Diabetes Update

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Disclosures

- I have worked with a number of industry partners, and am confident that this will not influence the content of this course. I have in some capacity been a consultant to, on advisory boards or spoken for the following:

  – AI Optics, American Diabetes Association, Bausch & Lomb, EyeNuk, EyePromise, Genentech, Macular Degeneration Association, Notal Vision, OcuTerra, Regeneron, VSP, Zeiss

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Increasing Prevalence of DM

- **37.3 million Americans now have diabetes** (11.3% of pop)
  – 7.3 million undiagnosed   Incidence: 1.5 million (2018)
- 96 million Americans have prediabetes (38%) and 85% unaware
- 100+ million had NAFLD associated with insulin resistance in 2020
- **You won't lose vision to DR if you don't get diabetes**

Centers for Disease Control and Prevention. National Diabetes Statistics Report website. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed 5/21/2022.
Curr Pharm Des. 2020;26(10):993-997.

PROJECTED FUTURE PREVALENCE

2012 = 1 in 10

2050 = 1 in 3 to 5

✓ Significant increase in prevalence of total diagnosed and undiagnosed diabetes in adults in the US over the next 40 years.

Boyle JP, et al. *Population Health Metrics.* 2010;8:29. http://www.pophealthmetrics.com/content/8/1/29. Accessed February 11, 2015.

## Building Your Practice with Vision

- Patients with diabetes are often overwhelmed, have poor diabetes knowledge and will benefit from on-going care by diabetes-savvy ODs

- PCPs/endocrinologists are often eager to work with diabetes-savvy ODs

- Letting patients/providers know your practice emphasizes diabetes eye care & education offers huge potential for practice growth

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Prediabetes: Real or Not?

- Up to 70% of PreD patients ultimately develop T2DM
- 6.6-11% of prediabetes patients have retinal lesions consistent with diabetic retinopathy
- Risk of CVD is doubly high in prediabetes versus normoglycemia

Lancet. 2012 Jun 16; 379(9833): 2279–2290.   Surv Ophthalmol 2022 Apr 14;S0039-6257(22)00045-5

CVD is PreD and T2DM
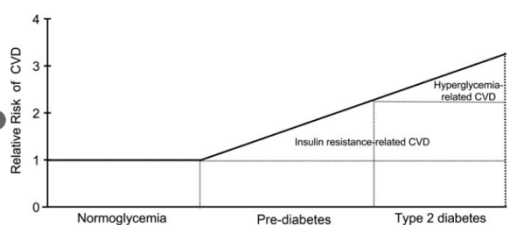
Diabetes Care. 2010 Feb;33(2):442-9.

26-Year Data from the DPPOS

- Diabetes Prevention Program Outcomes Study
- Prediabetes subjects: Usual care v. metformin v. lifestyle intervention with 150 min moderate exercise/week (mean age = 72 yrs)
- 25% risk reduction with exercise vs 18% metformin vs usual care
  - No significant difference in DKD/DR/CV disease between metformin & exercise in those who developed T2DM
  - 12% reduction in cancer; not statistically significant)

Exercise Beats Metformin at ALL Time Points

ADA Scientific Sessions, June 16,2020

So.....Why are Many Pre-DM Patients Started on Metformin?

- DPP showed metformin was most effective for patients < age 60 and with BMI > 35 kg/M^2 and women with a history of gestational DM
  - Lifestyle intervention still had equivalent efficacy in these groups
 - Taking a pill may promote compliance > ongoing lifestyle modification

N Engl J Med. 2002 Feb 7;346(6):393-403
Diabetologia. 2017 Sep;60(9):1601-1611

A Patient for Your Consideration – 45 yo man

- Presents for initial evaluation
  - He has not visited a physician in > 5 years
  - Recently gained 20 pounds during pandemic
- Complaint: "Blurry Vision"; no meds
- Physical exam:
  - BP 152/95
  - Height 5'-9"
  - Weight 226 Lbs.
  - BMI 33 & Waist 40"
  - Reports being tired all the time → + ESAP

Ocular Dx:
1+ NS
Presbyopia
20/20 OD/OS
Retina appears normal
IOP = 17/16

+ ESAP = Easy Sleep Apnea Predictor

≥ 1 cm gap
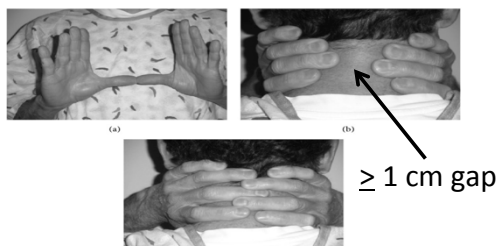
Neck Grasp Predicts Obstructive Sleep Apnea in Type 2 Diabetes Mellitus. Sleep Disord. 2019 Jul 1;2019

In-office Random Blood Glucose =212 mg/dl

→ **Refer to primary care physician**

Lab Results: What do they mean?

- Fasting glucose 165 mg/dl (65-99 mg/dl)
- AST 42 IU/L (0-40 IU/L)
- ALT 54 IU/L (0-44 IU/L)
- ALK PHOS 110 IU/L (39-117 IU/L)
- BUN 18 mg/dl (6-24 mg/dl)
- Cr 1.2 mg/dl (.76 – 1.27 mg/dl)
- Total Chol 232 mg/dl (100-199 mg/dl)
- Trig 302 mg/dl (0-149 mg/dl)
- HDL 30 mg/dl (>39 mg/dl)
- LDL 164 mg/dl (0-99 mg/dl)
- Urine Albumin / Creatine 110 mcg/mg (<30 mcg/mg)

HbA1c of 8.2%

Diagnoses:
Elevated LFTs
→ ?NAFLD

Metabolic Syndrome
High TG/Low HDL
HTN (>130/85)
FBG ≥ 100
waist ≥ 40 inches

Diabetes mellitus
DKD

2

➜ Referred for Sleep Study by PCP

- In-home polysomnography (PSG)

  - **Apnea-Hypopnea Index: 32 events/hour**

Severe OSAS

Mild = 5-15
Moderate = 15-30
Severe > 30

What You Gonna Do?

- Pharmacotherapy for hyperglycemia/HTN/lipids
  - Why? Prevent MACE, ESRD and eye disease
  - Probable: metformin, lisinopril, high potency statin
- Sleep therapy
  - Why? Increased risk of CV events and DR/DME
  - Weight loss, CPAP+
- Weight loss
  - Why? Improves all metabolic markers of DM
  - Not a candidate for bariatric surgery (BMI ≥ 35 w DM)
  - Discuss Fasting Regimes
  - Drug therapy – unimpressive until NOW

Breaking News: Hi-dose Semaglutide
Wegovy® approved June 2021 for Weight Loss

- Semaglutide 2.4 mg weekly + lifestyle intervention (LI) used in patients with BMI ≥ 30 (or ≥ 27 with 1+ weight-related comorbidities) versus LI + placebo injection (n= 1961 without diabetes)
  - 2.4X FDA-approved dose in T2DM
  - Nausea/vomiting in 80%/40% of treatment vs control subjects
  - **Mean weight loss = 33 lbs at 68 weeks**
- **1/3 of subjects lost ≥ 55 lbs**

N Engl J Med. 2021 Feb 10.

But Wait…there's more!

- **Tirzepatide** is a dual GLP-1/GIP analog
  - GIP = glucose-dependent insulinotropic peptide (↑insulin secretion with higher blood glucose levels)

- SURPASS-2 Trial compared weekly tirzepatide versus semaglutide injection in T2DM
  - After 40 weeks, mean A1c reduction was 2.46 vs 1.86
  - **51% vs 20% achieved A1c < 5.7%**
- Mean weight loss was 27.3 lbs vs 13.7 lb

- Approval May 13, 2022 (Mounjaro®) for treating T2DM, not weight loss

Press Release, Eli Lilly & Company, March 4, 2021

SURMOUNT-1 Trial
2,539 obese subjects w/o DM in 9 countries

- Tirzepatide tested at 5/10/15 mg

- Mean body weight 231 lbs at entry

- **Mean weight loss at 72 weeks: 35/49/52 lbs (placebo group lost 5 lbs)**

Presentation at the Advanced Technologies
and Treatments in Diabetes 2022 meeting, Barcelona, April 30

SURPASS-3 and Fatty Liver Disease

Total LFC (liver fat content) significantly reduced on tirzepatide versus insulin degludec

Exemplary Responder LFC from 27.3% to 2.6% at week 52
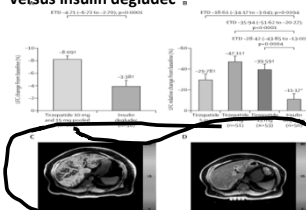
Also ↑Bone Density About 18%

Lancet Diabetes Endocrinol. 2022 Apr 22:S2213-8587(22)00070-5.

Typical Medication Regimen

- **T2DM**
  - **Metformin – multiple effects** **+**
    - OTHER glucose lowering agents PRN
    +
  - **ACEI or ARB**: lower BP & renoprotective
    +
  - **Statin**: inflammatory dyslipidemia
    +
  - **81 mg Aspirin**: reduce platelet adhesion to MI/stroke risk

What is HbA1c?

- **The "average blood glucose"?**
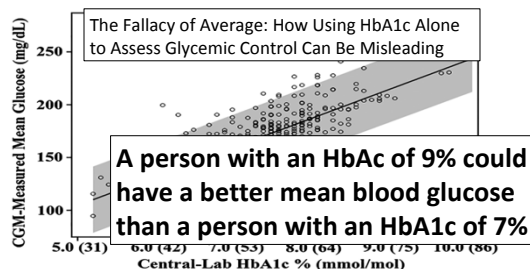- **NO!!**
- **HbA1c is related to mean BS over 3 months but patients with the same A1c often have significantly different mean BS**
- **How do we measure the TRUE average BS?**
  - **HARD: 7 to 700 fingersticks each day!**
  - **EASY: CGM or Flash glucose monitoring systems**

Continuous Glucose Monitoring (CGM)

- **Continuous glucose monitoring systems (CGM) render fingerstick glucose testing irrelevant except for purposes of calibration**
- **These systems are becoming increasingly popular amongst all DM patients (especially on insulin Tx)**
  - **40% of T1DM**
  - **≈9% of T2DM**
- **Allow real-time alerts for high and low blood glucose and calculation of glucose time-in-range**
  - **Predict DR & DKD independently of A1c**
- **Helps correct deficiencies of A1c** Sensors (Basel). 2019 Feb; 19(4): 800.

Plot of CGM-measured mean glucose concentration vs. laboratory-measured HbA1c.

The Fallacy of Average: How Using HbA1c Alone to Assess Glycemic Control Can Be Misleading

A person with an HbAc of 9% could have a better mean blood glucose than a person with an HbA1c of 7%

Roy W. Beck et al. Dia Care 2017;40:994-999

Measured A1c versus CGM-derived A1c
(AKA GMI = glucose management index)

641 patients from U Wash Endocrinology wearing CGM
- Measured and calculated A1c differed by > 0.5% in 50% of patients
- Measured and calculated A1c differed by > 1.0% in 22% of patients

- *"Our gold standard ain't so golden"*
  - Personal correspondence with Irl B. Hirsch, MD, FACE
  - Clinical Director of UW Endocrinology
  - 2017 Endocrine Society Laureate

Perlman JE, Gooley TA, McNulty B, Meyers J, Hirsch IB. HbA1c and Glucose Management Indicator Discordance: A Real-World Analysis. Diabetes Technol Ther. 2021 Apr;23(4):253-258.

Benefits of Glucose Time-In-Range

- TIR refers to the percentage of the day a patient's blood glucose is 70-180 mg/dl
- For any given TIR, there is WIDE variability in HbA1c (e.g. TIR = 60%, HbA1c range = 7-12%)
  - 1441 participants from the DCCT
  - 3262 T2DM patients in China
- **A 10% decrease in TIR increases DR risk 64% and risk of microalbuminuria 40%** (p < 0.001)
  - **→ INDEPENDENT of HbA1c**

Diabetes Care. 2019 Mar;42(3):400-405   Diabetes Care 2018 Nov; 41(11): 2370-2376
J Diabetes Sci Technol. 2019 Jul;13(4):614-626.

Validation of time in range as an outcome measure for diabetes clinical trials

Goal is TIR > 70%%

Relationship between TIR (70–180) and HbA1c
(TIR: 7-point SMBG profiles on 1,440 patients in DCCT)

In DCCT, the TIR difference in those with and without DR was 2.5 hours

CGM in Poorly Controlled T2DM

- 8-month RCT of 175 pts on basal insulin and mean HbA1c > 9%
- CGM vs. conventional SMBG lowered HbA1c a mere 0.4% (p = 0.02)
- CGM increased TIR 15% (3.6 hrs/d) and decreased time-above-range (TAR $_{>250}$) by 16% (p<0.001)
- Equivalent to a 60% risk reduction for the development of DR

JAMA. 2021;325(22):2262-2272.

Improved HbA1c 1-1.5% in non-insulin users
ADA Scientific Abstract 84-LB June 13, 2020
Equivalent to adding insulin

Glucose Targets Should Be Individualized

Approach to Individualization of Glycemic Targets

Not ALL patients need or should attempt to get HbA1c < 7%

If short life expectancy, frequent hypoglycemia, cognitive decline, established CVD → BACK OFF

Diabetes Care. 2020 Jan; 43 (Suppl 1): S66-S76 [20]

Management Goals for Adults: A1C and TIR

CGM Reduces Hospitalization for Hypoglycemia in ALL Insulin Using Patients

- 3800 T1DM and 38,000 T2DM patients on CGM
- CGM use vs non-use reduced ED visits for acute hypoglycemia by 2.7%
  - Equivalent to annual saving of $55 million
- The Freemantle Diabetes Study (W. Australia) showed hospitalization for acute hypoglycemia = biggest risk factor for 2+ lines of vision loss in subjects with DM

*JAMA. 2021;325(22):2273-2284.*

Avoid SEVERE Hypoglycemia

- Kills retinal cells in animal models   PLoS One. 2011;6(6):e21586.

- Fremantle Diabetes Study (Western Australia) showed that risk of 2+ lines of vision loss in T2DM was significantly & independently linked to hospitalization for severe hypoglycemia and cigarette smoking (n = 1551 over 4 years)
  – Smoking HR = 3.17
  – Severe Hypoglycemia HR = 5.59 $p < 0.0001$

Drinkwater, Jocelyn J., et al. "Incidence and Predictors of Vision Loss Complicating Type 2 Diabetes: The Fremantle Diabetes Study Phase II." Journal of Diabetes and Its Complications, Elsevier, 22 Feb. 2020

Hypoglycemia Symptoms

- **Confusion or irritability** (fight or flight)

- **Tremor (shakiness, poor motor coordination)**

- **Perspiration**

- **Acute change in affect (patients often become significantly more or less talkative)**

- **CGM trend arrow helps patients avoid hypoglycemia, especially in patients with hypoglycemia unawareness**
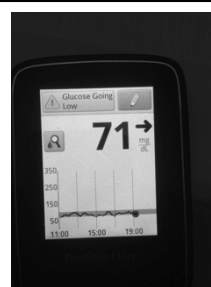
Good Function   Poor Function

Hypoglycemia - continued

- **Over-compensation for hypoglycemia results in hyperglycemia**
  - **Drives insatiable hunger to correct with foodstuffs**

- **Acute hypoglycemia significantly increases the risk of another episode in the next 24 hours**

- **The ONLY diabetes meds that cause hypoglycemia in isolation are:**
  - **Insulin (both long- and short-acting forms)**
  - **Sufonylureas (glipizide, glyburide, glimeperide)**
  - **Glinides (Starlix, Prandin)**

Optometry's Role with Hypoglycemia

- **AOA clinical practice guidelines state that ALL ODs should have a rapid-acting CHO (fruit juice, sugar sweetened beverage) in-office to rescue hypoglycemic patients**

- **Check glucose in-office with patient's meter or CGM (or an office meter if you have one)**

- **15 grams of carbohydrate will raise blood sugar 30-40 mg/dl in 15 minutes (NOT IMMEDIATE -- DO NOT EXPECT Patient coherence to improve immediately!) - folow-up with re-test and protein (cheese, peanut butter)**

DR Progression with Insulin Pump vs Multiple Daily Insulin Injections in T1DM

- Retrospective Scottish cohort study
  - NPDR progression with continuous subcutaneous insulin infusion (CSII) versus MDI (n = 415) over 2+ years follow-up
- 18.6% versus 26.5% had significant worsening of NPDR after all controls (p = 0.009)
- Baseline HbA1c > 9% was only associated with worsening DR in the MDI group (p < 0.005 vs 0.93)
- Change in HbA1c at follow-up had no association with DR progression in either group
- **In T1DM, using an insulin pump is protective against DR progression, especially in patients with high baseline HbA1c**

Why is diabetes a risk factor for bad outcomes, including death, from COVID-19 infection?

- Glycation of ACE2 receptors facilitates spike protein attachment and release of viral genetic material into host epithelial cells *J Diabetes Sci Technol*. 2020
- Increased cytokine storm/ARDS and thrombosis secondary to pro-inflammatory state associated with IR/hyperglycemia
  Front. Endocrinol., 14 July 2020
- Retospective analysis of COVID-19 outcomes in hospitalized patients with diabetes shows:
  - 7.2X increased risk of mortality and 10X risk of acute cardiac injury if glucose on admission ≥ 196 mg/dl
    Diabetes Res Clin Pract. 2020;166:108299.

CORONADO Study
Coronavirus SARS-CoV-2 and Diabetes Outcomes

- French multi-center study of DM patients hospitalized with COVID-19 (n = 2796)
- Assess factors associated with discharge ≤ 28 d & mortality
- **Protective factors**: long duration between symptom onset & hospitalization, metformin use, younger age
- **Deleterious**: older age, microvascular DM complications, insulin use, dypsnea, ↑CRP/AST, ↓platelets

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Covid-19 and DR

- Presence of DR in hospitalized DM patients with PCR-confirmed SARS-CoV-2 infection increased odds of ventilation 5.2-fold (p < 0.001) but not mortality (50%)
  - 187 patients at a single UK hospital
  - Mean HbA1c 8.6% in those with & without DR

- DR ↑mortality or critical care up to 67% in Scottish analysis of 1000+ (p < 0.0001) with highest risk if 'referable DR'

COVID-19 Increases Risk of New-Onset Diabetes
Nutr. Diabetes 11, 21 (2021)
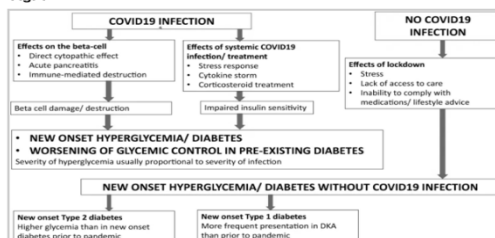
Glycemic Index & CV Disease/Mortality

- 138,000 35-70 yo on 5 continents (9% with DM)
- FFQ to determine GI over median 9.5 yrs
- For Highest vs lowest GI quintiles:
  - **HR for CV event (MI/CVA/HF/CV death) or all-cause mortality was 1.51 for those with pre-existing CVD after all adjustments**
  - **HR for CV event/death for those without preexisting CVD was 1.21**
  - all p< 0.001

 - **Eat more whole vegetables/fruits, less doughnuts/rice/corn/potatoes**

NEJM April 2021; 384(14):1312-1322

Measure the food's effect on your blood sugar with the Glycemic Index

The more processed the food, the higher the glycemic index

Juice has a higher GI than 'real' fruit

Is There Beneficial "Fruit Juice"?

Vinegar lowers post-prandial glucose ≈ 30 points 2-hours after a high-GI meal in T2DM
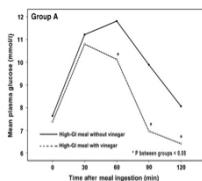
N = 16
**Meal consisted of mash potatoes/milk**
P = 0.05

Only effective if hi-GI meal

Liatis, S., Grammatikou, S., Poulia, KA. et al. Vinegar reduces postprandial hyperglycaemia in patients with type II diabetes when added to a high, but not to a low, glycaemic index meal. Eur J Clin Nutr 64, 727–732 (2010)

Meta-analysis of Acetic Acid

Figure 2: How the effects of acetic acid compare to select drugs
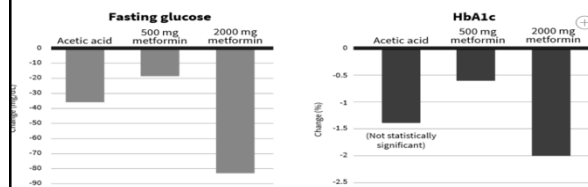
Effect of Dietary Acetic Acid Supplementation on Plasma Glucose, Lipid Profiles, and Body Mass Index in Human Adults: A Systematic Review and Meta-analysis. J Acad Nutr Diet. 2021 May;121(5):895-914.

Another Beneficial "Fruit Juice"?

- Multiple studies show that caffeinated and decaffeinated coffee consumption reduces the risk of developing type 2 diabetes after all controls

- Not caused by lowering blood glucose

- Chlorogenic acid (CGA) reduces fatty liver disease, preserves functioning beta cells and activates NrF2 – the master switch of antioxidant defense

Kolb H, Martin S, Kempf K. Coffee and Lower Risk of Type 2 Diabetes: Arguments for a Causal Relationship. Nutrients. 2021;13(4):1144. Published 2021 Mar 31. doi:10.3390/nu13041144

What About Coffee & Diabetic Retinopathy?

- 2022 cross-sectional study of 1350 T2DM patients (KNHANES)
- 4 comparators: no coffee , < 1 cup/d, 1 cup/day, $\geq$ 2 cups/day
- **2+ cups/d was 47% less likely to have any DR and 70% less likely to have vision-threatening DR** (severe NPDR, PDR, CI-DME) compared to no consumption after all controls (P for trend 0.025-0.005)

- CGA reduced VEGF in a rat model of DR

Sci Rep 12, 3547 (2022)
J. Korean Med. Sci. 28, 608–613.

DR Severity Linked to CVD Outcomes

- Retrospective analysis of 62K+ DM patients at Kaiser Permanente
- After all adjustments, including elimination of prior MI, CVA, CHF

Degree of Diabetic Retinopathy	Cerebrovascular Accident	Myocardial Infarction	Death
	Adjusted Hazard Ratios		
Mild	1.40	1.30	1.20
Moderate	1.76	2.13	1.62
Severe	2.34	2.08	1.72

Modjtahedi, et al. American Society of Retina Specialists (ASRS) 2020 Annual Meeting. Presented July 25, 2020

Hyperuricemia & VTDR

- Cross-sectional study of 3481 T2DM pts in China
- VTDR defined as severe NPDR, PDR and/or CSME
- **Hyperurcemia was positively associated with VTDR (OR = 1.49, p = 0.019) after all adjustments**
- Each 100 μmol/L increase in serum uric acid increased risk of VTDR by 22%
- Hyperuricemia was defined as SUA levels of ≥420 μmol/L for males and ≥360 μmol/L for females
- Reductions in uric acid are achievable with allopurinol/dietary reduction of HFCS → rationale for a prospective trial

Investigative Ophthalmology & Visual Science April 2021, Vol.62, 23.

DR or Prediabetic Retinopathy?

- Observational study of 112K Danish patients without DM
  - Random plasma glucose range 84-167 mg/dl
- 13.9% with evidence of retinopathy

- **"Diabetic retinopathy is prevalent in many non-diabetic patients with 'normo-glycemic' non-fasting values"**

Diabetes Care 2020 Apr; 43(4): 894-902

What Has Been the Standard Treatment of NPDR?

- Counsel on improving metabolic control if sub-optimal
- Counsel on importance of follow-up examination to detect progression to PDR/DME
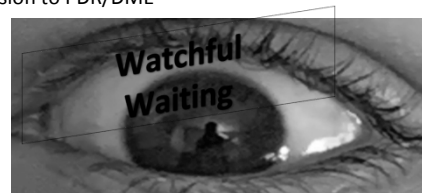
Watchful Waiting

Management of NPDR

- Can we do better than 'watchful waiting' for some patients?

DR IMPROVES WITH ANTI-VEGF TREATMENT

In DME or PDR ~30% to 50% Improve by ≥ 2 DRSS Steps with anti-VEGF
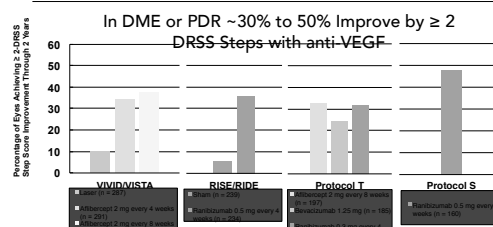
Dhoot D, et al. Ophthalmology. 2018;125(1):51-56. Brown DM, et al. Ophthalmology. 2015;122(10):2044-2052. Ip MS, et al. Arch Ophthalmol. 2012;130(9):1145-1152.
Bressler SB, et al. JAMA Ophthalmol. 2017;135(6):558-568. Gross JG, et al. JAMA. 2015;314(20):2137-2146.

Case Study: 3-Step DR Improvement from RIDE/RISE in a Ranibizumab-Treated Patient With PDR at Baseline

Screening
High risk PDR (71A)

Month 36
Mild NPDR (35E)

Image courtesy of Michael Ip, M.D.

PANORAMA – only patients with moderately severe or severe NPDR without DME

PANORAMA – 24, 52 & 100 Week Primary Outcomes

% Patients with ≥2-Step Improvement From Baseline in DRSS

≈ 30% of eyes in the Q8 week arm were UNDERGRADED
For DR severity by retina specialists & thereby under-treated per study protocol requiring add-on injection if DRSS > 43

† nominal p < 0.0001 vs. sham for all comparisons

Aflibercept reduces Vision-Threatening Complications

Aflibercept Treatment for 100 weeks Reduces Risk of Progression to PDR, ASNV and/or CI-DME

% Patients Developing^

% reduction in likelihood of developing the event over time

* nominal p < 0.0001 vs. sham for all comparisons
^Derived from hazard ratios from Kaplan-Meier estimates.

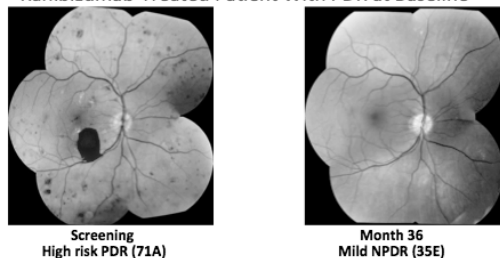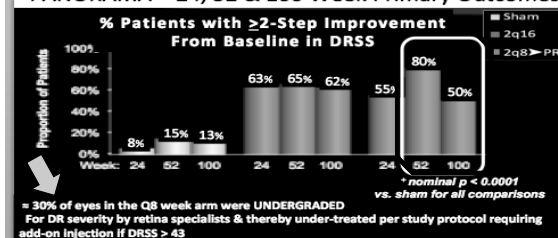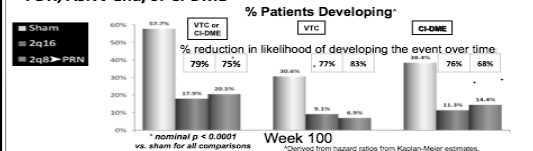- >92% of eyes that achieved ≥ 2-step DRSS improvement at year 1 maintained DRSS improvements from baseline with decreased dosing through Week 100
- Less frequent dosing in year 2 appeared to be associated with a higher rate of PDR+CI-DME development (although numbers are small)
  - Physician assessment of DRSS scores was suboptimal; independent reading center review of investigator PRN decisions suggests under treatment during the 2ⁿᵈ year

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My Key Takeaways from PANORAMA

- Even retina specialists under-grade DR severity on clinical exam
  - without FA, referral of moderate NPDR (DRSS Level 43) or worse makes pragmatic sense
- Anti-VEGF therapy can 'turn back the clock' on NPDR severity and significantly reduce the risk of bad outcomes, but serial Tx is required AND defined-interval treatment may be better than PRN treatment

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Who Would Benefit From Earlier Referral to a Retinal Specialist?

- Recent evidence shows that **anti-VEGF therapy** (aflibercept, ranibizumab, and, to a lesser extent, bevacizumab) can *significantly improve NPDR severity by > 2 DRSS steps,* especially when ETDRS level 47 (moderately severe NPDR) or worse

- The risk of developing vision-threatening complications (VTC) like PDR, iris neovascularization and center-involved DME is also reduced about 80% in these patients with treatment

1. Scott IU, et al. *Retina.* 2008;28:36-40. 2. Srinivasan S, et al. *PLoS One.* 2016;11:e0163108. 3. Ip MS, et al. *Ophthalmology.* 2015;122:367-374. 4. Mitchell P, et al. *Ophthalmol Retina.* 2018;2:988-996. 5, Wykoff CC. PANORAMA data presented at Angiogenesis, Exudation and Degeneration Annual Meeting; February 8, 2020; Miami, FL.

Diabetic Retinopathy Severity Score (DRSS)
Example of 2-Step Improvement

Severe NPDR DRSS Level 53 (Level 6)	Moderate NPDR DRSS Level 43 (Level 4)
• Severe retinal hemorrhages in 4 quadrants, or • Venous beading in ≥2 quadrants, or • Moderately severe intraretinal microvascular abnormalities (IRMAs) in ≥1 quadrant	• Microaneurysms, plus • Mild IRMAs, or • Moderate retinal hemorrhages

NNT FOR LEVEL 47/53 NPDR

Only 3 patients with moderately severe or worse NPDR need to be treated to prevent 1 vision-threatening complication (PDR/ASNV or CI-DME)

IS THIS A FAVORABLE NNT?

- NNT to prevent one CV death with 5 years of statin therapy in a patient with known heart disease = 83
  - NNT to prevent one non-fatal MI is 39 (NNT = 104 if no Hx of CVD)

- NNT = 333 to prevent a first, non-fatal MI with aspirin therapy

- NNT = 17 to prevent one case of PDR and/or CSME with oral fenofibrate therapy in T2DM with mild NPDR

Data from thennt.com, accessed September 14, 2019
Lancet 2007;370(9600):1687-97

Protocol W

- DRCR.net Protocol W found significant regression of DR severity/ 63% reduced risk of VTC in moderate to severe NPDR, but no VA benefit at 2 years with aflibercept versus close monitoring for Tx of VTC as needed (4-year data pending) (consistent with PANORAMA trial)
- **In real-world settings, patients may be lost-to-follow-up (LTFU) and fare worse**
- **Post-hoc analysis of PANORAMA/RISE/RIDE data extrapolated to the US diabetes population shows a 57.7% relative decrease/2.6% absolute decrease in blindness (BCVA < 20/200) over ten years in severe NPDR with anti-VEGF Tx versus monitoring**

Maturi RK, Glassman AR, Josic K, et al. Effect of Intravitreous Anti–Vascular Endothelial Growth Factor vs Sham Treatment for Prevention of Vision-Threatening Complications of Diabetic Retinopathy: The Protocol W Randomized Clinical Trial. JAMA Ophthalmol. Published online March 30, 2021.
Lim JI. Prevention of Severe Nonproliferative Diabetic Retinopathy Progression With More at Stake Than Visual Acuity. JAMA Ophthalmol. Published online March 30, 2021.
Lim J. Long-term clinical impact of intravitreal anti-VEGF therapy for severe non-proliferative diabetic retinopathy (NPDR): Analyses through a discrete event simulation model, paper presentation from ARVO 2021 abstracts, accessed 6/1/2021 at

Lost-to-Follow-up (LTFU) in Diabetes

- 25% of anti-VEGF treated DME patients did not return for f/u within the first year
- 25-50% of PDR patients did not return for F/U within 1-2 years
  - AVT patients were more 10X likely to develop TRD
- **Highest risk if younger, lower SES, Black/Latino/Native American, worse VA post-Tx**
- Surveyed LTFU/FUNA cited **3 unmet needs** that would have helped with follow-up:
  - **Connection with others having the same Dx**
  - **More disease-specific education**
  - **Easier transportation to appointments**

Ophthalmol Retina. 2019 Mar;3(3):230-236.; Ophthalmology. 2018 Sep;125(9):1386-1392 Am J Ophthalmol. 2020 Jul;215:66-71
Ophthalmology. 2019 Mar;126(3):407-413 BMJ Open Diabetes Res Care. 2020;8(1):e001154

Projected Reduced Risk of Legal Blindness in Severe NPDR Patients Receiving anti-VEGF Therapy vs Monitoring based on data from PANORAMA/RISE/RIDE Trials

ANTI-VEGF THERAPY REDUCED THE RATES OF VISION LOSS (20/200 OR WORSE) IN SEVERE NPDR

57.2% ↓ risk of severe vision loss over 10 yrs with anti-VEGF for severe NPDR

RRR	57.7%
ARR	2.5%

Notes: First data point simulated at 2 years after study start. Projections of vision loss rates based on PDR events estimates by Nguyen QD et al. Presented at Retina Society Annual Meeting, 2020.
Lim J. Long-term clinical impact of intravitreal anti-VEGF therapy for severe non-proliferative diabetic retinopathy (NPDR): Analyses through a discrete event simulation model paper presentation from ARVO 2021 abstracts, accessed 6/1/2021 at https://www.arvo.org/globalassets/annual-meeting/arvo-2021/arvo-2021-abstracts.pdf

DRCR.NET PROTOCOL V

- Is there benefit to 'preventive' anti-VEGF or focal laser therapy in patients with center-involved DME and very good visual acuity?
- 20/25 or better at enrollment
- Main outcome is % with loss of
  ≥ 5 ETDRS letters at 2 years

Center involving DME

Non center involving DME

Accessed at https://clinicaltrials.gov/ct2/show/NCT01909791

RESULTS

- % of patients losing ≥ 5 ETDRS letters at 2 years

  - 16% aflibercept Q 4 weeks PRN
  - 17% grid/focal laser
  - 19% observation

  NO Stat Significant Difference

  - No significant difference in subjects losing ≥ 2 lines
  - Mean VA at baseline and 2 years was 20/20 in all 3 groups
  - 3/4 of laser group and 2/3 of observation group **did not** require AVT @ 2 years

DME: Who does poorly?

- 56 eyes w 20/25 or better (similar to protocol V)
  - Average starting of 20/22 followed for mean 5.1 yrs
- Severe NPDR (3.0x) or PDR (7.7x) were more likely to lose vision (≥ 10 ETDRS letters = 2 lines of acuity)
- Baseline OCT findings not associated with vision loss, but change in central subfield thickness was

- **Lends more credence to the idea of treating to cause regression of DR with anti-VEGF therapy**

Lent-Schochet et al. Natuaral History and Predictors of Vision Loss w DME and Good initial VA. Retina. 2021 Oct 01;41(10)2132-2139.

Practical Advice For Patients with NPDR and/or DME

- If CI-DME with any reduced VA → refer to retina
- If CI-DME with good vision, monitor closely with OCT or refer to retina if DR > moderate
- If non-CI-DME, monitor closely or refer to retina
- If moderate or less NPDR → monitor Q 3-6 mos
- If moderate or worse NPDR → consider retina referral and find out if the RS you work with favors preventative anti-VEGF

Which Patients with T2DM develop PDR?

- Followed over 71k pts for 5 yrs to check for incident PDR
  - 1.74% (1,249 of 71,817) developed PDR, 0.25% of TRD, and 0.14% NVG.
    - BTW: 1.74 may sound like small percentage, but that's 1 for every 57 people!
- **Any insulin use was greatest risk factor for PDR at 3.6x risk**
- A1c over 9.0 was 2.1x risk

Gange et al.PDR and Other Neovascular Sequelae at 5 Yrs Following Diagnosis T2DM. Diabetes Care 2021 Sep; dc210228.

Metabolic Memory

- Patients with tight glucose control within 1-8 years of Dx are significantly less likely to develop severe DR despite worsening glucose control over time

- Patients with poor glucose control within 1-8 years of Dx are significantly more likely to devlop severe DR despite improved glucose control over time

- **Tight glucose control is WORTHLESS for protection against PDR/CI-DME once NPDR becomes moderately severe or severe (post-hoc analysis of the PANORAMA trial)**

  Kowluru RA. Diabetic retinopathy, metabolic memory and epigenetic modifications. Vision Res. 2017 Oct; 139:30-38.   JAMA Ophthalmol. 2021 Sep 1;139(9):946-955.

Presnted at Retina Society 2020 virtual meeting
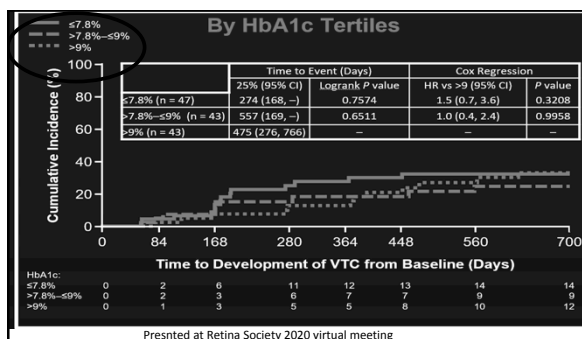
Metabolic Memory aka "Legacy Effect"
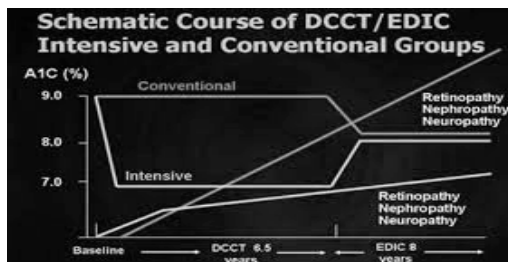
It's IMPERATIVE to Get Good Blood Glucose Control As SOON After Diabetes Diagnosis as is Possible[1]

REAL WORLD
DIABETES CONTROL

The Vast Majority of T2DM Patients Don't Achieve Metabolic Targets within 5 YEARS of DX!
DISCOVER Trial of 16K T2DM Subjects Worldwide: 38 Nations

- After 5 years Dx with T2DM:
  - Mean A1c = 8.3%   (Europe = 8.1%; US = 8.6%)
  - Mean Age at Dx = 51.6 years (EU = 61.9; US = 58.3)
  - **Only 17.6% with HbA1c $\leq$ 7% (18.7% EU; US = 17.1%)**
  - **Only 49.2% with HbA1c $\leq$ 8% (53.9% EU; 47.1% US)**
  - Microvasccular Dz = 18.9%   CAD/Stroke = 12.9%
  - Metformin alone = 55.6%   met + SFU = 20.9%
  - Metformin + DPP4 inhibitor (Januvia) = 23.5%

Diabetes Res Clin Pract. 2019;151:20-32.

Diabetes Control Inertia

- MOST patients on mono- and dual therapy (e.g. metformin or metformin + 2nd-line agent) do NOT achieve glucose targets within 5 years
- **55.6% of PCPs displayed clinical inertia (not initiating intensified Tx based on sub-optimal HbA1c**
- This significantly increases risk of DR/DR progression given harmful 'metabolic memory' shown in EDIC/ UKPDS/ACCORD-Eye RCCT studies
- Can we do better?   Med Sci Monit. 2015; 21: 403–411.

Efficacy of Glucose Lowering Agents

- ◉ <u>SINGLE</u> Oral agents lower HbA1c by 1-2% at most
- ◉ Diet plus exercise lowers HbA1c by about 1%
- ◉ American Association of Clinical Endocrinology (AACE) guidelines strongly recommend an HbA1c $\leq$ 7% for most pts
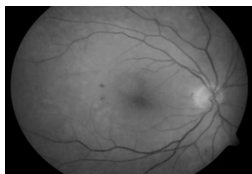- ◉ Selecting hypoglycemic agents to achieve the ADA/AACE targets for HbA1c $\leq$ 6.5/7%% is

3rd Grade Math

Case Example

- 54 yo with T2DM and HbA1c is 9.1% with mild NPDR and is "diet controlled"
- PCP started pt on glipizide – A1c Target ≤ 7%
- Had an MI at age 50

- What is likely outcome?
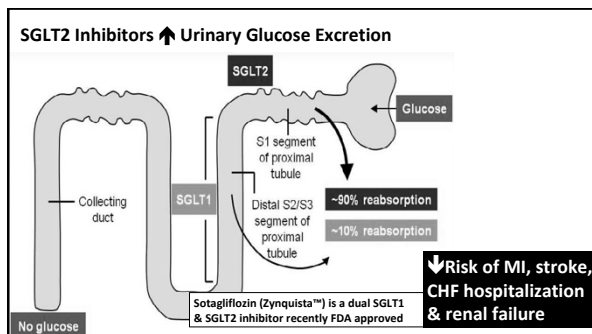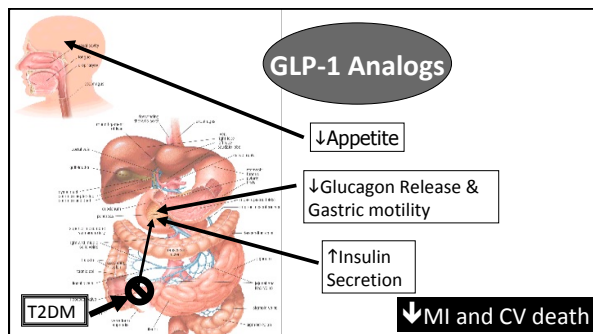
- What might the OD suggest?

Likely Outcome

- A1c likely to drop to 8%
  - Is 8% ≤ 7% ??

- Diabetic Retinopathy likely to progress

- Patient's risk of having an MI, stroke or dying from these is HIGH

Newer Diabetes Drugs that Significantly Decrease CV Risk

- **GLP-1 analogs (Victoza, Ozempic, Trulicity)**
  – LEADER, SUSTAIN-6, REWIND trials

- **SGLT2 inhibitors (Jardiance, Farxiga, Invokana)**
  – EMPA-REG , CANVAS, DEPICT trials

- Meta-analysis showed reduced CV risk with any GLP-1/SGLT2 compared to SFUs
  - **Patients on older SFUs (glipizide/glyburide) were 42 to 45X more likely to have an MI/CVA/CV death**
  – EASD 2015, Stockholm → Diabetes Obes Metab. 2017 Mar;19(3):329-335.

Recommendations for Our Patient

- Talk to your PCP about discontinuing the SFU and starting metformin and either an SGLT2 inhibitor or GLP-1 analog

- Tell the patient all the SGLT2 companies have patient coupon cards

- Send a letter with your specific eye recommendations to the PCP AND the patient's cardiologist

- Refer to endocrinology IF the patient returns without a treatment regimen

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GLP-1 Analogs

↓Appetite

↓Glucagon Release & Gastric motility

↑Insulin Secretion

T2DM

↓MI and CV death

SGLT2 Inhibitors ↑ Urinary Glucose Excretion

SGLT2

Glucose

S1 segment of proximal tubule

~90% reabsorption

~10% reabsorption

Collecting duct

SGLT1

Distal S2/S3 segment of proximal tubule

No glucose

Sotagliflozin (Zynquista™) is a dual SGLT1 & SGLT2 inhibitor recently FDA approved

↓Risk of MI, stroke, CHF hospitalization & renal failure

Battle Plan for ODs in Systemic Management of Diabetes

- Refer patients to another provider if A1c > 10%
- Refer if A1c > 9% on two visits
- Refer if patient is < 60 yo and on glyburide/glipizide as monotherapy for blood sugar control
- Recommend patients with known CVD/HF ask about GLP-1 agents or SGLT2 inhibitors
- Recommend healthy lifestyle habits
  - Exercise, more plant foods, adequate sleep, stress reduction

Impact of Exercise on Glucose

- **Aerobic exercise improves insulin sensitivity**
  - **30 minutes steady state lowers BS 50-100 mg/dl**
- **Most profound effect right after a meal**
- **Resistance training can elevate BS immediately and modestly, but increased muscle mass improves insulin sensitivity long-term**

Impact of Different Exercise Interventions on Glycemic Control and Insulin Resistance in Prediabetes

- Meta-Analysis of 13 studies with 567 patients
  - Aerobic exercise training (AET) vs resistance training (RT) vs aerobic + resistance
  - All 3 groups benefited vs control
  - AET + RT group showed greater control of BMI and insulin and FBG levels than those in the other groups
  - AET was the most effective in controlling HbA1c (--.75) and also insulin resistance.
- **BOTTOM LINE: Activity is important, do something!**

Comparisons exercise interventions on glycemic control and insulin resistance in prediabetes: a network meta-analysis *BMC Endocr Disord 2021 Sep 06;21(1)181, L Huang, Y Fang, L Tang*

Does Nutrition Affect DR?

- **OF COURSE : results of 2 meta-analyses**
- Studies suggest that adherence to the Mediterranean diet and high fruit, vegetable and fish intake may protect against the development of diabetic retinopathy
- Dietary fiber, oily fish, a Mediterranean diet and a reduced caloric intake are associated with lower risk of DR
- In PREDIMED trial, 500 mg/week of marine sourced omega-3 fatty acid intake reduced the risk of severe STDR by 48% after controls!

2 servings of Fish
. Eur J Epidemiol. 2018;33(2):141-156.
JAMA Ophthalmol 2016 Oct 1;134(10):1142-1149.
PLoS One. 2018; 13(1): e0186582

Impact of Foods on Blood Glucose

- General Rule: 15 grams of carbohydrate will elevate blood glucose 10-50 mg/dl depending on insulin sensitivity & production
- Each patient has his/her own CHO sensitivity factor ("Carbohydrate : △ Blood Glucose Ratio)
- "Net Carbs" = total carbs per serving minus fiber (need to read food labels or have an app)
- Dietary Protein & Fat moderates BS elevation
- Dietary protein & fat have limited effects on RAISING glucose

What About Fasting?

- **Umbrella review examining intermittent fasting (IF) effects on health outcomes (8 meta-analyses/130 RCTs)**
- **Moderate to high grade evidence for improvement in BMI, fasting glucose, fasting insulin, blood pressure, LDL-C & insulin sensitivity**
- **Most studies were small or had identifiable bias**

JAMA Netw Open. 2021 Dec 1;4(12):e2139558.

Why Fast in Pre-diabetes or T2DM?

- T2DM is a PROGRESSIVE Disease
- Most pre-DM patients ultimately develop T2DM
- Medical-Nutrition Therapy (MNT) including drugs/dieting/exercise RARELY results in disease remission
- Remission DOES occur after bariatric surgery or with fasting + reduced carbohydrate diet

Diabetes Care. 2016 Jun;39(6):893-901
Indian J Endocrinol Metab. 2012 Jul;16(4):552-7.

Patient GM – At Risk

- 58 yo male with recently Dx pre-diabetes
- A1c = 6.3%   Fasting glucose = 118 mg/l
- 'My PCP recommended more exercise and weight loss'
- Meds include atenolol, HCTZ, d/c lisinopril ('made me cough'), ranitidine, rosuvistatin
- BMI = 36 kg/m²   Waist Circumference = 42"
- Smokes 1 pack/day
- Eats 1 serving of fruits/vegetables/day → Low macular pigment
- Mom developed T2DM in her 70s

- ◆Has Prediabetes   ◆Abdominally obese   ◆Smoker
- ◆Male > 50 yo   ◆Thiazide Diuretic   ◆ Potent statin
- ◆Little Plant Food   ◆First Order Relative had T2DM

WHAT ARE GM'S RISK FACTORS FOR T2DM?

Prevention Beats Cure

My Plan For GM

- Send a note to his PCP
- Copy the patient on the note
- Give him my handout titled "Practical Tips to Avoid Diabetes "
- Give him a card for a local smoking cessation program
- Have GM write down my recommendations and pick 1 or 2 things he wants to fix before his next eye exam – circle those and enter in record
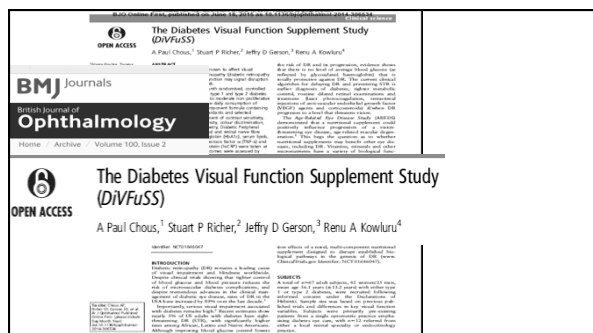
MEMORY BUY-IN ACCOUNTABILITY

Practical Tips To Avoid Diabetes

- Exercise 30 minutes perday (after waking) & minimize added sugars
- Eat a predominantly plant based diet including a variety of fruits and vegetables and more vegetables
- Minimize processed meats
- Drink coffee or tea   • Avoid hi-dose thiazide diuretics
- Sleep > 6 hours per night and < 9 hours
- Get your serum vitamin D > 40 ng/ml
- Don't smoke
- Live away from smog
- Breast Feed
- Turn down the thermostat
- Reduce Light at Night
- Fast if you're obese

Curr Nutr Rep. 2014 Dec 1; 3(4): 364–378.
PLoS One. 2015; 10(11): e0141724.
Sleep Med Rev. 2015 Oct 21;30:11-24
Am J Med. 2013 Jul;126(7):583-9
Am J Med. 2013 Jul;126(7):583-9
Am J Med. 2013 Jul;126(7):583-9
Am J Med. 2013 Jul;126(7):583-9
2014 US Surgeon General's Report
Am J Med. 2013 Jul;126(7):583-9
Environ Health Perspect. 2015 May; 123(5): 381–389

GM Outcome – 8 months later

- 55 lb weight loss using alternate daily fasting
- Walking 10K steps each day
- Last A1c = 5.0%
- Taken off HCTZ and now using low dose ARB (valsartan)
- Discontinued smoking
- MPOD increased from 0.28 to 0.60 on DiVFuSS supplement
- GM says "this was the best thing I've ever done"

Slide 1

The Diabetes Visual Function Supplement Study (*DiVFuSS*)

A Paul Chous,[1] Stuart P Richer,[2] Jeffry D Gerson,[3] Renu A Kowluru[4]

Slide 2

**Di**abetes **V**isual **Fu**nction **S**upplement **S**tudy (DiVFuSS)

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

Br J Ophthalmol. 2016 Feb;100(2):227-34

Slide 3

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
Contrast Sens (%)	+19.1+8.9		-6.2+5.1	<0.0001
Color Error Score	-20.55+24.37		+7.5+22.01	<0.0002
5-2 MD (db)	+2.78+9.83		-0.75+0.98	<0.0001
MPOD (du)	+0.09+0.05		-0.01+0.03	< 0.0001
LDL-C (mg/dl)	-7.61+16.08		+0.82+10.15	0.01
HDL-C (mg/dl)	+3.82+6.24		-1.61+5.31	0.0004
TGs (mg/dl)	-10.46+28.48		+2.39 +11.56	0.01
hsCRP (mg/L)	-2.14+3		-0.28+1.83	0.01
HbA1c (%)	-0.1+0.4		+0.1+0.4	0.06
Foveal Thickness	2.66+11.25μm		0.34+3.48 μm	0.35
DPNSS	-30.7%		+10.7%	0.0024 Fisher's Exact Test

Big effect on Visual Function & hsCRP

No effect on HbA1c
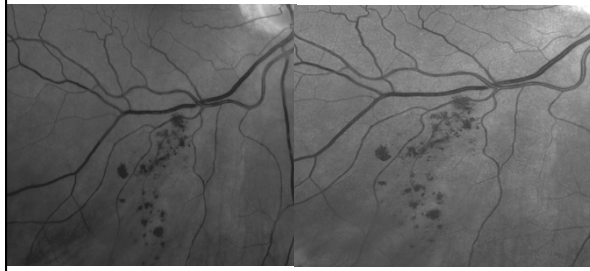
Slide 4

Slide 5
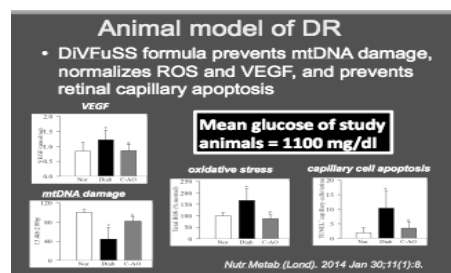
We Can Do More than Counsel, Watch & Wait to Treat
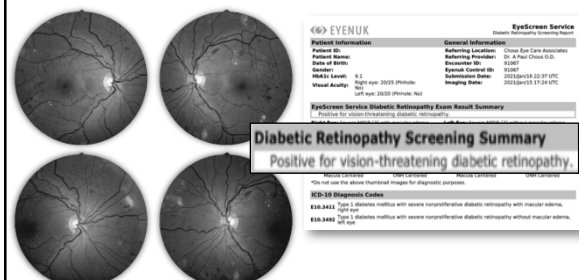
Slide 6

Detection of DR/DME

- Use red-free illumination or photography
- Use wife-field or ultrawide-field imaging
- Use OCT routinely in any patient with DR
- Dilate the pupils for medico-legal reasons and to improve views
- Consider use of FDA-approved AI systems
  - Two currently available – multiple others awaiting market entry

Red-Free Really Helps See Vascular Lesions


AI Report – T1DM x 19 years

Diabetic Retinopathy Screening Summary
Positive for vision-threatening diabetic retinopathy.

Some Staggering Numbers

- **Seventeen people on our planet develop diabetes every minute**
  - **3 people every minute in the US**

- **580,000,000 people have diabetes today** (projected 1 billion by 2050)
  - **> 40 million Americans have diabetes in 2021**

- **Diabetes costs the World economy $2.5 trillion annually**
  - **The US spent $327 billion on diabetes in 2017**

- **A child born in 2020 has a 40% chance of developing diabetes in her/his lifetime**

International Diabetes Federation, 2020; www.diabetesatlas.org

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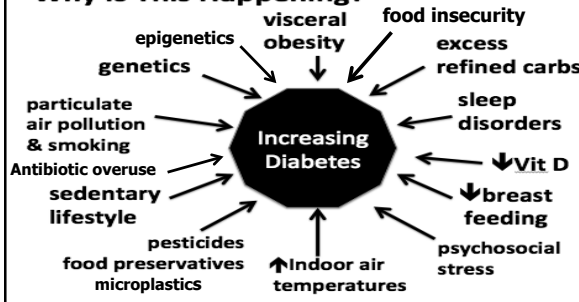
Food Insecurity

- Defined by USDA as "a lack of consistent access to enough food for an active healthy life"
- More common amongst those with diabetes (16% vs 9%)

- 22% of those with diabetic retinopathy

Diabetes Care 2021 Jun; 44(6): e131-e132

Food Insecurity

- Food insecurity is associated with consumption of highly processed, cheap foods, elevated cortisol, obesity and insulin resistance

- Food insecurity is causally linked to type 2 diabetes and poor glucose control

J Nutr. 2019 Jun 1;149(6):982-988.

Diabetes Care 2021 Jun; 44(6): e131-e132

Curr Cardiovasc Risk Rep 2021;15(9):15

Food Insecurity

- 32% of all Medicaid enrollees
  - 40% on SNAP are food insecure
- 44% of Medicaid enrollees on insulin therapy
  - Highest risk for blindness

- 15% increase in SNAP (Supplemental Nutrition Assistance Program) in 2020 stabilized food insecurity levels during the COVID-19 pandemic

Diabetes Care 2021 Jun; 44(6): e131-e132
Agency for Healthcare Research and Quality. January 2014. AHRQ Publication No. 14-EHC005-EF.

October 1, 2021

" the plateauing of food insecurity rates represents the incredible success that our programs had in creating new ways for families to afford food

" Given that people with diabetes experience food insecurity at rates almost double the national average, this expansion of benefits could be critical in making sure people have the ability to purchase healthy foods throughout the entire month.

Hilary Seligman, MD
Professor of Medicine
UC San Francisco

My Final Thoughts on Diabetes/DR

AVOID THEM

MITIGATE THEM

MANAGE THEM

Thank You!!!

- dr_chous@diabeticeyes.com