### ADA 2018 Summary

**Plus Snippets of Science**

San Diego Pump Club
July 9, 2018
John Walsh, PA, CDTc

This presentation covers devices recently approved by the FDA, along with several abstracts from the 2018 ADA Convention related to Type 1 diabetes.

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**Sensionics Eversense XL**

SQ-implanted CGM worn for 90 days with transmitter to phone attached to skin

Available now in Europe and soon in U.S.

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**Dexcom G6**

- Stick applicator, 10 day wear; 2 yrs and older
- No fingersticks (But calibrate if it’s off!)
- See BGs on display device, phone, or watch
- Sensible alarms
- Covered by Medicare
- First FDA approval as a fully interoperable CGM or iCGM
- Used for AP systems in Tandem, OmniPod, Sooil, OpenAPS
- Sponge by Medicare
- First FDA approval as a fully interoperable CGM or iCGM
- Used for AP systems in Tandem, OmniPod, Sooil, OpenAPS

Available

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**Tandem t:sling X2 Basal.IQ**

First half of an AP system.

Basal.IQ suspends basal delivery to prevent or reduce hypoglycemia.

Easy software updates from the web

Full TypeZero Control.IQ expected in early 2019.

Available in August

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**Medtronic 670 Data**

105 T1D children (10.8±1.8 yr) in 3 mo. study

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Overnight to Early-Morning Glycemic Outcomes in Children Using the MiniMed 670G Hybrid Closed-Loop (HCL) System. 236-OR ADA 2018 Orlando; US study. This and the next slide cover data regarding use of the Medtronic 670G closed loop in children.

A1c Improvement on 670G

67 T1D patients aged 5-23

HbA1c decreased from 7.98% ± 1.03% to 7.39% ± 1.03%

(P=0.0008) Light blue line shows est. A1c from BG readings

Time in range (70-180) rose from 50% at baseline to 61% at 12 weeks (P=0.0001)

Time in Auto Mode declined from 75.1% at start to 68.4% at 12 weeks

Estimated A1c is derived from current BG readings. This drops rapidly at first, later climbing near the actual A1c lab value above it. Time in range and time in auto mode are substantially lower in younger patients, partly due to the low time in auto mode.

Clinical Experience with the MiniMed 670G System in Children, Adolescents, and Young Adults with Type 1 Diabetes. 84-LB ADA 2018 Orlando; U.S. study.
Sooil Dana RS Insulin Pump

- Bolus delivery from phone, pump, or meter via Bluetooth
- Open protocol, later appeal to FDA for OpenAPS (used now in Orient and EU)
- Bolus calculator subtracts IOB from carb and correction for improved safety
- More Chinese and Korean pumps and CGMs soon

FDA Submission Shortly

Omnipod Horizon Closed Loop

11 people, 1 week home CGM compared to 4 day hotel CGM with unrestricted meals plus >30 min exercise per day on closed loop.

Glycemic outcomes during hybrid closed-loop (HCL) and open-loop (OL) phases

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<tr>
<th>Glycemic outcomes</th>
<th>HCL</th>
<th>OL</th>
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<tr>
<td>Overall</td>
<td>10.9 ± 3.1</td>
<td>10.9 ± 3.1</td>
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<tr>
<td>Night (23:00 – 06:00)</td>
<td>9.4 ± 2.9</td>
<td>9.4 ± 2.9</td>
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<tr>
<td>Mean glucose (mg/dL)</td>
<td>140.4 ± 39.4</td>
<td>135.5 ± 37.4</td>
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<tr>
<td>Percent time &lt;70 mg/dL (%)</td>
<td>5.7 ± 7.2</td>
<td>5.7 ± 7.2</td>
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<tr>
<td>Percent time &lt;180 mg/dL (%)</td>
<td>23.9 ± 10.5</td>
<td>23.9 ± 10.5</td>
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This study added exercise with an unclear impact. Other Omnipod studies show significant improvements without an added exercise component.

Cell Novo Closed Loop

Cell Novo pump and Dexcom G5 sensor in 68 people, age 47.2 ±13.4 years, HbA1c 7.6 ±0.9%, diabetes 27.9 ±13.2 years. Randomized 12 weeks on and off of closed loop.

Time in 70-180 mg/dl range: 58.7% [45.2;64.9] in open loop versus 69.5% [62.4;75.6] in closed loop.

Time in hypoglycemia <70 mg/dl: 4.1% [1.9;6.1] in open loop versus 2.1% [1.2;2.6] in closed loop.

OpenAPS Closed Loop

Twenty T1D patients aged 11.9 ± 6.9 years used openAPS, Dexcom G4® CGM, and Sooil Dana R® insulin pump for an average openAPS duration of 180 days.

- Time in 70-180 mg/dl range increased from 70.1% (± 16.4) to 83.3% (± 10.1), p<0.001.
- A1C fell from 6.8% to 6.3%, p<0.001
- Time above 180 mg/dl fell from 24.7 ± 16.5% to 13.3 ± 9.4%, p=0.001.
- Time below 70 mg/dl fell from 5.1 ± 3.3% to 3.4 ± 2.3%, p=0.004.

This OpenAPS study shows a significant improvement in time in range and in A1C values in patients who were already well controlled.

OpenAPS Features

- Open source developed by parents whose children have Type 1 diabetes.
- Fast adjustment when exercising or ill
- Carbs on board – fast, med, slow
- User selects own glucose target
- Always in AutoMode if CGM active
- Works on Medtronic 512-723 with firmware 2.4 or earlier, Sooil; Dexcom 4-6, Medtronic
- Cost: OpenAPS $200, Loop $135 plus $99 a year as Apple developer
- Options: Eating Soon, Autosensitivity (settings optimizer), OpenAPS Simulator (virtual testing of food/insulin options)

Glycemic Variability Associated with Time Spent in Hypoglycemia in Type 1 Diabetes—Explorative Data in Real-World, Real-Time Continuous Glucose Monitoring. 80-LB ADA 2018 Orlando; Denmark study

<table>
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<th>Coefficient of Variation (CV) and Hypoglycemia</th>
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<tr>
<td>CV = standard deviation/average BG</td>
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<td>CV ranged from 11% to 56% in 112 Type 1s</td>
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<td>Panel A: CV versus %time/day below 54 mg/dL (1% = ~15 min a day)</td>
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<td>Risk of hypog greater when CV &gt;33%</td>
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<tr>
<td>Panel B: mean BG versus %time per day below 54 mg/dL, Avg glucose has less impact on hypoglycemia</td>
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<td>Less BG swing = less hypog! Keep CV less than 33.</td>
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Insulin + Symlin in Closed Loop

Comparison of 1) rapid insulin-alone (AP), 2) rapid insulin & Symlin/pramlintide (DAP), and iii) regular insulin & amylin (R-DAP) in 12 adults with type 1 diabetes, all run in a closed loop system.

The addition of Symlin creates a dramatic increase in time in range (delivered in a second pump?) Adding pramlintide or other amylin derivative into a fast insulin appears long overdue. The pancreas does it, why not us?

Companion Medical InPen

- Easy to use
- Bluetooth to phone
- Excellent bolus calculator with IOB tracking
- View Dexcom data and history

New BioChaperone Lispro Insulin

Adocia BioChaperone (protein-bound) Lispro, in development, consistently shows faster onset and offset of exposure than Lispro (Humalog in graphic) in T1D and T2D.

- 8 min earlier to half max insulin
- 10 min earlier to max insulin
- 22 min earlier to late half max insulin
- 1.2 hr post meal rise may be ~30% lower versus lispro

When to Lower Basal for Exercise

13 Type 1s on Omnipods. Basal reduced by: a) 80%, 90 min pre-exercise; b) 50%, 90 min pre-exercise or; c) 100% at exercise onset. Full basal resumed at end of exercise with 75% of normal meal bolus afterward.

Victoza in Type 1 Diabetes

Year-long study of 26 people on 1.8 mg Victoza/day vs 20 on placebo. Mean HbA1c 7.38%, mean age 46.7 ± 9.9 years, age of T1D diagnosis: 22.3 ± 17.7 years, BMI: 28.9 ± 1.4 kg/m²

- HbA1c fell by 0.57% from 7.92 to 7.45% (p=0.009)
- Weekly average glucose fell by 15 mg/dl from 174 to 156 mg/dl (p=0.021). Total insulin dose did not change.
- Systolic BP fell from 128 ± 120 ± 3 mmHg; diastolic BP fell from 79 ± 72 to 75 ± 76 mmHg.
- Weight loss: 2.3 ± 0.9 kg, (p=0.041) from 83.6 ± 1.6 (186 lbs) to 80.5 ± 4.0 kg (p=0.01).
- No change in hypoglycemia or time spent below 70mg/dl on CGM.

Victoza in Adult-Onset Type 1

Victoza 1.8 mg a day was combined with insulin doses for 11 people with Type 17? diabetes over 12 weeks.

- Mean age of diabetes diagnosis: 37 ± 5 years; mean duration of diabetes: 6 ± 2 years.
- C-peptide concentrations increased significantly from 0.43 ± 0.09 to 1.42 ± 0.42 ng/ml (p=0.01).
- HbA1c fell from 7.6 ± 0.7% to 7.45 ± 0.52% (p=0.01).
- Total insulin dose fell by 64% from 36.45 ± 5.1 to 12.27 ± 4.0 units (p=0.01).
- 5 out of 11 patients no longer required insulin.

Odd study. BMI not given, but weights do not suggest obesity. Victoza (along with metformin and Actos) has been shown to reverse and stabilize pre-diabetes. Can Victoza benefit adult onset Type 1s?
**Are GLP-1 or GIP Agonists Better for BG?**

Antagonists were given to 12 healthy men for gut-derived glucose-dependent insulinotropic polypeptide (GIP) and for glucagon-like peptide 1 (GLP-1) to find which is stronger at lowering glucose. More infusion of glucose was needed when GIP was blocked.

**Cautions with SGLT-2 Inhibitors**

Preventing DKA is critical when taking an SGLT2 inhibitor. DKA begins at lower glucose levels when insufficient insulin levels are hidden by excess glucose passage into the urine. Dehydration may also cause a rapid rise in the glucose.

- Drink plenty of water each day.
- Test the urine periodically with Diastix or Ketodiastix strips for large glucose – a sign that insulin doses need to be increased.
- Check the blood with a blood ketone meter.
- More Type 2s are admitted to hospitals for DKA than Type 1s.
- Exercise caution on an SGLT-2 inhibitor, as well as the upcoming SGLT-1 and SGLT-2 combination drugs.

**AGEs Predict Kidney Disease in DCCT**

109 people with diabetic kidney disease (>40% eGFR decline from baseline on 2 consecutive visits) compared to 350 controls. GFR decline was predicted by 3 Advanced Glycated Endproducts:

- Carboxymethyllysine (CML, p=0.003)
- Carboxyethyllysine (CEL, p=0.021), and,
- 3-deoxyglucosone hydroimidazolone (3DG-H, p=0.0007).

3DG-H significantly increased predictive value for progression of kidney disease (and atherosclerosis) above traditional risk factors.

**Lysulin as AGE Blocker**

Company formed by CEO John Burd PhD, former CEO of Dexcom.

**New Therapy: SGLT-2 Inhibitors in Type 1**

A meta-analysis of SGLT-2i treatments in Type 1 diabetes: 14 studies with 4,591 subjects:

- A1c reduced by 0.4%
- FBG lowered by 20 mg/dL.
- Weight down 5.9 lbs (2.68 kg), systolic BP lowered 3.3 mmHg
- Approx. 2 more hours a day (8.3%) in time in range
- Total daily dose decreased 6.0 u/day, about 50% basal and bolus
- SGLT2s protect against heart failure with the metabolic syndrome
- SGLT2s increase DKA and genital infection by 3.4 fold. Avg. cost of DKA is $7,142 per episode plus some increased risk of death.

**Alternative AGE Inhibitors**

SuperLysine

- 1,500 mg lysine a day, vit C, propolis, echinacea, licorice root, and garlic bulb for 60 days: $10.72.

Carnosine or beta alanine or L-histadine

- Composed of amino acids beta alanine and L-histidine, now being analyzed in a study in Obesity.
- Extensive animal and some human research shows reduced oxidation, glycation, protein cross-linking, mitochondrial dysfunction, telomere shortening, and transition metal accumulation.
N-Acetyl Cysteine Lowers REDD1

- High glucose levels in diabetic mice raise stress response protein REDD1 in retina. REDD1 forms an oxidation complex that creates excess free radicals.
- This causes nerve cells to die in early retinopathy, first recognized as a loss of contrast sensitivity.
- In mice, the antioxidant N-acetyl-L-cysteine (NAC) prevents the rise in free radicals, nerve cell death, and loss of contrast sensitivity.
- NAC increases the major cell antioxidant glutathione.

Risks for CVD from Type 1 Exchange

4,463 T1Ds (55% female, 91% non Hispanic white, avg age 41 years, T1D duration 21 years); avg enrollment, avg HbA1c was 7.7%, 43%) used statins, and 49%) used BP meds. Incident CVD was reported by 419 (9.4%) participants during the 5-year follow-up.

Sex, mean HbA1c (0.97), HbA1c variability (0.95), pulse pressure (1.03), LDL (0.99), and hypertension (1.16) were not associated with CVD.

Risk factors for having 2 or more early diabetes complications were evaluated at baseline and at each follow-up visit. The co-occurrence of 2 or more complications was significantly more common in those with prior retinopathy, nephropathy, and/or microalbumin.

Over time, smoking, insulin resistance, kidney disease, high A1c carry the greatest risks for CVD. All are clearly or potentially modifiable.

More food/nutrient research is needed!!!

CVD Risks: DCCT/EDIC vs Pitt. EDC

DCCT/EDIC: 27 yo & 12 yr DM duration at start; #726; 27 yr FU; high BP & chl pts excluded:
- A1c major predictor
- T1D duration, SBP, LDLc, & smoking have similar impacts
- ACE inhibitors and lower heart rate are protective
- Renal status not a factor

Pittsburg Epi; of DM Study; 27 yo with 18 yr DM duration at start; #658; 25 yr FU; high BP & chol pts included:
- Bl smoking (HR 1.9), MA-creat (HR 1.3).
- Avg. A1c (HR 1.2)
- BL T1D duration (HR 1.1)
- Avg. Syst. BP (HR 1.03)
- Avg. LDLc (HR 1.01)

Risk factors for major Atherosclerotic Cardiovascular Events (MACE) in Type 1 Diabetes (T1D)—The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study; 27/11/18; AHA 2018 Orlando; U.S. Study.

New Therapy? BCG Tuberculosis Vaccine

Denise Faustman, MD, Massachusetts Gen. Hospital has followed 6 T1Ds, 3 of whom received two Connaught BCG vaccines a month apart 8 yrs earlier.
- A1cs lower: 6.18% vs 7.07%, at 5 yrs, and 6.65% vs 7.22%, at 8 yrs (p<0.0002), with no additional hypoglycemia. On insulin pumps, no CGms.
- Increases aerobic glycolysis for faster cell glucose utilization.
- Stimulates production of tumour necrosis factor (TNF) that in turn triggers cell death in abnormal, disease-causing T cells. Clinical trials are underway in multiple sclerosis and Type 1 diabetes.
- Results: Temporal genes for improved immune tolerance with short-term increase in insulin production.
- Benefit start 2-3 years after vaccination; cost <$20; various BCG strains – Connaught and Moreau strains may be more protective.
- Small but very interesting study with good outcome data in MS. Testing of various BCG strains and vaccination number/interval seems warranted.

Risk factors for having 2 or more early diabetes complications were evaluated among 1572 SEARCH T1D participants aged 10-30 years followed up for 18 yrs with annual visits. Risk factors for having 2 or more early diabetes complications were evaluated among 1572 SEARCH T1D participants aged 10-30 years followed up for 18 yrs with annual visits. Risk factors for having 2 or more early diabetes complications were evaluated among 1572 SEARCH T1D participants aged 10-30 years followed up for 18 yrs with annual visits.

Lack of insurance, higher A1c and cholesterol, abdominal obesity, and high BP all carry a significantly higher risk for developing complications. Lack of insurance, higher A1c and cholesterol, abdominal obesity, and high BP all carry a significantly higher risk for developing complications. Lack of insurance, higher A1c and cholesterol, abdominal obesity, and high BP all carry a significantly higher risk for developing complications.

More food/nutrient research is needed!!!

An Anti-AGE Regimen

- Alpha lipoic acid (strong antioxidant), 240 mg BID
- Alternate 2 flax with 2 borage oil capsules a day
- N-acetyl-cysteine (strong antioxidant), 600 mg BID
- Alternate 2 flax with 2 borage oil capsules a day
- More food/nutrient research is needed!!!
Future Technology
ConvaTec Lantern 7-Day Infusion Set

Study of 16 C-peptide negative T1Ds (44.2 ± 15.4 years, BMI 24.5 ± 2.3, A1c 7.2%, diab. duration 20 ± 9 years)

GIR curve over 8 hours (874.2 ± 1.4 vs. 744.5 ± 1.7 vs. 509.2 ± 2.0 on days 1, 4 and 7, respectively; p<0.05). That is, insulin action declines over 7 days.

The novel Lantern catheter can be worn for 7 days but further testing is needed to find why insulin action is lost.

Other companies also working on longer infusion set wear.

Assessment of Infusion Set Survival of the Newly Developed Lantern Catheter in Type 1 Diabetes by Glucose CLA Technique, 89-LB  ADA 2018 Orlando; U.S. study

Shows Lantern Technology but fails in an infusion set.

Glucose Impact of Dietary Fat

Six adults with T1D using insulin pump therapy attended the research clinic on 9 to 12 occasions. On the first 6 visits, participants consumed meals containing 45g CHO with either 0g, 20g, 40g, or 60g fat and either saturated (SFA), monounsaturated (MUFA) or polyunsaturated (PUFA) fat.

Postprandial Glucose Response to Varying Amounts of Dietary Fat Added To Carbohydrates in Six Adults with Type 1 Diabetes Using GIR with Dose-More

Fat requires 20-60% more bolus insulin, delivered as a combo bolus over 1.25-2 hrs.

Relationship between Amount and Type of Dietary Fat, Postprandial Glycemia, and Insulin Requirements in Type 1 Diabetes, 290-OR  ADA 2018 Orlando; Australia and US study

Seasonal Trends in Type 1

The average A1c was shown to vary by season in 453 Polish Type 1 over a 9 year period:

- July – 6.8%
- February – 7.3%

The Good: insulin doses will go farther with global warming.

The Bad: Type 1 diabetes will increase as enterovirus and dust levels rise.

The Ugly: it’s already well underway.

Take home: more insulin in winter, no change in summer? And what the hell is Poland doing to get these A1cs?

Seasonal Trends in HbA1c Level in Adult Patients with Type 1 Diabetes Treated with Personal Insulin Pumps, 1677-P  ADA 2018 Orlando; Poland study

Thank You