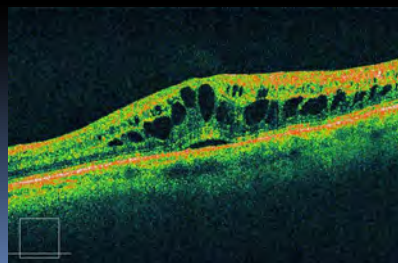


DIABETES UPDATE: CONTEMPORARY CARE OF PATIENTS WITH DIABETES

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Disclosure

- I have been on advisory boards/a consultant to/received honoraria from/ or been on speakers bureau list of the following:
 - Allergan, Alcon, Arctic Dx, Bausch & Lomb, Freedom Meditech, Kemin, Maculogix, Optos, Optovue, Thrombogenix, VSP, ZeaVision

These affiliations will have no affect on the content of this lecture

Objectives

- Discuss caring for patients with diabetes
 - Systemic disease
 - Eye disease
 - How systemic disease relates to eyes
 - Facts / trivia that may make conversations easier, and help out patients (while making you sound REALLY smart)

Diabetes in your practice

- Who has seen a patient this week with diabetes?
- Who has seen diabetic retinopathy within the last month?
- Have you ever asked a patient if they want you to care for more than their eyes?

Where do you live?

THE DIABETES BELT

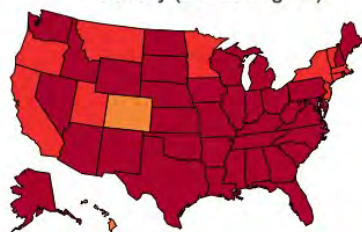


Diabetes Belt

Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

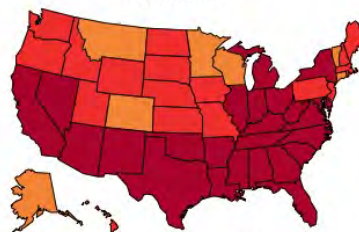
2013

Obesity (BMI ≥ 30 kg/m²)



Missing Data
 <14.0%
 14.0%–17.9%
 18.0%–21.9%
 22.0%–25.9%
 $\geq 26.0\%$

Diabetes



Missing data
 <4.5%
 4.5%–5.9%
 6.0%–7.4%
 7.5%–8.9%
 $\geq 9.0\%$



CDC's Division of Diabetes Translation, National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>



How is SC doing?



- What percentage of adults have DM?
 - 12.5% (4th in the US) affecting over 430,000
- What percentage have an annual DFE?
 - 57.7%
- Have A1c x2 per yr?
 - 76.1%
- SMBG?
 - 66.3%
- Percentage of 10-17yo's that are obese
 - 21.5%: 2ND WORST IN US



How's Indiana Doing?

- What percentage of IN adults have DM?
 - 10%
- What percentage of IN w DM get annual DFE?
 - 60.4%
- Get A1c at least 2x/yr?
 - 73%
- SMBG?
 - 65%
- DM and overweight or Obese?
 - 89%



More specific...

- What county has lowest % w DM?
 - Monroe: 8.1%
- What county has highest % w DM?
 - Lawrence: 14.1%
- Lowest Obesity?
 - Monroe: 21%
- Highest Obesity?
 - Jackson: 39.3% (Lawrence: 37.6%)



Some Kansas statistics

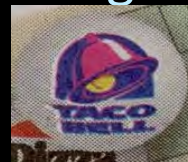
What counties have highest and lowest diabetes and obesity prevalence

- Highest: Jewell (14.1%)...32.4% obesity
- Lowest: Riley (6.0%) and Douglas (6.1%) 27.1 and 24.6% obesity
- Obesity: highest: Cherokee (39.5%) Lowest: Johnson (22.7%)
- Adults with DM getting annual eye exam
 - 68.5%
- % that do SMBG
 - 62.2%
- % getting routine A1c
 - 70.8%



What are some of the things you may hear

- "I have borderline diabetes"
- "I used to have sugar but now I don't"



- "My diabetes is diet controlled"



Coffee for better health






- Drinking coffee per day may help to prevent type 2 diabetes published by Institute for Scientific Information on Coffee (ISIC)
 - Presented at 2012 World Congress on Prevention of Diabetes and Its Complications (WCPD)
 - 3-4 c/d cuts DM development b 25% vs 0-1c/d
 - Energy Expenditure Hypothesis suggests caffeine stimulates metabolism and increases energy expenditure
 - Carbohydrate Metabolic Hypothesis: coffee components play a key role by influencing the glucose balance within the body
 - theories that suggest coffee contains components that improve insulin sensitivity through modulating inflammatory pathways, mediating the oxidative stress of cells, hormonal effects or reducing iron stores.



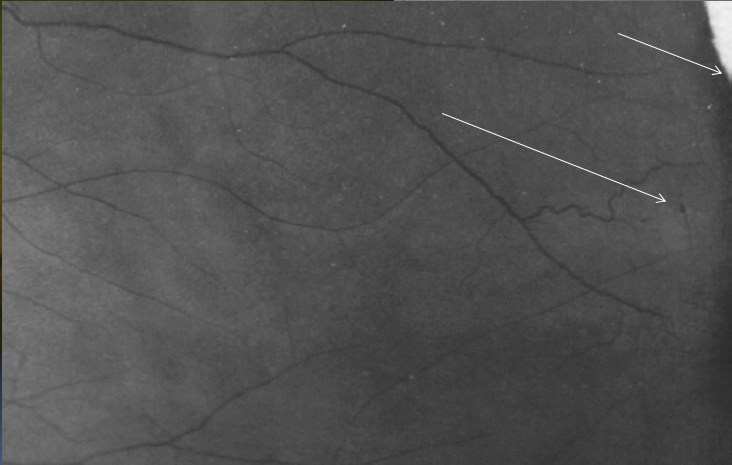
How important is Breakfast?

- Over 29k men followed over 16yrs for incident DM (1944 incident T2DM)¹
 - Skipping breakfast vs daily OR: 1.21
 - snacks also increased risk, but not significant
- Coffee may not affect incident stroke, Ca, CVD but does decrease incident DM²
 - Followed 42k adults for 9yrs
 - 4c/day drinkers had 23% decreased risk (caf or decaf)
- May be better to drink coffee at lunch³
 - French study of 70k women over 11yrs w 1400 incident T2DM
 - At least 1c/lunch were 33% less likely to develop T2DM
 - Black with or without sugar (regular or sweetner)

1. Am J Clin Nutr. 5/2012 Mekary et al. Eating patterns and t2DM in men.
 2. Am J Clin Nutr. Floegel. Feb 2012 3. Am J Clin Nutr. Online 2/2010.

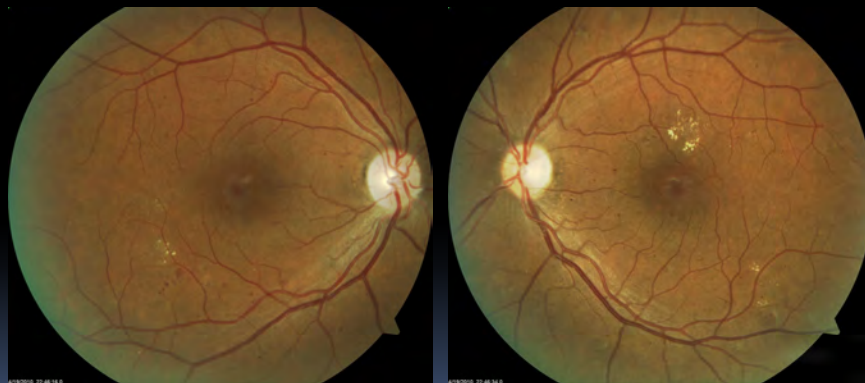
Early Detection?



Referral for “funny macula”

- 43yo referred for “funny looking” macula
- HHx: No disease to report
- OcHx: Wears glasses
- Fam Hx: Mother with T2DM
- Exam:
 - VA: 20/20 Pupils, motility, VF: Full
 - Ant seg Normal
 - Post pole: see images

What do you think?



Further information

- Further History: "I get up 3 times a night to get a drink and pee" "I am hungry and eating all of the time"
- Last visit to any doctor: 2 yrs for eye exam. Last MD/physical: >2 yrs, and don't really have a PCP
- In office A1c:

□ **>13!**

What next?

- Impressed on pt the importance of care!
- Called and made appt with a new PCP
- Gave her resource materials
- F/u w pt after PCP appt

The Challenge for OD's in Diabetes Care...

t h i n k i n g



Diabetes

- Lifetime risk of DM for Caucasian individuals born in 2000 is 32.8% for males and 38.5% for women (approx 20% more for hispanic)
- DM affects approximately 1:16 Americans, and approx 1/3 to 1/2 unaware they have DM
- NPDR may predate diagnosis of Type 2 DM by 6 years and detected in >20% at diagnosis
- BMI and weight are major risk factors: for every increase in wt by 1kg, increase risk by 4.5%
- Obesity by BMI is well over 20% in the US

Diabetes

- Type 1 (previously insulin dependent)
 - Only about 5-10% of diabetes cases*
 - B cell destruction leads to absolute insulin deficiency
 - Glucose stays in blood since can not enter insulin dependent tissues
- Type 2 (previously non-insulin dependent)
 - Peripheral insulin resistance, maybe relative insulin deficiency or secretory defect
 - Treatment to decrease hepatic glucose production &/or decrease peripheral insulin resistance
 - May become insulin dependent

Who Gets Diabetes?

- Genetics with Type 2
 - If 1 parent with T2DM, then 50% likelihood
 - If 2 parents with T2DM, then 80%
- Genetics with Type 1
 - If 1 parent with T1DM, then 10% likelihood*
 - If 2 parents with T1DM, then 20%



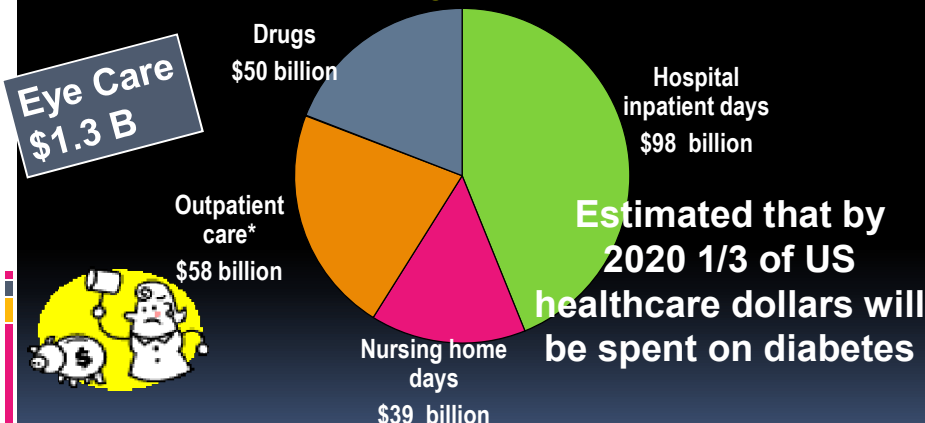
By 2030



**500,000,000 WORLDWIDE
WILL HAVE DIABETES**

JG2

US Healthcare Costs Attributable to Diabetes, 2012
For Patients of All Ages: Total = \$245 Billion



Category	Cost
Hospital inpatient days	\$98 billion
Outpatient care*	\$58 billion
Eye Care	\$1.3 B
Drugs	\$50 billion
Nursing home days	\$39 billion

Estimated that by 2020 1/3 of US healthcare dollars will be spent on diabetes

* Includes office-based physician encounters, emergency department encounters, hospital outpatient and free-standing ambulatory surgical center encounters, home health visits, hospice care days, and ambulance services.

American Diabetes Association. Diabetes Care. 2008 Mar;31(3):596-615.

Slide 24

JG2 Jeffrey Gerson, 5/30/2007

Obesity

- BMI classifications:
 - Normal: $<25 \text{ kg/m}^2$
 - Overweight: $25\text{-}29.9 \text{ kg/m}^2$
 - Obese: $>30 \text{ kg/m}^2$
- Waist circumference classifications:
 - Obese: $>88 \text{ cm}$ (34.6 inches) women & $>102 \text{ cm}$ (40.1 inches) men
 - Normal: $\leq 88 \text{ cm}$ women & $\leq 102 \text{ cm}$ men
- Increased BMI and waist circumference are both associated with decreased insulin sensitivity, higher glucose and triglycerides



Farin et al. Am J Cardiol 2006;98:1053-1056

Obesity - Classic Definition

- BMI > 25 **overweight**
- BMI > 30 **obese**
- BMI > 35 **severely obese**
- BMI > 40 **morbidly obese**
- BMI > 45 **super obese**
- BMI > 50 **super morbid obese**
- BMI > 70 **mega-obese**



There's An
AppforThat!

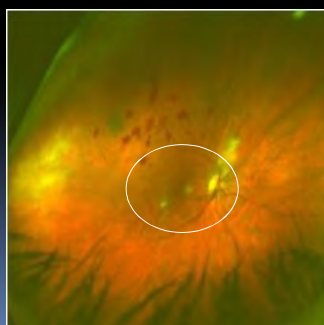
Diabetes

Testing

- Should be more frequent if obese, family history, birth to large baby, hypertensive or dyslipidemia, ethnic groups (hispanic, african american),

Diagnosis

- Fasting BG $>125\text{mg/dl}^*$
- Symptoms + casual BG $>200\text{mg/dl}$
- 2 hour BG $>200\text{mg/dl}$ during OGTT
- A1c over 6.5%
- Repeat test to confirm

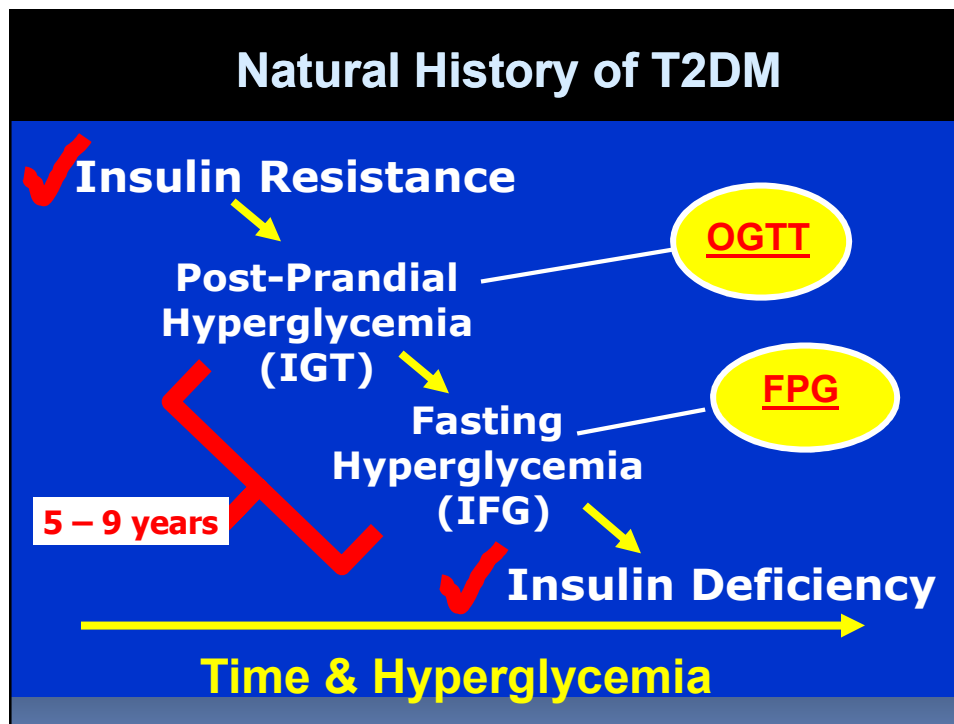


A1C for Diagnosis

- ADA, EASD, IDF expert panel recommends HbA_{1c} now be used as front-line test for diabetes Dx
- HbA_{1c} $\geq 6.5\%$ diagnostic for DM
- HbA_{1c} of $\geq 6\%$ but $< 6.5\%$ diagnostic for pre-diabetes

HbA_{1c} is a better predictor of DR than FPG

Diabetes Care 2009 November;32(11): 2027-32



I test in my office, do you?

- Are there potential positive ramifications?
- What about potential negative ramifications?
 - What about false sense of security by a “good” test result?
 - Can my/your BS testing replace that of PCP (care)?
- Must be prepared to discuss findings with patient and relay to PCP
- Can testing in your office make a difference?

What does A1c mean to your patients?

- Likely not much
- When did they have it done last? What was it? What is it supposed to be?

What SHOULD A1c Mean?

- **QUALITY OF LIFE!!**



Besides blood testing, are there other ways we can definitively diagnose diabetes?

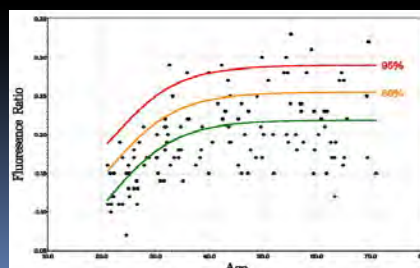


Diabetes Diagnosis in the ECP's Office

- Measurement of fluorescence (AGEs) in the lens is a biomarker of long-term glycemic stress



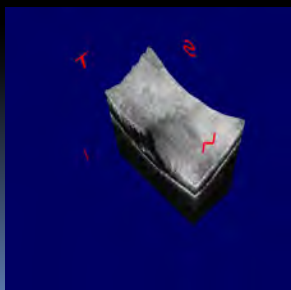
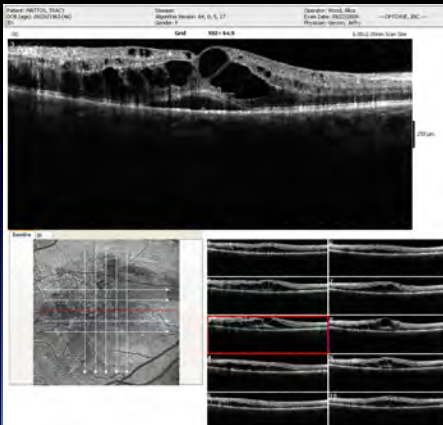
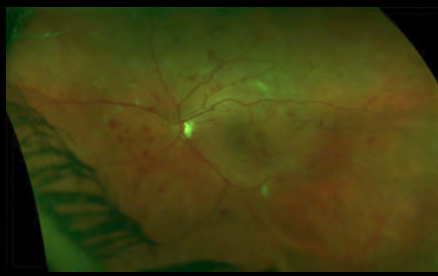
- The ClearPath DS-120 is designed for early detection of DM by patient comparison with age-matched norms
- Superior accuracy to blood tests
- FDA clearance 2/2013



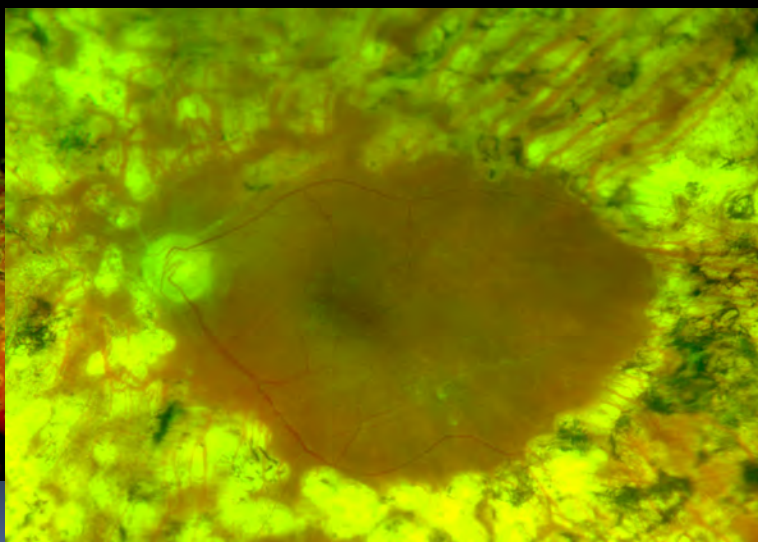
Journal of Diabetes Science and Technology, November 2012

You never know..

- Diagnosed with T2DM 2 wks ago
- Vision not good, Endo said due to BS fluctuation
- 20/50



And today...

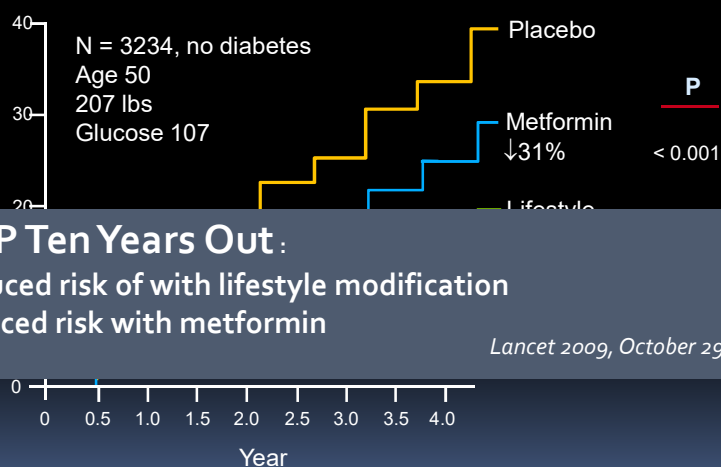


Treatment goals per EASD/ADA

- Not “guidelines” as are to algorithmic
 - Individualize glycemic targets
 - Lifestyle and education are foundation of tx
 - Metformin 1st,
 - Then add w goal of minimizing AE's
 - Ultimately, insulin if needed
 - Involve pt in decisions: values
 - Comprehensive cardio. risk reduction

oint AESDA and ADA position, as published: Diabetes Care 2012;35:1364-79

Impact of lifestyle intervention or metformin on diabetes*



The DPP Ten Years Out:

- 38% reduced risk of with lifestyle modification
- 17% reduced risk with metformin

Lancet 2009, October 29

DPP Research Group. *N Engl J Med.* 2002;346:393-403.

Are you surprised to know...

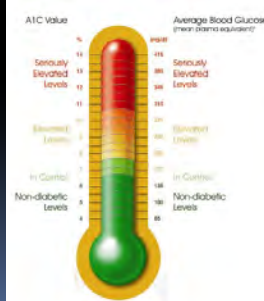
- Exercising in small amounts may be better than doing more when it comes to prevention
 - 1 2/3 min per 1/2 hour better than 30 minutes at beginning of work day: lower post-prand ¹
- Marijuana may improve metabolic markers²
 - Current and previous users had 16% lower fasting insulin and 17% less insulin resistance (and smaller waist circumference)
 - NO DOSE RELATED RESPONSE FOUND

¹ AJ Clin Nutr 7/13. ² Penner, E. "Impact of Marijuana on Metabolic". Amer J of Medicine: 7/13



Hemoglobin A_{1c}

- Importance of A_{1c} monitoring
- Critical to disease control and prevention of problems
- Newly accepted for Dx
- Does a patient know their last reading?
 - Good, bad, or worse response
- In office testing
 - www.a1cnow.com
- POC is more impactful¹



1. Diabetes care 30:713-715, March 2007.

Diabetes Control and Complications Trial & UK Prospective Diabetes Study

- Pts randomized to conventional or intense control
 - Showed slower progression for intense control group
 - For those with no NPDR at start, if intense, then 76% less devel. of retinopathy
 - If A1c down by 2%, PDR would decrease by 50%
 - Decrease in A1C by 1 %:
 - 14% decrease in MI
 - 12% decrease in stroke
 - 37% decrease in microvascular dz
 - 21% decrease in any DM endpoint
- DCCT reported relationship of A1C and avg. Glucose
- | %HbA1C* | Avg Glucose (mg/dL) |
|---------|---------------------|
| 4.0 | 60 |
| 5.0 | 90 |
| 6.0 | 120 |
| 7.0 | 150 |
| 8.0 | 180 |
| 9.0 | 210 |
| 10.0 | 240 |
| 11.0 | 270 |
- Control group in DCCT: 9-10%
Strict control group: 7%

Sources: NEJM 329:977-986 1993 UKPDS: Lancet 352:837-853 1998

10 years after DCCT¹

- Remember: In DCCT, pts with lower A1c, did better, and had less complications
- 10 yrs later A1c was 8.07% vs 7.98% in the groups
- Prevalence of retinopathy progression or PDR less in intensive group after 10 yrs (24 vs 41% & 6.5 vs 19%)
- **Other studies have confirmed retinopathy linked to initial BS control²**
- Similar effect seen in neuroathy and albuminuria
- Metabolic memory appears to last 10 years, but may wane at some time

1. Prolonged Effect of Intensive Therapy with T1DM. DCCT group. Arch Opth 12/08. 2. Reichard P. Glycemic thresholds for complications. J Diab Complic. 199;9(1);25-30.

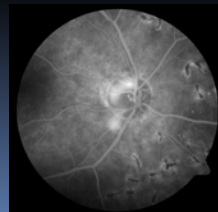
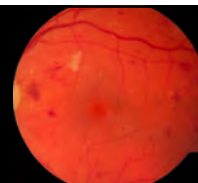
18 yr update

- 18yrs after DCCT, Intensive control group still lower complications but SAME current A1c
- “The HbA_{1c} matters today, tomorrow, and for many, many years to come. It matters.”
 - DCCT/EDIC biostatistician John M. Lachin, ScD
- Remaining differences:
 - Retinopathy: 46%
 - Cataract: 48%
 - RD or Vitrectomy: 44%
 - CV: 33%
 - Fatal cardio event 31%

American Diabetes Association (ADA) 2013 Scientific Sessions. DCCT/EDIC 30th Anniversary Symposium-Contributions and Progress, presented June 22, 2013

Diabetic Retinopathy

- Virtually 100% of people with diabetes have at least NPDR within 20yrs of diagnosis
- Up to 20% of newly diagnosed T2DM have NPDR at diagnosis
- Major cause of vision loss is CSME
- Today's treatment based on ETDRS
 - Should the standard shift to more modern treatment?




Individualized Risk Assessment for Sight Threatening Diabetic Retinopathy


- Risk calculator for STR (PDR and/or CSME) based on a few simple inputs
 - DM sub-type, gender, age, HbA1c, SBP, presence of NPDR
- Generates annualized risk for developing STR
- Excellent predictive accuracy when compared to outcomes from the Danish Diabetes Cohort (n=5199 followed for 20 yrs)

Diabetologia. 2011 Oct;54(10):2525-32.

Risk Calculator

Clinical Data





1 year

1%

Based on your clinical data, we evaluate that you are in **low risk** of developing sight-threatening retinopathy.

Your calculated risk of developing sight-threatening retinopathy is **1.0%** every year.

<p>Name / ID (*optional)</p> <input type="text"/>	<p>Duration of diabetes</p> <input type="text" value="10"/> years Default value given.
<p>Gender</p> <p><input checked="" type="radio"/> Male <input type="radio"/> Female</p>	<p>HbA1c</p> <input type="text" value="8"/> % Default value given.
<p>Type of diabetes</p> <p><input type="radio"/> Type 1 <input checked="" type="radio"/> Type 2</p>	<p>Average whole blood glucose</p> <input type="text" value="0"/> <input checked="" type="radio"/> mM <input type="radio"/> mg/dl
<p>Do you have diabetic retinopathy?</p> <p><input type="radio"/> Yes <input checked="" type="radio"/> No</p>	<p>Systolic blood pressure</p> <input type="text" value="130"/> mmHg Default value given.
	<p>Diastolic blood pressure</p> <input type="text" value="80"/> mmHg Default value given.

www.risk.is/optometry

More to Retinopathy than Retinopathy

- Retinopathy predicts CV mortality and coronary heart disease (CHD)¹
 - PDR>NPDR>no retinopathy in likely CVD and CHD mortality, and women>men, especially in NPR
 - In women, PDR yields nearly 5x risk of CHD death!
 - Independent of smoking, HTN, Cholesterol, HDL, duration or control of DM or proteinuria
- Retinopathy predicts stroke rate²
 - Those with DR have 2.34x risk for ischemic stroke
 - Independent of smoking, cholesterol, insulin use, htn..

1. Diabetes Care. Feb. 2007;30:292-99. 2. Cheung et al. Is DR independent risk for stroke. Stroke. Feb 2007

Depression and diabetic retinopathy

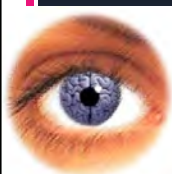
- Study of 2350 pts over 5 years: looking for correlation of depression and DR
 - Pathways Epidemiologic Study and assessed their levels of depression using the Patient Health Questionnaire-9 (PHQ-9)
- Found that worse depression correlated with more DR
 - Controlled for obesity, smoking, sedentary lifestyle & A1c
 - 22.9% of those with major depression developed DR
 - 19.7% of those w/out depression developed DR
 - A 5pt increased correlated with 15% increase in DR cases
 - 0-4 normal 5-9 mild 10-14 moderate 15-20 major 21-27 severe

Sieu N, et al. Depression and incident DR: a prospective cohort study. Gen Hosp Psych online, 2011

Is Brain Health in the Eye of the Beholder?



- Can retinopathy gauge cognitive function?
 - Screening for retinopathy may be valuable predictor Womens Health Initiative Memory Study (WHIMS)
 - >500 women >65yo w baseline fundus photo and cognitive testing over time
 - Women w retinopathy performed worse on visual and nonvision-dependent tests of mental ability



Pts w retinopathy had 47-68% more ischemic volume
 Conclusion: Retinopathy is vascular, brain ischemia is vascular: therefore related and related to cognitive decline

Haan et al. *Neurology* 2012;78:936-937, 942-94

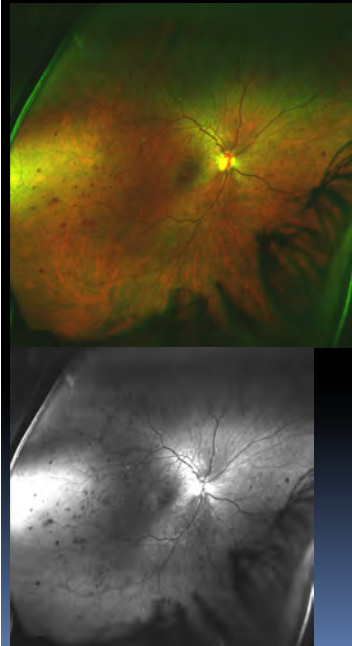
Diabetic retinopathy

Prevalence

- DR in USA 2005-2008
 - National Health and Nutritional Examination Survey (NHANES)
 - Published JAMA 8/2010
 - Looked at 1006 individuals with DM (A1c >6.5%)
 - DR vs VTDR vs PDR vs CSME
 - 28.5% DR 4.4% VTDR
 - 1.5% PDR and 2.7% CSME
 - Higher in Hispanic and AA
 - VTDR > if >65yo
 - DR more if on insulin
 - >DR if >A1c, HTN, duration and insulin use
 - 21% of those in NHANES with DM were undiagnosed
- Extrapolate: 3.8% of US has DR and .6% VTDR!!!**

Prevalence DR in US. Zhang et al. JAMA 8/10.

NPDR




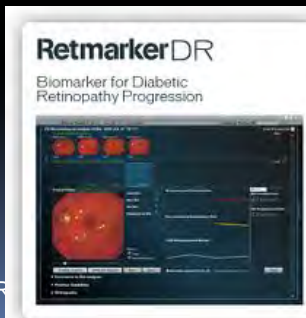
- Mild
 - At least 1 ma
- Moderate
 - Hemorrhages &/or ma's (≥2A), CWS, or VB(< 6B) or IRMA (<8A)
- Severe
 - 4/2/1 (Heme, Beading, IRMA)
 - 15% to PDR in 1yr^{1*}
- Very Severe
 - 2 or severe findings without neo.
 - 45% to PDR in 1 yr¹

1. As reported by ETDRS

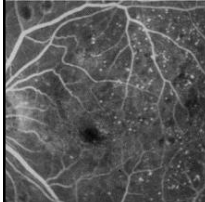
Microaneurysms: What can they tell you?

- MA turnover in the macula may predict CSME
 - 410 pts over 2 yrs measured for MA turnover and ultimate development of CSME
 - Low MA turnover had 95.9% negative predictive value for CSME
 - Turnover rate in CSME was >2x
 - Only other significant predictor A1c





RetmarkerDR
Biomarker for Diabetic Retinopathy Progression



Ribeiro et al. MA Turnover and CSME in NPDR
Diabetes Care. 11/2012 online

ACEIs for Retinopathy

- Previous analysis demonstrated 65%/70% less DR progression with use of enalapril/losartan in pts with T1DM [N Engl J Med](#). 2009 Jul 2;361(1):40-51.
- Analysis of the ACEI captopril shows a 40% decreased risk of DR progression and 30% less DME by OCT in pts with T2DM
 - [Chin Med J \(Engl\)](#). 2012 Jan;125(2):287-92

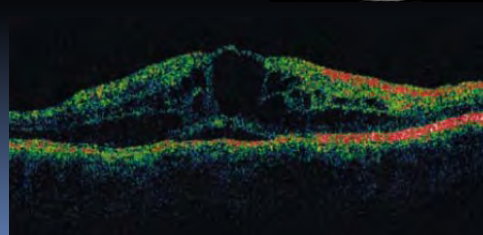
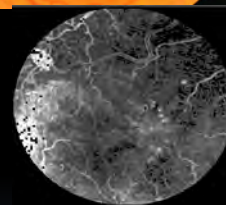
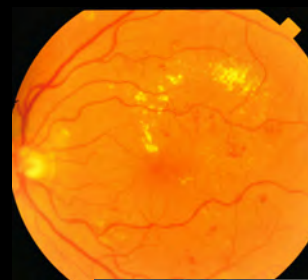
Do you even follow patients with retinopathy or just refer to somebody else (Notice, I did not say to an MD...)

SO, HOW OFTEN DO YOU FOLLOW YOUR PATIENTS?

HOW IS CSME DEFINED? IS OCT NECESSARY TO DIAGNOSE CSME?

Macular Edema

- 3 classic criteria*
 - Thickening $<1/3$ DD from center of macula
 - Heme/exudate with thickening of adjacent retina $<1/3$ dd from center of macula
 - Thickening >1 dd size within 1dd center
- Current treatment: Anti-VEGF (often with laser)
- Investigational treatments
- Failed treatments (steroid)



Why talk about CSME

- Is it a rare complication?¹
 - 955 subjects dx before 30yo
 - 25yr cumulative incidence was:
 - 29% for ME
 - 17% for CSME**
 - Higher incidence in males, more severe DR, *higher A1c*, proteinuria, Higher BP
 - Risk seemed to slightly decrease at end of study
WHY?
- By the way, still treated with traditional laser...no better vision with micro-pulse laser²

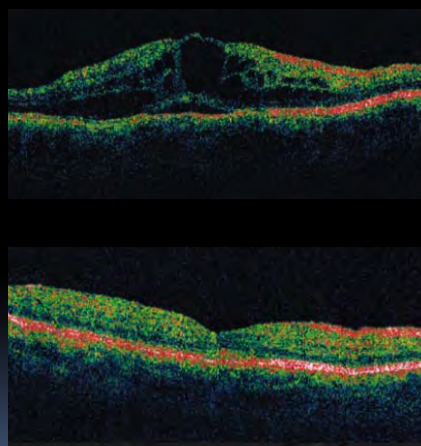
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Diabetic Retinopathy/Maculopathy and OCT

- Tissue thickening
- Cystic changes
- Disruption of NFL
- Monitor efficacy of Tx.


Pre Treatment

4 days s/p injection





What about oral Tx for DR

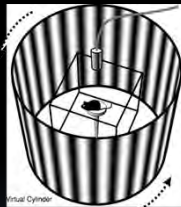


- Fenofibrate (Tricor)¹
 - As part of ACCORD-EYE and FIELD, looked at 11,400 Dm
 - ½ fenofibrate +/- statin
 - Presence of Fenofibrate reduced progression to need laser by 31% (PRP or focal)
 - Stronger results in those w existing DR than w/out
 - NNT w retinopathy: FIELD: 9 ACCORD: 14 (s ret: 333/500)
- Minocycline
 - 2012 ARVO paper² reporting improvement in DME w 100mg BID
 - +5.8 letters and 7% decrease OCT in 6mos (n=5)
 - Previous studies in animals and some human showing efficacy

Fenofibrate for DR. Wong et al. AJO 7/12. 2. Minocycline for DME. Cukras et al. ARVO 2012.

Oral Therapy for Prevention of DR is a Hot Topic

- ACEIs/ARBs – appear to reduce DR progression
- Fenofibrate (Tricor®) – approved for T2DM with early NPDR in Australia
- L-DOPA (improved vision in mice using OKN drum) [J Neuroscience Jan 2014](#)
- Tetracyclines (inhibit MMP-9) may improve CSME and FDT perimetry



Invest Ophthalmol Vis Sci. Jun 2012; 53(7): 3865–3874
[JAMA Ophthalmol. 2014 Mar 6.](#)

What about oral supplement?

- What would be in an ideal oral supplement for diabetes?
 - Vitamin D
 - Lutein / Zeaxanthin
 - Pycnogenol
 - Benfotiamine
- DiVFUSS Study
 - Dr. Paul Chous
 - Stable retinopathy, but improvement in systemic biomarkers and symptoms
 - CRP, TNF, contrast, MPOD, glare, PN pain score



Diabetic retinopathy: some real numbers

- Pooled analysis from almost 23k w DM
 - 34.6% prevalence for any DR
 - 6.96% for PDR
 - 6.81% for DME
 - 10.2% for VTDR
 - All DR end points increased with DM duration, A_{1c} & BP
 - Higher in people with T1DM compared w T2DM
 - Worldwide: 93M w DR, 17M PDR, 21M DME, 28M VTDR

Yao et al. Prevalence of DR. Diabetes care 3/12


LUCENTIS RANIBIZUMAB INJECTION **DRCR.net** 2yr f/u

- Lucentis + Laser vs steroid + laser vs laser

Improvement in VA at yrs

Lucentis + prompt	+3.7
Lucentis + deferred	+5.8
IVTA + Laser	-1.5

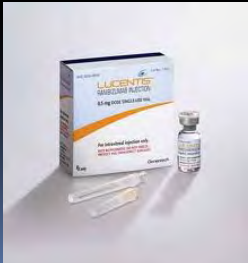
Lucentis grps injections: 2 & 3
Lucentis grps improvement: 29% >15ltrs



DRCR.net: Elman et al. 2yr Ranibizumab vs others for DME. Opth 4/11

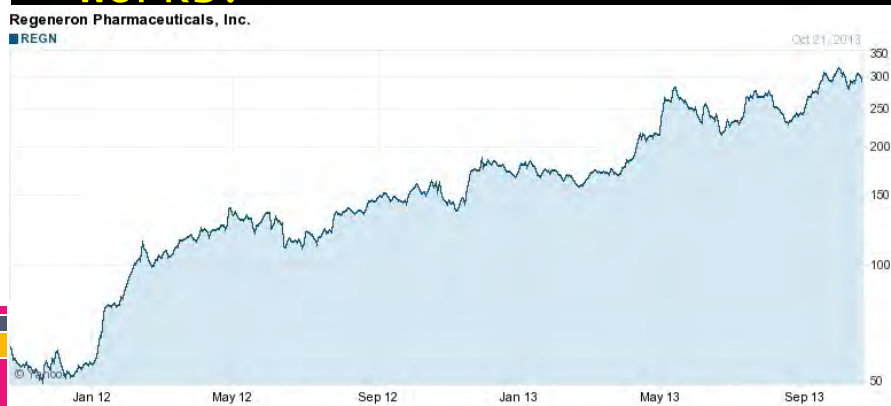
Previously Approved

- Lucentis approved for use in diabetic macular edema: August 2012
- Now it is official...it works for everything
- But, will it cause strokes?
 - Comparison of stroke rates in Ontario unchanged in retinal Dz pts w Lucentis/Avastin use



Stroke after VEGF. Campbell et al. Opth 8/12.

How do you know if a drug works?



When Wall Street likes the company that makes it!!

More Eylea for DME

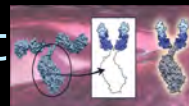
- Eylea (Aflibercept) superior to laser for DME
- 2 parallel Phase III studies: VISTA-DME and VIVID-DME at 127 centers and 865pts
- Mean gain at 1 yr of 10.5-12.5 letters vs only +.7 avg in laser groups
- Protocol was 2mg monthly x5 then either q1 or 2mos and will follow for 3 yrs

What anti-VEGF is Best for DME?

- Avastin, Lucentis & Eylea have not been studied head-to-head (a la CATT)
- Outcomes appear comparable by 15 RCTs and 8 observational studies, but evidence for superiority is insufficient
- Cost-effectiveness is best with Avastin
- Adverse events with Avastin are under-reported

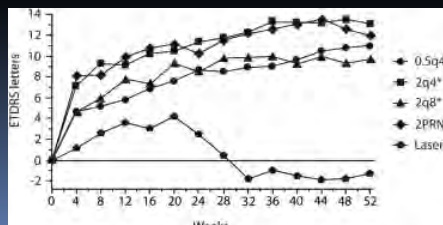
Int J Technol Assess Health Care. 2013 Oct;29(4):392-401

Eylea in Diabetes: Newest approval



- DaVinci study: change in vision at 24 and 52 wks n=221 w center involved DME
- 5 groups: .5mg q4wks vs 2mg q4wks vs 2mgq8wks vs 2mg prn vs macular laser
- At 52wks, laser: -1.3letters, and all VEGF-TRAP groups gained from 9.7-13.1 (2mgq4)
- PRN group got 7.4 injections over year
- More than 3x decrease in macular thickness in VEGF-TRAP group

1 yr DaVINCI trial. Do et al.
Ophthalmology. 8/12



Latest on Eylea

- 100 week results: VIVID and VISTA
- Eylea q4wks vs q8wks vs laser
- Improve 15 letters: 38 vs 33 vs 13%
- Lose 15 letters: 3 vs 1 vs 10%
- Most frequent ocular adverse: cataract: 2.4 vs 1 vs .3%
- Down side: Thromboembolic events: 4.2 vs 6.4%, and Vascular death: 1 vs 2%



Brown et al. Eylea for DME. Opth 10/15.

What is

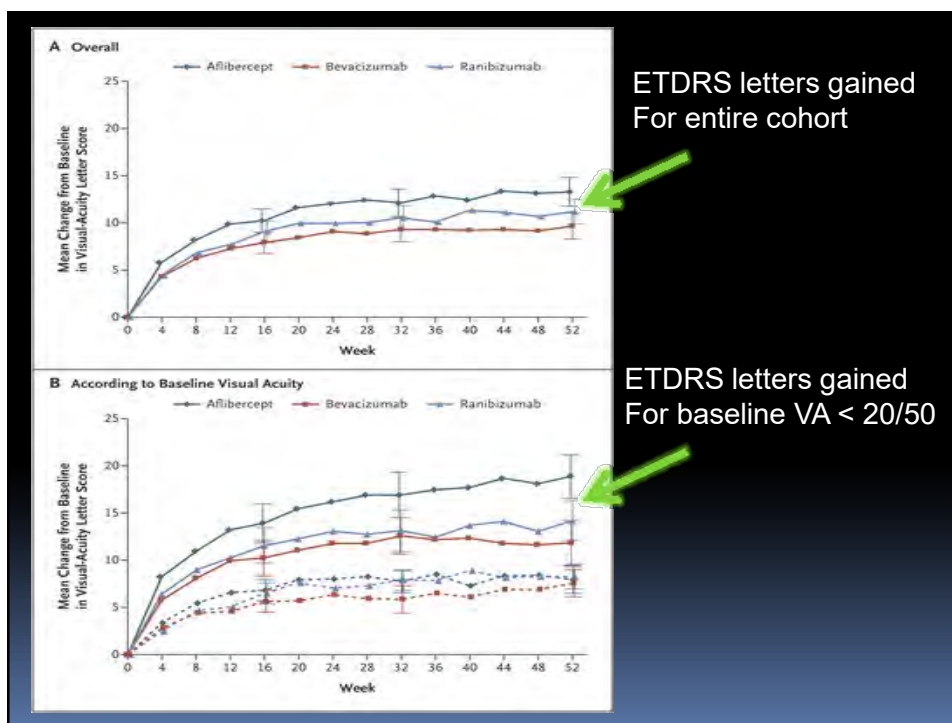
■ protocol



Protocol T – Published Results

- Aflibercept yielded 5-7 additional ETDRS letters compared to bevacizumab & ranibizumab when baseline VA was 20/50 or worse
 - Fewer pts needed rescue laser
 - 1 fewer injection
- Few adverse events in all 3 groups
 - No difference for serious events, hospitalization or death
- Still only 1-year data

N Engl J Med 2015; 372:1193-1203



Time to Switch It Up?

- DME patients unresponsive to Avastin and/or Lucentis were switched to Eylea
- Retrospective analysis
- Mean of 90/120 micron decrease in CFT at 1 and 5 months follow-up ($p < 0.001$)
- VA improved 2.5 ETDRS letters on average ($p = 0.04$)
 - $n = 19$ subjects/21 eyes

Clin Ophthalmol. 2015 Sep 16;9:1715-8.

**OD'S ARE NOT DOING
INTRAVITREAL INJECTIONS, SO
LETS TALK PRACTICAL...**

High Intensity Interval Training (HIIT)

- Alternating short bursts of all-out work with periods of rest
- Interval periods & duration vary
- Wingate Protocol
 - 30 seconds max effort (90% $\dot{V}O_2$)
 - 4 minutes recovery
 - 4-6 X per session, 3X/week

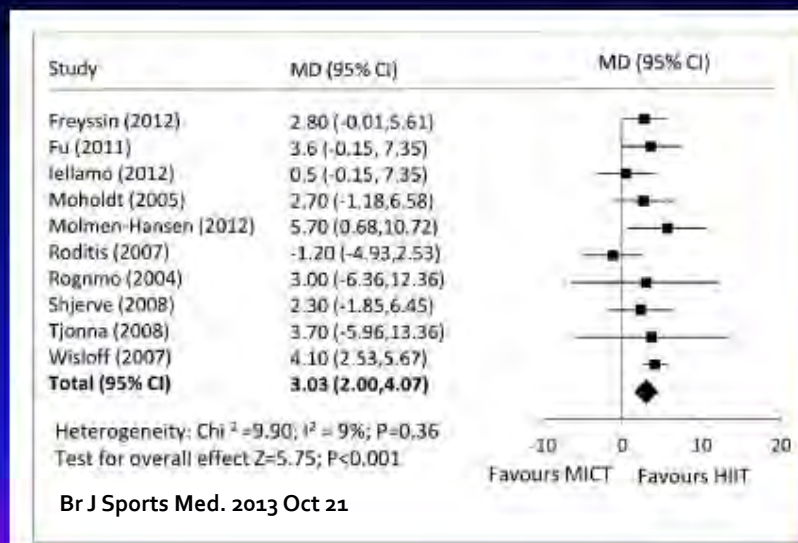
J Strength Cond Res. 2012 Oct;26(10):2866-71

HIIT

- Reduces abdominal & total fat
- Improves insulin sensitivity
- Burns more calories, increases HDL & post-exercise metabolic rate > steady state exercise
- 100 seconds Q 30 minutes results in better fasting glucose than 30 continuous minutes of medium intensity exercise

AJ Clin Nutr 7/13

Improving Cardio-respiratory Fitness in Patients with Metabolic Syndrome



SOME DIETARY POINTS OF INTEREST


Portion Control




1. H. Rabinovitz, et al. Big breakfast rich in protein improved glycaemic control and satiety feeling in adults w T2DM. 2. MK Piya, et al. The impact of high fat meal frequency on metabolic profile and energy expenditure in obese subjects.



Ben RW, et al. Cinnamon Use In Type 2 Diabetes: An Updated Systematic Review and Meta-analysis. 2013; 11(5): 452-459.




Not all fruits created equal



- >185k health professionals followed for incident DM and over 12k developed DM
- HR for DM: every 3 servings/wk of total whole fruit consumption was 0.98
- HR for fruit juice: 1.08
- Best: Blueberries: .74 Worst: Cantaloupe 1.10
 - Grapes and apples also very beneficial
- Maybe due to the difference in fiber, antioxidant, or phytochemical content

Yuraki I, et al "Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies" BMJ 2013;347:f5001.

Diet soda...



- 66,188 women monitored x16yrs
- Diet drinkers drink more (1.6vs2.8)
- Higher risk of developing DM in "light" or "diet" drinkers: 59% higher if 1.5L/wk
- May be due to Aspartame causing increase in glycemia and insulin levels (than sucrose)
- Overall increase in sweet cravings

Am Jnl Clin Nutrition. 2/2013

Alcohol...not all bad



- Alcohol use may help reduce incident DM
 - 82k nurses followed over 26 years
 - 6950 cases of incident diabetes
 - Although glycemic load on its own increased incident diabetes, alcohol intake attenuated it:
 - 1.29x for 5-5g/d
 - 1.34x for 5-15g/d
 - .99x fo >15g/d **same relationship not true with glycemic index

Assoc of GL and alcohol w T2DM in women. Mekary et al. Am J Clin Nutr. 2011 Dec;1525- 32.

Vitamin D and Retinopathy

Mean Serum 25-OH vitamin D (ng/ml)

DM (n=123) **22.9**

No DM (n=98) **30.3**

DM without DR **23.2**

DM with NPDR **21.5**

DM with PDR **18.0**



44% of pts taking a multivitamin were vit D insufficient
83% of pts not taking a multivitamin were insufficient

American Academy of Ophthalmol:
Abstract PO223. Presented October 17, 2010.



VS

BUT...HOW ARE MOST PEOPLE'S DIET?

So, might there be a need for supplementation

- Ideally something that doesn't have affect on A1c
- Can potentially improve/prevent retinopathy
- Have other potential benefits

- Oh yeah....and be safe

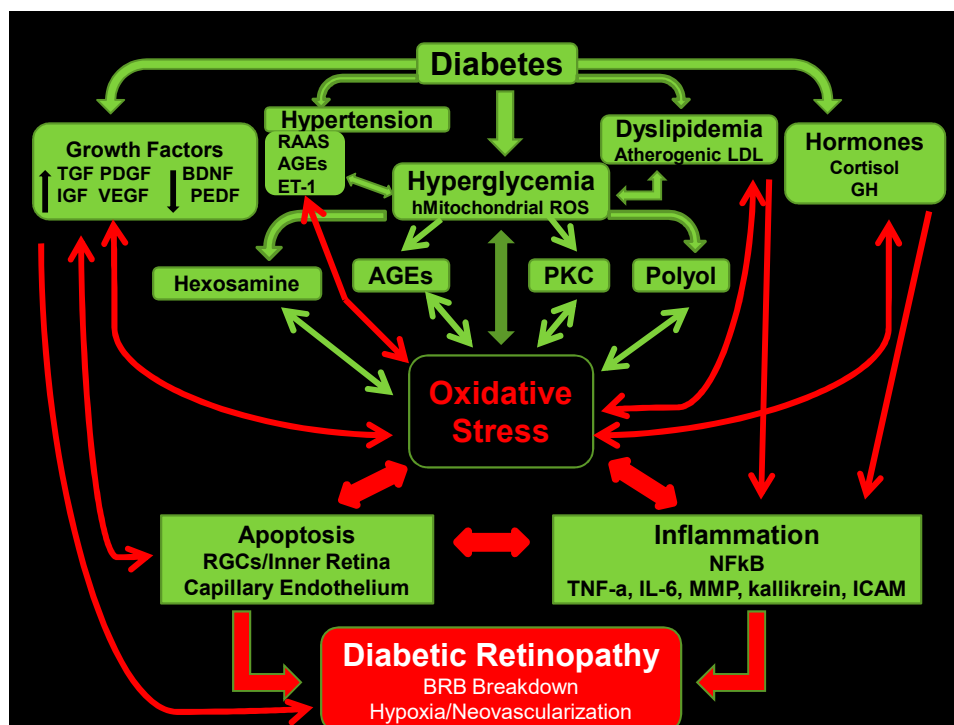




AMD Supplementation as a Working Model

- Numerous studies show beneficial effects of micro-nutrient supplementation in Age-related Macular Degeneration
- Reduced risk of progression to advanced AMD
 - e.g. AREDS, AREDS2
- Improvements in Visual Function
 - e.g. LAST, LUNA, CARMIS, ZVF Study

What Causes Diabetic Retinopathy?

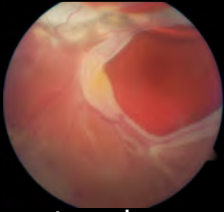
- **Hyperglycemia**
- **Hypertension**
- **Inflammatory Dyslipidemia**
- **Oxidative Stress**
- **Release and Suppression of Growth Factors**
- **Hormonal influences**
- **Apoptosis**
- **Up-regulation of inflammatory cytokines**
- **BRB breakdown and hypoxia**



**SCIENTIFIC RATIONALE
FOR SELECTION OF
CONSTITUTENTS IN A
MULTI-COMPONENT FORMULA
FOR DR**

Zeaxanthin & Lutein



- Higher serum ratio of non-provitamin A carotenoids:pro-vitamin A carotenoids is associated with a 2/3 lower risk of any DR
- MPOD is lower in diabetes and lower still in DR
- L/Z supplementation increased MPOD and improved VA ,contrast and foveal thickness in NPDR patients
Int J Ophthalmol 2011;4(3):303-6
Br J Nutr 2009 Jan;101(2):270-7.
- Lutein reduces nfkB & increases BDNF
- Zeaxanthin reduces VEGF and ICAM-1
Exp Biol Med 2011 Sep 1;236(9):1051-63.
Invest Ophthalmol Vis Sci 2008 Apr;49(4):1645-51

Key Messages

- **MPOD is lower in patients with diabetes and lower still in patients with diabetic retinopathy**
- **Higher serum Z/L is associated with 2/3 lower risk of developing type 2 diabetes and early NPDR**
- **ECPs should measure and optimize MPOD in our patients with and at-risk for diabetes**

Invest Ophthalmol Vis Sci. 2010 Nov;51(11):5840-5
 Br J Nutr 2009 Jan;101(2):270-7.



Vitamin D

- Vitamin D deficiency and insufficiency are associated with diabetes and retinopathy in both T₁DM and T₂DM
- Retinopathy severity is associated with worsening serum vitamin D status in T₂DM
- Down-regulates nfKB, TNF-alpha & inhibits neovascularization independently of VEGF
- Inhibits foam cell formation

Endocr Pract 2012 Mar-Apr;18(2):185-93

Clin Biochem 2000 Feb;33(1):47-51

Diabetes Care 2011 Jun;34(6):1400-2

J Immunol 2012 Mar 1;188(5):2127-35

Pycnogenol

French Maritime Pine Bark Extract

- 30+ RCTs showing health benefits, including 4 showing lower A1c, oxidized LDL-C & BP
- Reduced retinal edema & improved blood flow in NPDR

J Ocu Pharmacol Ther. 2009;25(6):537-40

- Inhibits nfKB, VEGF
- Inhibits ACE/eNOS to lower BP
- Inhibits MMP-9 to reduce capillary leakage
- Lowers post-prandial glucose spikes



Inflamm. 2006 Jan 27;3:1)

J Ethnopharmacol. 2011 Jan 27;133(2):261-77

Benfotiamine

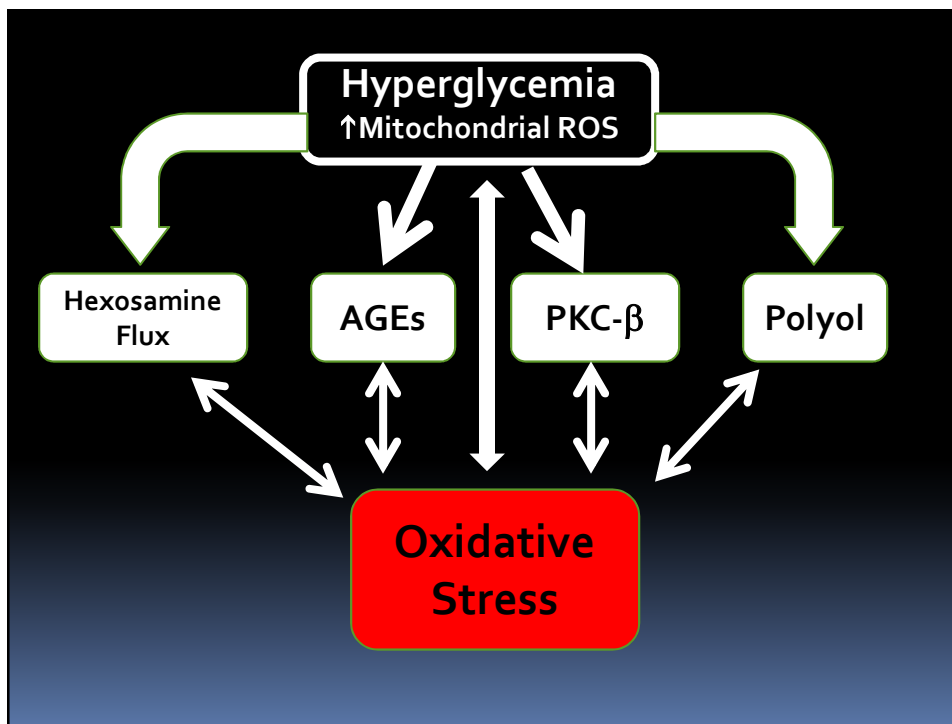
Fat Soluble Thiamin (vit B1) Analog

- Normalized activity in polyol, hexosamine, AGE, pathways in T1DM
- Totally prevented diabetic retinopathy in an animal model
- Normalized 4 major pathways of biochemical insult due to hyperglycemia (polyol, PKC, hexosamine, AGE)
- Blocks pericyte apoptosis due to hyperglycemia

Diabetologia. 2008 Oct;51(10): 1930-2

Nat Med. 2003 Mar;9(3): 294-9

Diabetes Metab Res Rev. 2009 Oct;25(7):647-56



Test Formula

- Zeaxanthin & Lutein
- Benfotiamine
- Alpha Lipoic Acid
- Vitamin D
- Vitamins C & E
- Mixed Tocopherols/Tocotrienols
- Resveratrol
- Green Tea
- Curcuminoids
- N-Acetyl Cysteine
- Grape Seed Extract
- CoQ10
- Zinc Oxide
- EPA/DHA
- Pycnogenol

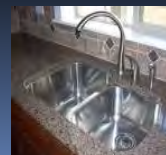


Figure 9 – Rationale for Inclusion of Specific DiVFuSS Micronutrients^{4, 18}

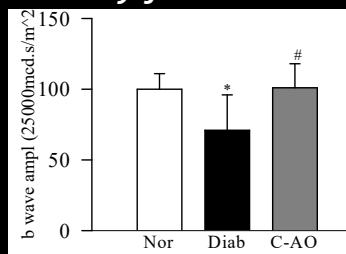
DiVFuSS Constituents	Mitigates DR in animal models	Blocks capillary cell apoptosis	Improves retinal capillary fragility	Reduces VEGF	Reduces oxidative stress	Reduces AGE activity	Reduces Polyol activity	Reduces PKC activity	Reduces NF-Kβ
Alpha-Lipoic Acid	*		*		*				*
Benfotiamine	*	*				*	*	*	
Vitamins C/E	*				*	*			*
Curcumin	*			*	*	*			*
Vitamin D3	*								
DHA/EPA	*	*							
Grape Seed Extract	*	*			*	*			
Resveratrol	*	*			*				
Green Tea Extract	*			*	*				
N-Acetyl Cysteine	*			*	*				
CoQ10	*				*				
Zinc	*								
Pycnogenol	(in AREDS)		*		*				*
Lutein/ Zeaxanthin	*			*	*				*

DiVFuSS Constituents	Improves visual function in humans	Reduces retinal edema in humans	Improves endothelial dysfunction in humans	Improves retinal blood flow in humans	Reduces HbA1c in humans	Improves Dyslipidemia in humans	Reduces blood pressure in humans	Reduces DPN symptoms in humans
Alpha-Lipoic Acid			*	*				*
Benfotiamine			*	*		*		*
Vitamins C/E			*	*		*		
Curcumin	*	*	*	*				
Vitamin D3					*	*	*	
DHA/EPA			*			*	*	
Grape Seed Extract			*		*			
Resveratrol			*		*			
Green Tea Extract			*			*	*	
N-Acetyl Cysteine			*					
CoQ10			*			*		
Zinc						*		
Pycnogenol	*	*	*	*	*	*	*	*
Lutein/ Zeaxanthin	*	*	*	*	*	*	*	*

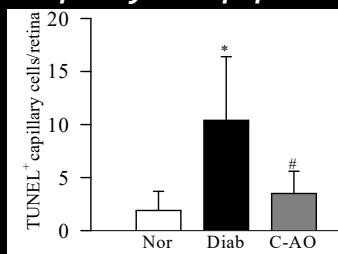
Note: Suggested improvements marked by * include published evidence in animal and/or cell models, except as specifically noted, but do not reflect grading of that evidence.

Supplementation with Test Formula prevented diabetes-induced retinal dysfunction

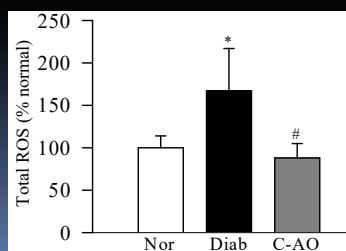
dysfunction



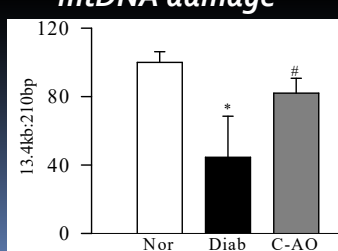
capillary cell apoptosis



oxidative stress



mtDNA damage



**SO DID THIS FORMULA WORK IN
HUMANS WITH DIABETES MELLITUS?**



Diabetes **V**isual **Fu**ncion **S**upplement **S**tudy

- 6 month placebo-controlled RCCT of adults with T1DM or T2DM \geq 5 years
- With and without retinopathy
- Daily use of a novel, multi-component nutritional supplement
- CSF, MPOD, color vis., macular perimetry, OCT, A1c, lipids, 25(OH) vit. D, TNF- α , hsCRP, DPNS score

ClinicalTrials.gov Identifier:
NCT01646047



OPEN ACCESS

The Diabetes Visual Function Supplement Study (DiVFuSS)

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Revised 8 April 2015
Accepted 26 May 2015

Background Diabetes is known to affect visual function before onset of retinopathy (diabetic retinopathy (DR)). Protection of visual function may signal disruption of mechanisms underlying DR.

Methods This was a 6-month randomised, controlled clinical trial of patients with type 1 and type 2 diabetes with no retinopathy or mild to moderate non-proliferative retinopathy assigned to twice daily consumption of placebo or a novel, multi-component formula containing xanthophyll pigments, antioxidants and selected botanical extracts. Measurement of contrast sensitivity, macular pigment optical density, colour discrimination, 5-2 macular threshold perimetry, Diabetic Peripheral Neuropathy Symptom, foveal and retinal nerve fibre layer thickness, glycohaemoglobin (HbA1c), serum lipids, 25-OH-vitamin D, tumour necrosis factor α (TNF- α) and high-sensitivity C-reactive protein (hsCRP) were taken at baseline and 6 months. Outcomes were assessed by differences between and within groups at baseline and at study conclusion using mean \pm SDs and t tests ($p < 0.05$) for continuous variables.

Results There were no significant intergroup differences at baseline. At 6 months, subjects on active supplement compared with placebo had significantly better visual function on all measures (p values ranging from 0.008 to < 0.0001), significant improvements in most serum lipids (p values ranging from 0.01 to 0.0004), hsCRP (p=0.01) and diabetic peripheral neuropathy (Richer's exact test, p=0.0024). No significant changes in retinal thickness, HbA1c, total cholesterol or TNF- α were found between the groups.

Conclusions This study provides strong evidence of clinically meaningful improvements in visual function, hsCRP and peripheral neuropathy in patients with diabetes, both with and without retinopathy, and without affecting glycaemic control.

Trial registration number www.ClinicalTrials.gov Identifier: NCT01646047

INTRODUCTION

Diabetic retinopathy (DR) remains a leading cause of visual impairment and blindness worldwide. Despite clinical trials showing that tighter control of blood glucose and blood pressure reduces the risk of microvascular diabetes complications, and despite tremendous advances in the clinical management of diabetic eye disease, rates of DR in the USA have increased by 89% over the last decade.¹

Importantly, serious visual impairment associated with diabetes remains high.² Recent estimates show nearly 30% of US adults with diabetes have sight-threatening DR (STR), with significantly higher rates among African, Latino and Native Americans. Although improving blood glucose control lowers

the risk of DR and its progression, evidence shows that there is no level of average blood glucose (as reflected by glycosylated haemoglobin) that is totally protective against DR. The current clinical algorithm for delaying DR and preventing STR is earlier diagnosis of diabetes, tighter metabolic control, routine dilated retinal examinations and treatment (laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents and corticosteroids) if/when DR progresses to a level that threatens vision.

The *Age-Related Eye Disease Study* (AREDS) demonstrated that a nutritional supplement could positively influence progression of a vision-threatening eye disease, age-related macular degeneration.³ This begs the question as to whether nutritional supplements may benefit other eye diseases, including DR. Vitamins, minerals and other micronutrients have a variety of biological functions potentially beneficial in diabetes, serving as enzymatic cofactors mediating glucose homeostasis, as regulators of cell growth and differentiation, and as building blocks of antioxidant defence. Thus, there has been renewed interest in their potential for preventing or treating a host of diabetes complications.⁴

A number of investigators have shown that diabetes affects visual function prior to the development of DR detectable by ophthalmoscopy. This includes deficits in contrast,⁵ visual field,⁶ and colour vision sensitivity.^{7–10} As such, amelioration of these visual function deficits may serve as an additional, useful biomarker for the onset and progression of retinopathy in patients with diabetes, yet no clinically evident DR, as well as those with established diabetes-induced retinal pathology.^{11–13}

In Diabetes Visual Function Supplement Study (DiVFuSS), we prospectively examine visual function effects of a novel, multi-component nutritional supplement designed to disrupt established biological pathways in the genesis of DR (www.ClinicalTrials.gov Identifier: NCT01646047).

SUBJECTS

A total of n=67 adult subjects, 42 women/25 men, mean age 56.1 years (± 13.2 years) with either type 1 or type 2 diabetes, were recruited following informed consent under the Declarations of Helsinki. Sample size was based on previous published trials and differences in key visual function variables. Subjects were primarily pre-existing patients from a single optometric practice emphasising diabetes eye care, with n=12 referred from either a local retinal specialty or endocrinology practice.

Brit J
Ophtha
E-publis
18, 2015

To cite: Chou AP, Richer SP, Gerson JD, et al. *Br J Ophthalmol* Published Online First: (please include Day Month Year) doi:10.1136/bjophthalmol-2014-306534



DiVFuSS Results

Mean Change/SD in visual function measures, serum lipids, hsCRP, TNF- α , glycohemoglobin, foveal thickness and symptoms of diabetic peripheral neuropathy with 95% p-Values

Δ from baseline	Suppl	v. Plac	p-Value
Color Error Score	-20.55 \pm 24.37	+7.5 \pm 22.01	<0.0002
5-2 MD (db)	+2.78 \pm 9.83	-0.75 \pm 0.98	<0.0001
MPOD (du)	+0.09 \pm 0.05	-0.01 \pm 0.03	< 0.0001
LDL-C (mg/dl)	-7.61 \pm 16.08	+0.82 \pm 10.1	0.01
HDL-C (mg/dl)	+3.82 \pm 6.24	-1.61 \pm 5.31	0.0004
TGs (mg/dl)	-10.46 \pm 28.48	+2.39 \pm 11.56	0.01
hsCRP (mg/L)	-2.14 \pm 3	-0.28 \pm 1.83	0.01
TNF-a (pg/ml)	+0.78 \pm 5.04	+0.56 \pm 2.79	0.88
HbA1c (%)	-0.1 \pm 0.4	+0.1 \pm 0.4	0.06
Foveal Thickness	2.66 \pm 11.25 μ m	0.34 \pm 3.48 μ m	0.35
DPNSS	-30.7%	+10.7%	0.0024

Summary of Findings in Humans

- DiVFuSS formula significantly improved visual function, including contrast sensitivity, visual field sensitivity and color perception
- DiVFuSS formula significantly increased MPOD
- DiVFuSS formula significantly reduced hsCRP and DPNS scores, and improved blood lipids
- Formula had minimal positive affect on A1c
- NO adverse events occurred during the study



Supplement Facts
Serving Size: 2 Softgels / Servings per Container: 30

Amount Per Serving		%DV
Vitamin C (Ascorbic Acid)	60 mg	100%
Vitamin D3* (Cholecalciferol)	2,000 IU	500%
Vitamin E* (d-alpha Tocopherol)	60 IU	200%
Vitamin B12 (Cyanocobalamin)	6 mcg	100%
Zinc (Zinc Oxide)	15 mg	100%
Fish Oil EE* 70%	320 mg	†
Total Omega-3 A%	240 mg	†
EPA 40% (Eicosapentaenoic Acid) A%	128 mg	†
DHA 30% (Docosahexaenoic Acid) A%	96 mg	†
Alpha Lipoic Acid	150 mg	†
Coenzyme Q-10 (Ubidecarenone)	20 mg	†
Mixed Tocotrienols/tocopherols*	20 mg	†
Zeaxanthin*	8 mg	†
Lutein*	4 mg	†
Proprietary Blend*	530 mg	†

† Daily Value not established * From natural sources

Other Ingredients: Gelatin, glycerin, soybean oil, purified water, beeswax, colors (annatto extract, titanium dioxide), lecithin oil.



Gluten Free
Contains NO Yeast
Contains soy & fish (cod, pollack, whiting)



Some of this too impractical?

- Visual impairment in Diabetes¹
 - Vision Impairment (<20/40) is more common in people with diabetes than those without (11.0 vs 5.9%)
 - Patients with VI and DM, approx 70% correctable!



Bottom Line: Don't Forget The Basics!

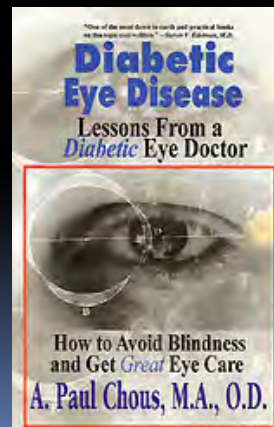
1. Zhang et al. DM and VI. Arch of Ophth. 10/08.

Conclusion

- Diabetes is reaching epidemic proportions
- Early detection is crucial!
- Eyecare is at the leading edge of diabetes care
- New treatments are improving care: both systemic and ocular
- Multidisciplinary approach critical
- Be a resource...


Resources

- www.diabetes.org
- www.diabetes.com
- www.diabetesincontrol.com
- www.diabeticeyes.com
 - "Diabetic Eye Disease..." by Paul Chous, O.D.
- www.ndep.nih.gov
- Endocrinologist



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THANK YOU



Telemedicine

- DR can be graded accurately through teleretinal exam/imaging
 - Good agreement between trained observers¹
 - In particular, non-mydriatic widefield imaging is at least as good as dilated ETDRS imaging²
 - Automated systems can be very helpful/accurate and potentially less expensive to use and still take the images needed (to be read by trained observer)³
- Jerry Cavallerano is an OD at Joslin center for Diabetes as part of Harvard School of Medicine

1. Cavallerano J et al. Diabetes Care 3/2012 2. Cavallerano J, et al. Am J Ophth 9/2012 3. Maker, Cavallerano et al. Diabetes Technol Ther. 2012 Jun;




A FEW MORE INTERESTING POINTS...

Get Social!

- >1000 DM patients 18-70yo
- 61% of pts that died over 6yrs were among the 20% most socially deprived: lower quality of life (income, employment, health, skills, crime, living environment, housing)
- Those in highest quartile of deprivation up to 5x mortality!
- Those that died were 50% less social
- **Stronger association than duration of DM**

Thomas S, et al "Age, glycaemic control and social deprivation predict 10-yr mortality in UK T1DM" EASD 2013;

Oh, the joys of parenthood

- Data obtained from >5100 T1Dm from Finnish Diabetes Epidemiology Research International cohort presented at EASD
- People w DM higher mortality than those w/out
- DM pts with at least 1 child had lower mortality than those w/out children: stronger affect in women
- More children generally lowered mortality
- Possibly due to better educated about health or more motivated

Be Careful Who You Marry!

- If one spouse has T2DM, the other spouse's odds for developing T2DM are elevated 26%
- Analysis of 75,000+ couples

BMC Medicine, January 2014

- If a parent has T2DM
the risk is 50% per offspring

