Significant Macular Edema Can occur at any stage of retinopathy

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Clinically Significant Macular Edema

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Clinically Significant Macular Edema

- Can occur at any level of retinopathy.
- ETDRS Study: demonstrated benefit of focal and or grid laser in maintaining vision.
- Untreated, 25-30% of patients with CSME exhibit a doubling of the visual angle within 3 years.
- Treated, the risk drops by 50%.
- Would you refer a patient for focal laser to treat CSME if they were seeing 20/20?

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Proliferative Diabetic Retinopathy

- Is a vascular response to retinal hypoxia
- Many theories about the cause of retinal hypoxia. .
  - Capillary closure
  - Alterations in capillary b. membrane
  - Increase blood viscosity
  - Altered ability of blood to transport oxygen
  - Abnormal metabolic pathways in the retinal capillaries

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Proliferative Diabetic Retinopathy

- Vascular Endothelial Growth Factor – thought to play a significant role in the proliferation of neovascularization.
- The neovascularization is initially intraretinal but breaks through the ILM and lies between it and the vitreous.
- Fibrous component / ground substance develops and contracts as the neovascularizaton increases.

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Vascular Endothelial Growth Factor

- What is VEGF?
  - Is a chemical signal (signaling protein) produced by cells that stimulates the growth of new blood vessels. It assists in restoring the oxygen supply when blood circulation is inadequate.
  - Normal Function
    - Create new blood vessels. . .
      - During embryonic development
      - After injury
      - To bypass blocked vessels (collateral circulation)
  - Over expressed –proliferative DR

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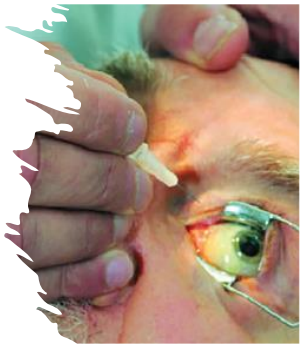
Anti-VEGF Therapies

- Medications developed to inhibit the process of angiogenesis.
- Treatments can slow down vision loss but there risks to the treatment.
- Typically treatment is not just a single dose/injection. Can be as frequent as monthly.



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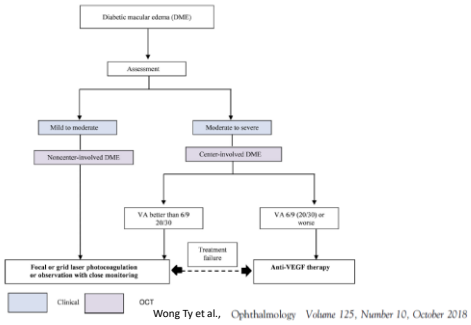

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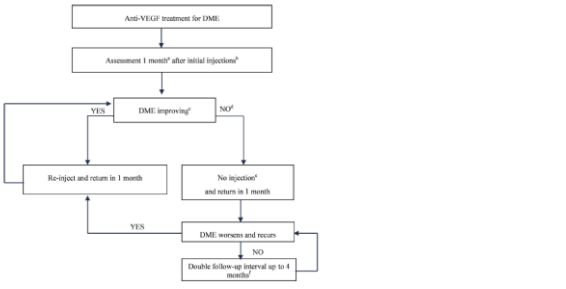

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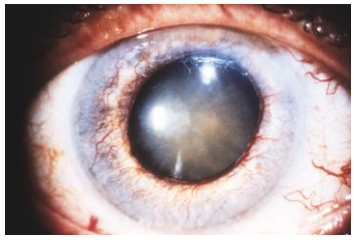
Proliferative Diabetic Retinopathy:
NVI – neovascularization of the iris



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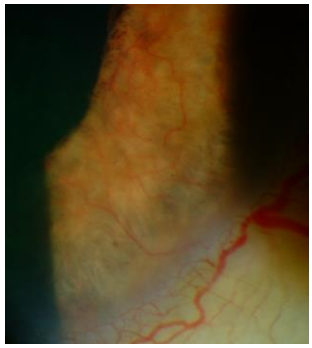

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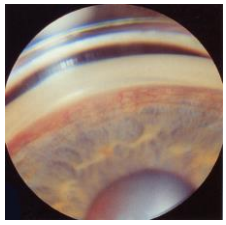
Proliferative Diabetic Retinopathy:
NVI – neovascularization of the iris



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Proliferative Diabetic Retinopathy:
NVI – neovascularization of the iris

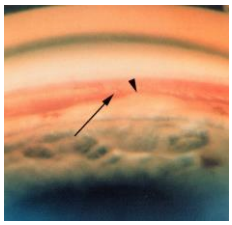

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Table 4. Follow-up Schedule and Management Based on Diabetic Retinopathy Severity for High-Resource Settings

Disease	Follow-up Schedule for Management by Ophthalmologists
DR severity	
No apparent DR	Re-examination in 1–2 yrs; this may not require re-examination by an ophthalmologist
Mild nonproliferative DR	6–12 mos; this may not require re-examination by an ophthalmologist
Moderate nonproliferative DR	3–6 mos
Severe nonproliferative DR	<3 mos; consider early panretinal photocoagulation
PDR	<1 mo; consider panretinal photocoagulation
Stable (treated) PDR	6–12 mos
DME severity	
Non–center-involving DME	3–6 mos; consider focal laser photocoagulation
Center-involving DME	1–3 mos; consider focal laser photocoagulation or anti-VEGF therapy
Stable DME	3–6 mos

DME = diabetic macular edema; DR = diabetic retinopathy; PDR = proliferative diabetic retinopathy; VEGF = vascular endothelial growth factor.

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Complications/Side Effects of PRP

- Decreased night vision and dark adaptation
- Decreased visual field / peripheral vision
- Atrophic creep- Becomes problematic when the laser is applied too close to the macula or nerve
- Choroidal detachment
- Makes RNFL testing / analysis difficult.

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