Diabetes in 2019 & 2020

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Disclosures

- I have spoken for or been on advisory boards for Bausch & Lomb, dLife, Genentech, Konan, Novo Nordisk, Optos, Regeneron, Risk Medical Solutions, ZeaVision, Zeiss

- None of these relationships will knowingly affect the content of this presentation

Blue Things

- Worldwide diabetes prevalence is now 483 million
- Half (50%) of people who have diabetes are undiagnosed
- Five million deaths attributable to diabetes in 2017 – half of these were in patients < 60 yo
- You or the person next to you almost certainly has or soon will have diabetes or prediabetes

Cost of Diabetes to the US Economy

- $92 Billion in lost productivity
- 1 in 4 health care dollars

Cost of Diabetes Every Year in the US

x 2.2 =
New Things

CGM Updates

• monitoring systems
• current blood glucose and trend

• CMS requires insulin use and intensive glucose management with 4 home blood glucose
  • Measurements/day

Continuous Glucose Monitoring For Patients on Insulin

• diabetes
• Distinct from an insulin pump, but may interface with a pump (Medtronic, Tandem pumps)
• Shows blood glucose trends (temporal stability)
• Improve glycosylated hemoglobin (HbA1c)
• Alarms for hypoglycemia and hyperglycemia
• Allow calculation of “glucose time-in-range” (TIR)

DexCom G6 CGM

• High accuracy – not affected by acetaminophen & easier insertion (1 button)
• No finger stick calibrations required
• Approved 10-day sensor life
• Approved for Medicare patients with any type of diabetes requiring multiple daily dose insulin (MDDI)

“Flash” Glucose Monitoring

• Hand held scanner swiped over arm sensor
• Samples Q1 minute; stores data for 8 hrs
• Factory calibrated
• $108-150/month (sensor replaced Q14 days)
• Approved for T1 and T2 diabetes on insulin
• Increased scan frequency 20/d vs 4-6/d lowered HbA1c from 8.2% to 6.9%

Eversense 90-day CGM
- minimize 1st-day error
- NOT affected by acetaminophen
- TCN does interfere
- FDA approved 6/18 - $7/day

CGM Facts
- 30-40% of patients with T1DM in the US
- Increasing popularity in T2DM on insulin Tx
- 1-3% worldwide for insulin using patients
- Mean reduction in HbA1c about 1% without increased dose and less hypoglycemia
  *Ann Intern Med.* 2018 Apr 3;168(7):526-527
  *JAMA.* 2017 Nov 24;317(22):2371-2378
- Increases short-term cost of care by $1500-2500/year

Why HbA1c Isn’t the Whole Story
- Doesn’t reflect glucose variability or the burden of acute hypoglycemia

Benefits of Glucose Time-In-Range
- 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%)
- and risk of microalbuminuria 40% (p < 0.001) → INDEPENDENT of HbA1c

Validation of time in range as an outcome measure for diabetes clinical trials – Hazard Ratio for DR Progression

Goal is TIR > 70%
Practical Implications of TIR

- Moderate NPDR T1DM x 10 years
- HbA1c = 7% TIR = 60% (14.4 hours)
- To achieve a 40% reduction in risk of progressing to STDR, he could:
  - Reduce HbA1c to 4.1%
  - Increase TIR to 73.6% (17.6 hours)

Source: www.RetinaRisk.com

Biggest Benefit When HbA1c Is Already Lower and TIR is also LOW

TIR – Afrezza versus Novolog in T1DM

- Afrezza is Ultra-rapid acting inhaled insulin
- Post-prandial glucose 20-25 mg’dl lower on Afrezza and TIR increased 90 minutes/day (+12% TIR)

Study Comparing Prandial Insulin Aspart vs. Technosphere Insulin in Patients With Type 1 Diabetes on Multiple Daily Injections: Investigator-Initiated A Real-life Pilot Study—STAT Study (STAT)
Presented at ADA Scientific Meeting, June 22, 2018, Orlando, FL

Super-fast-Acting Insulin

- Fiasp aspart (Novolog with niacinamide adjuvant forms insulin monomer to penetrate SC fat more rapidly)
  - 29 point 1-hour reduction in post-prandial glucose; 12 point reduction at 2 hours
  - 0.15% drop in HbA1c
  - UK study estimates 1% drop in diabetes-related blindness and 1715 pound savings per patient
  - TIR increased 2+ hours

Diabetes Care. 2017 Jul;40(7):943-950

The Perils of Transient Hyperglycemia

- A 6-hour episode of elevated glucose (>190 mgd/l) results in a 6-day massive increase in mitochondrial reactive oxygen species AFTER blood glucose is totally normalized
  - High ROS persist for 2 weeks before normalizing
  - ROS are the driving force underlying DR
  - These glycemic excursions are often too short to be captured by mean glycemia (HbA1c)

Production of reactive oxygen species (Superoxide) by mitochondria exposed to any glucose

Intracellular Glucose

\[
\text{ATP} + \overset{\uparrow}{\text{Superoxide (O}_2^{-})}\text{ }\Rightarrow \text{ mtDNA Damage Mitochondrion}
\]

Inflammatory Cytokines & Injurious Glucose Metabolites

DR
**Can We Detect It?**

- Retinal Flavoprotein Autofluorescence detects in vivo mitochondrial oxidative stress in diabetes

University of Michigan OcuSciences OcuMet Beacon

Not yet commercially available

Detection Before Cell Death Occurs

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**TIR with Hybrid Closed-loop Insulin Pump**

- Omnipod Horizon system increased **TIR by 2.7 hours** with no change in average glucose (n=11 for 36 hours; carb intake/meal = 30-90 grams)

*Diabetes Technol Ther. 2018 Apr 1; 20(4): 257–262*

- Medtronic 670G **increased TIR by 1.2 hours** and decreased HbA1c by 0.5%/hypoglycemia by 50% compared to a conventional insulin pump with CGM (n=124 for 3 months)

*Diabetes Technol Ther. 2017 Mar;19(3):155-163*

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**FACTS**

- blind from diabetes

- Most patients with diabetes do develop cardiovascular complications

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**Preventing MACE**

- Major adverse cardiovascular events
  - MI, stroke, HF/Angina hospitalization, CABG, CV death

- Diabetes increases risk 2-3 fold

- Some SFUs increase risk

- DR increases risk

- DKD increases risk

- Some newer agents/therapies decrease risk:
  - SGLT2 inhibitors, GLP-1 analogs, high-dose EPA, triple therapy

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**CVD-Real published data**

- 470,000 patients from 6 countries (Japan, Singapore, Canada, Israel, South Korea, Australia) – retrospective data analysis

- Use of any SGLT2 drug lowered risk of all-cause mortality by 49%, MI by 19%, stroke by 32%; HHF by 40% in subjects with AND without CVD

- ADA guidelines now recommend SGLT2 as 2nd-line therapy for T2DM after metformin, especially if pre-existing CVD

*Journal of the American College of Cardiology Mar 2018, 24748; DOI: 10.1016/j.jacc.2018.03.009*

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**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

*Journal of the American College of Cardiology Mar 2018, 24748; DOI: 10.1016/j.jacc.2018.03.009*
MOA for SGLTIs

↑Renal and urinary excretion of glucose

MOA of GLP-1 Analogs

↓Appetite

↓Glucagon Release

↑Insulin Secretion

SGLT2-I Benefits Heart Failure Patients With & WITHOUT Diabetes

- DAPA-HF trial – 4474 patients with HF
  - 45% with diabetes, 37% with PreDM, 18% normal
- Dapagliflozin (Farxiga™) reduced risk of hospitalization for HF and CV death by 25% in those with T2DM and 27% in those without
  - Presentation at European Society of Cardiology 2019, Paris

Should We be Using SGLT-2 Inhibitors/ GLP-1 RAs Sooner?

- Prior evidence shows a significant 20-50% reduction in MI, CHF and CV death with these agents in T2DM both with and without established CV disease (SGLT2s: Jardiance, Farxiga, Invokana; GLP-1 RAs: Byetta, Victoza, Trulicity, Ozempic)
- European Society of Cardiology (ESC) now recommends SGLT2-Is or GLP-1 RAs as FIRST-LINE therapy for all T2DM with high or very high CV risk
  - European Heart Journal, ehe486. Published: 31 August 201

SGLT2-I in T1DM

- DEPICT-2 trial assessed dapagliflozin (Farxiga) in 800 T1DM subjects for 24 weeks
  - Reduced insulin dose & weight
  - 2.2-2.5 hour/day increase of TIR
  - Diabetes Jul 2018, 67 (Supplement 1) 213-OR; DOI: 10.2337/db18-213-OR
  - FDA denied approval for T1DM in 2019
  - Approved in the EU for T1DM with BMI ≥27

Oral GLP-1 RA Approved in US

- Rybelsus™ (semaglutide)
- 51% reduced risk of heart-related death in high-risk patients over 16 mos (n = 3183)
  - injectable form (Ozempic™) reduced weight/HbA1c/MACE best in class – but increased risk of DR progression
  - DR progression occurred in those with largest HbA1c decreases (glycemic re-entry retinopathy)
HighDose EPA - REDUCE-IT Trial

- 4.9 year RCCT
- 8179 patients with median LDL-C 75 mg/dL (all on statins) and median TG of 216 mg/dL with either a history of CVD or diabetes
- Treatments: EPA ethyl esters (4g/d - Vascepa, Amarin Corp) or placebo
- Primary Outcome: Major Adverse Cardiovascular Events

REduce-IT
NEJM published on-line 11/10/2018

Efficacy
Reduction in a composite of primary endpoint of approximately 25% (p<0.001). Primary endpoint result supported by robust demonstrations of efficacy across multiple secondary endpoints

In T2DM subjects: 23% reduction in MACE
In non-White subjects: 40% reduction

TT for PreDM: STOP DIABETES Trial

- 422 prediabetes patients stratified by low, moderate and high-risk for conversion to T2DM (based on 1-hour oral glucose tolerance test AKA OGTT > 155 mg/dl)
- Triple therapy (low-dose metformin, Actos, Byetta) prevented ALL cases of T2DM in high-risk subjects over 32 months (0/81)
- 11% conversion in the high-risk control group receiving lifestyle education (21/200)
**OCTA Identifies Pre-Clinical DR**

- Parafoveal vessel density in the choriocapillaris, superficial and deep capillary plexi of diabetes subjects is significantly reduced compared to controls (n = 138)
- Density normals > DM sans DR > DM with DR
- OCTA showed ma and nonperfusion in 11%/25% of patients without OPHTHALMOSCOPIC DR

*Acta Diabetol. 2018 May;55(5):469-477*

**OCTA shows DR NOT seen on clinical exam**

**DCP: Control verus Mild NPDR**

Images courtesy of Julie Rodman, OD, FAAO

**Automatic For the People?**

**IDx-DR**

- Topcon NW400 retinal camera images are uploaded to a cloud server running the IDx-DR algorithm for comparison to an image database
- No sensitivity data for DME
- No evaluation of periphery
- No grading of DR
- 13% false negatives

**Is Everything “A-IK”?**

- IDx-DR is the first FDA-approved system for AI-detection of DR in PCP offices
- 87% sensitivity for detecting ‘more than mild’ DR
- 100% sensitivity for DR equal to or worse than ETDRS moderate severity (level 43)
- Binary Output: (1) More than mild DR detected – refer to an eye care specialist; (2) Negative for more than mild DR – rescreen in 12 months
Importance of the Retinal Periphery in DR

- Joslin showed that patients with predominantly peripheral DR lesions (PPL) were significantly more likely to progress (3.2X) and develop PDR (4.7X) \( p = 0.005 \)  
- Patients with PPL had significantly more ischemia on UWF angiography  
- Compared to standardized seven-field stereo photos (ETDRS standard), UWF suggested a more severe level of DR in 10% of cases  
  *Ophthalmology.* 2013 Dec;120(12):2587-2595.
- DCRR.net Protocol AA will evaluate the predictive value of UWF imaging on ocular/systemic endpoints (study completion in 2020).

Something Old: O-3 Against DR

- PrediMed Trial comparing Mediterranean-type diet supplemented with extra virgin olive oil or tree nuts versus AHA diet against CV events in patients with T2DM (n=3482)  
- Primary trial halted early because both Med diets were significantly superior, especially for stroke prevention  
- Subjects consuming > 500 mg daily long-chain-w3PUFA were 48% less likely to develop STR over 6 yrs compared to those consuming < 500 mg (\( p=0.001 \))  

Something New: Oral DHA in DME

- 1050 mg of DHA added to ranibizumab AVT for DME versus AVT alone (n = 62, 71 eyes)  
- Significantly better sdOCT CST (-143 vs - 95 microns, \( p=0.024 \)) but not ETDRS BCVA (12 vs 8.3 letters, \( p < 0.066 \))  
- No difference in # injections at 24 mos (mean = 7.9)  
- \( \geq 10 \) letters gain 66.7% vs. 40.0%, \( (P = 0.044) \),  
  \( \geq 5 \) letter gain 88.9% vs. 73.3%, \( (P = 0.137) \)  

Diabetes & DR Affect Visual Function

- Snellen visual acuity is a 150+ yr old test that does not always reflect real world visual function  
- DM/DR also impair: color perception, contrast sensitivity, visual field sensitivity & dark adaptation  
  *IOVS.* 1997; 38(9): 1819-24  
**Diabetic Retinopathy**

- 6 month placebo-controlled RCCT of adults with T1DM or T2DM ≥ 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) vitamin D, TNF-a, hsCRP, DPNSS score

**Mechanisms of Action**

- **Reduce Free Radicals and Inflammatory Proteins**
  - zeaxanthin, lutein, curcumin, green tea, grapeseed, resveratrol, lipoic acid, zinc, NAC, vitamin C & E, tocotrienols
- **Reduce VEGF**
  - zeaxanthin, curcumin, Pycnogenol
- **Seal leaky retinal capillaries**
  - Pycnogenol
- **Neuroprotection of RGCs**
  - zeaxanthin, lutein, EPA/DHA, lipoic acid, curcumin, resveratrol
- **Block Toxic Glucose Metabolites**
  - benfotiamine

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

<table>
<thead>
<tr>
<th>A from baseline</th>
<th>Suppl</th>
<th>v.</th>
<th>Plac</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast Sens (%)</td>
<td>+19.1±8.9</td>
<td>-6.2±5.1</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td>Color Error Score</td>
<td>-20.55±24.37</td>
<td>+7.5±22.01</td>
<td>&lt;0.0002</td>
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<tr>
<td>5-2 MD (db)</td>
<td>+2.78±9.83</td>
<td>-0.75±0.98</td>
<td>&lt;0.0001</td>
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<td>MPOD (du)</td>
<td>+0.09±0.05</td>
<td>-0.01±0.03</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>-7.61±16.08</td>
<td>+0.82±10.15</td>
<td>&lt;0.0001</td>
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<tr>
<td>HDL-C (mg/dl)</td>
<td>+3.82±6.24</td>
<td>-1.61±5.31</td>
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</tr>
<tr>
<td>TGs (mg/dl)</td>
<td>-10.46±28.48</td>
<td>+2.39±11.56</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>-2.14±3</td>
<td>-0.28±1.83</td>
<td>0.01</td>
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</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.1±0.4</td>
<td>+0.1±0.4</td>
<td>0.06</td>
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<tr>
<td>Foveal Thickness</td>
<td>2.66±11.25µm</td>
<td>0.34±3.48 µm</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>DPNSS</td>
<td>-30.7%</td>
<td>+10.7%</td>
<td>0.0024</td>
<td></td>
</tr>
</tbody>
</table>

**Animal model of DR**

- DIVuSS formula prevents mtDNA damage, normalizes ROS and VEGF, and prevents retinal capillary apoptosis

**Mean glucose of study animals = 1100 mg/dl**

- oxidative stress
capillary cell apoptosis

**Mean glucose of study animals = 1100 mg/dl**

**Nutr Metab (Lond).** 2014 Jan 30;11(1):8.
We CAN Do More than Counsel, Watch & Wait to Treat

DiVFuSS Formula Future Directions

- **KNOC-Out Diabetes Study**: 150+ racially diverse subjects with PreDM, T1DM, T2DM will receive DSME from ODs
- **DiVFuSS Formula +/- Omega-3 FAs trial**
  - Change in A1c, DRSS status, hsCRP, omega-3 index
  - Color vision, MPOD, fERG, OSI, self-efficacy, OCTA FAZ area
- **DR Functional Evaluation Study** (3 sites, 6 month study)
  - Affect on cVEGF, fERG, OCT-A, MPOD
  - Mild to moderate NPDR only
- **PROSPECTIVE DME**: 150+ DME subjects receiving anti-VEGF injections +/- DiVFuSS (2 site, 24 month trial)
  - Change in BCVA, sDOCT subfield thickness, # injections, change in DR severity

Evidence-Based Tips To Avoid Diabetes

- Exercise 30 minutes each day (soon 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
- 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

Evidence-based Tips for Minimizing Diabetic Retinopathy

- Don’t get diabetes/Don’t get prediabetes
- Get HbA1c as low as safely possible a quickly as possible after Dx; keep BP < 140/90
- Limit post-prandial hyperglycemia < 5 hours
- Consume at least 500mg LCw3PUFA/day
- Increase fiber & macular pigment
- Consider a science-based nutritional supplement for DR

Regression of DR with anti-VEGF Therapy

- **RISE/RIDE and VIVID/VISTA** showed significant reductions in DR severity in DME patients receiving ranibizumab or aflibercept for the treatment of macular edema
- **DRCR.net Protocol S** and **CLARITY trials** showed that ranibizumab or aflibercept are non-inferior to PRP for the treatment of PDR
• RISE/RIDE and VIVID/VISTA showed significant reductions in DR severity in DME patients receiving ranibizumab or aflibercept for the treatment of macular edema.

• DRCR.net Protocol S and CLARITY trials showed that ranibizumab or aflibercept are non-inferior to PRP for the treatment of PDR.

Benefits of AVT Against DR

- Ranibizumab (Lucentis) and Aflibercept (Eylea) are now BOTH approved for the treatment of ANY level of DR both with and without co-existing DME.
- PANORAMA trial enrolled only patients with moderately severe or severe NPDR and NO DME → aflibercept versus monitoring

Anti-VEGF Approvals in Diabetes

- 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
  - 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

Diabetic Retinopathy Severity Score (DRSS)

Example of 2-Step Improvement

- Only 3 patients with moderately severe or worse NPDR need to be treated to prevent 1 vision-threatening complication

Can Alternate Daily Fasting Reverse T2DM?

- Yes
- My patients

- 8 people with BMI ranging from 32-54 and T2DM
- ADF x 3-5 months
- Weight loss ranging from 25-55 lbs
- HbA1c reductions from 1.5 to 2.3%
- 7/8 were able to D/C insulin

Data from thennt.com, accessed September 14, 2019.
Lancet 2007;370(9600):1687-97
Patient Case Series - University of Toronto

Learning points

- Medically supervised, therapeutic fasting regimens can help reverse type 2 diabetes (T2D) and minimise the use of pharmacological and possibly surgical interventions in patients with T2D.
- Therapeutic fasting is an underutilised dietary intervention that can provide superior blood glucose reduction compared with standard pharmacological agents.
- Fasting is a practical dietary strategy.
- With proper education and support, we found compliance to be good.

Mean 9 inch waist reduction; 23 lb weight loss; 1.5% HbA1c reduction; All patients discontinued insulin

BMJ Case Reports 2018; doi:10.1136/bcr-2017-221854

My Final Thoughts on Diabetes/DR

AVOID THEM

MITIGATE THEM

MANAGE THEM

THANK YOU!

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