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March 25, 2017
AACE Diabetes Day for Primary Care Clinicians:
Advances in Diabetes
1. Indications for the use of an insulin pump
   a. Hypoglycemia (recurrent)
   b. Retinopathy and elevated A1c
   c. Failure to achieve target glucose with multiple daily injections
   d. DKA prone adolescent patients
   e. All of the above

2. Individuals who can benefit from continuous glucose monitoring, pt’s with:
   a. Hypoglycemic unawareness
   b. Hyperglycemia, who will wear the sensor and act on results
   c. Nocturnal hypoglycemia
   d. A1c less than 7% to maintain control and help prevent hypoglycemia
   e. All of the above
Advances in Diabetes Care Technologies

1979

Placing insulin-pump needle under skin

Puzzling Ailment
Hope for juvenile diabetics

2015

THRESH SUSPEND
Introduction

• Roughly 20% to 30% of patients with T1DM and fewer than 1% of insulin-treated patients with T2DM use an insulin pump
• In 2007, the U.S. FDA estimated that the number of patients with T1DM using CSII was ~375,000
• By 2050, up to one-third of U.S. residents may have T2DM; many of these individuals will be insulin-requiring
• Therefore, more clinicians must develop a comprehensive understanding of insulin pumps and other diabetes medical devices

T1DM = type 1 diabetes mellitus
T2DM = type 2 diabetes mellitus
FDA = U.S. Food and Drug Administration
CSII = continuous subcutaneous insulin infusion
Why We Do It
Better Control Reduces Complications

- 76% Risk Reduction
- 59% Risk Reduction
- 39% Risk Reduction
- 54% Risk Reduction
- 64% Risk Reduction

Retinopathy Progression
- Laser Rx\(^1\)
- Microalbuminuria\(^2\)
- Albuminuria\(^2\)
- Clinical Neuropathy\(^3\)

Cumulative Incidence (%)

Insulin Pumps Reduce Incidence of Diabetic Retinopathy vs MDI in Patients with Similar A1C Levels

- Study followed incidence of DR in 1604 adolescents with T1DM ages 12-20 over 20 years.
- Incidence of DR declined by 38% as more patients were transitioned to MDI and CSII vs twice-daily injections.
- A1Cs were identical in all cohorts, suggesting that reduction in GV influenced progression towards DR.

CSII = continuous subcutaneous insulin infusion; DR = diabetic retinopathy; GV = glycemic variability; MDI = multiple daily injection; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Downie et al. *Diabetes Care.* 2011;34:2368-73
Improved Control: Decreased Hypoglycemia

EPISODES PER 100 PATIENT-YEARS

N=55

Pre CSII 1 yr 2 yr 3 yr 4 yr
------------ With CSII------------
138 22 26 39 36

CSII = continuous subcutaneous insulin infusion
Type 1 Diabetes

• A 2010 Cochrane review compared the use of CSII vs. MDI insulin regimens
  – 23 randomized studies involving 976 patients with T1DM
  – A significant difference was documented in A1C response, favoring CSII
  – CSII users showed greater improvements in quality of life measures
  – Severe hypoglycemia appeared to be reduced in CSII users

CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injection; T1DM = type 1 diabetes mellitus

Basal Bolus Regimen with Glargine and Lispro
Continuous Subcutaneous Insulin Infusion

Insulin Effect

Bolus
Basal

B L S HS B
Pharmacokinetics of CSII vs MDI

• Uses only immediate acting insulin
  – More predictable absorption

• Uses one injection site
  – Reduces variations in absorption

• Eliminates most of the subcutaneous insulin depot

• Closest match with physiologic needs

Advantages of Pump Therapy

• Improved blood glucose control
  – Improved A1C levels
  – Decreased hypoglycemia and hyperglycemia
  – Delay in incidence and progression of complications
• Precise dosage delivery
• Improved control for pre-conception and pregnancy
• Management of dawn phenomenon
• Increased flexibility in lifestyle
• Improved control during exercise
• Improved gastroparesis management
## Insulin Pumps on the Market

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</thead>
<tbody>
<tr>
<td>Roche Health Solutions</td>
<td>Medtronic MiniMed</td>
<td>Medtronic MiniMed</td>
<td>Medtronic MiniMed</td>
<td>Animas</td>
<td>Dexcom</td>
<td>Valeritas, Inc.</td>
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</tbody>
</table>

- Accu-Chek Combo System
- MiniMed Paradigm Revel Insulin Pump
- MiniMed 530G with Enlite
- MiniMed 630G with Enlite
- Vibe Pump and Sensor
- T-slim G5 Pump and Sensor
- V-Go Disposable Insulin Delivery Device
- Roche Health Solutions
- Medtronic MiniMed
- Medtronic MiniMed
- Medtronic MiniMed
- Animas
- Dexcom
- Valeritas, Inc.
Indications and Contraindications for CSII

Indications:
• Failure to achieve targeted A1C with MDI
• Hypoglycemia unawareness
• Athletes and patients who incorporate exercise into daily routines
• Persistent fasting hyperglycemia ("Dawn phenomena")
• Pregnancy
• Frequent travel
• Shift workers
• Poorly adherent, DKA-prone adolescent patients
• Insulin-resistant patients
• Females in whom glycemic control is lost during menstruation

Contraindications:
• Uncontrolled psychiatric disorders (until corrected or stabilized)
• History of lack of adherence to prescribed treatment regimen (pumps do NOT cure diabetes)
  — However, some insulin is better than no insulin. Some non-adherent patients may do better on a pump than MDI
• Lack of financial ability to pay for pump and supplies

DKA = diabetic ketoacidosis; MDI = multiple daily injection

Unger J. Diabetes Management in Primary Care. 2nd Ed. Lippincott. 2012.
Continuous Sensors Currently Available in the U.S.
Continuous Sensors Currently Available in the U.S. (continued)

Coming Soon... (Spring 2017)
Continuous Glucose Sensors Available Outside the U.S.

• The FreeStyle Libre Flash Glucose Monitoring System is available in Europe

• FreeStyle Libre Pro™ System has been FDA approved and is available in the U.S.

FDA = U.S. Food and Drug Administration
What is Continuous Glucose Monitoring?

- CGM consists of a sensor inserted through the skin that measures interstitial glucose levels every 5 minutes
  - Average 8- to 10 minute lag behind BG values
  - MARD between CGM sensor glucose readings and venous plasma BG measurements averages at about 10%-12%, but can vary by up to 20%

- Useful for identifying BG trends

- As yet not a replacement for SMBG
  - Currently available personal systems still require 2-4 BG checks daily
  - Should not use the values to calculate insulin dosing

BG = blood glucose; CGM = continuous glucose monitoring; MARD = mean absolute relative difference; SMBG = self-monitoring of blood glucose
Types of CGM

• **Professional**
  – Masked, retrospective
  – Reviewed in clinic typically by physician; can also be reviewed by ARNP, PA

• **Personal**
  – Monitor shows real-time glucose levels with trends

ARNP = advanced registered nurse practitioner; PA = physician assistant.
Benefits of Continuous Glucose Monitoring?

• A1C lowering with less hypoglycemia
  – 0.5% to 0.8% for adults with type 1 diabetes

• Hypoglycemia warning for individuals with hypoglycemia unawareness

Drawbacks To CGM

- Can be overwhelming for some patients
- Alarms can be annoying, lead to discontinuation
- Cost—not covered by Medicaid or Medicare
- Comfort
- Accuracy
- Frustration—the analog insulin we call “fast” can be slow to kick in!

Who Can Benefit From Continuous Glucose Monitoring?

• Patients with type 1 diabetes
  – With A1C <7.0% to maintain control with lower risk of hypoglycemia
  – With A1C above goal, if used on a daily basis
  – Severe hypoglycemia unawareness

• Intermittent, retrospective CGM useful in certain situations
  – Concern for nocturnal hypoglycemia
  – Dawn phenomena
  – Post-prandial hyperglycemia

AACE/ACE Consensus Statement on Continuous Glucose Monitoring. 2016.;
Continuous Glucose Monitor Use in Clinical Practice – Real-world Experience

• Retrospective review of university-based clinical practice patient base
• Review of 30 months of clinical encounters
• Severe hypoglycemia defined as needing assistance to treat
• Continuous CGM use vs intermittent (defined as <2/3 of time)
• All patients on pump therapy

## Real-world Experience: Reductions in Hypoglycemia

### Results of CGM Use

<table>
<thead>
<tr>
<th></th>
<th>Baseline A1C</th>
<th>A1C on CGM</th>
<th>Rate of Severe Hypoglycemia at Baseline*</th>
<th>Rate of Severe Hypoglycemia on CGM*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous Users</strong></td>
<td>7.5%</td>
<td>7.2% (P&lt;0.05)</td>
<td>66.4</td>
<td>22.3 (OR 0.34; CI 0.19-0.59)</td>
</tr>
<tr>
<td><strong>Intermittent Users</strong></td>
<td>7.7%</td>
<td>7.3% (P&lt;0.05)</td>
<td>44.8</td>
<td>29.0 (OR 0.65; CI 0.24-1.78)</td>
</tr>
<tr>
<td><strong>All Users</strong></td>
<td>7.6%</td>
<td>7.2% (P&lt;0.05)</td>
<td>58.9</td>
<td>23.6 (OR 0.40; CI 0.24-0.65)</td>
</tr>
</tbody>
</table>

* Per 100 patient-years

CGM = continuous glucose monitoring; CI = confidence interval; OR = odds ratio
Continuous Glucose Monitoring Data

Overall 24-hour blood glucose patterns over multiple days are displayed:

• Look for overlap patterns at same time of day
• Look for hypoglycemia – frequency, time of day
• Check timing of insulin injections, meal choice effect
• Check for effect of increased physical activity

Interpret the Data To...

• Look for patterns
  – Highs and lows occurring at the same time each day

• Fix lows first

• Basal insulin
  – Start overnight, then progress through the day

• Bolus insulin
  – Look at glucose response to meals and to correction doses

• Now practice!
Sensor Linked To Pump

- Glucose trends visible on pump or PDA
- Pump suspend feature available (one system)
- Integration of insulin delivery and real-time glucose trends

PDA = personal digital assistant
Pump + CGM patterns

- Adds information regarding blood glucose trends between checks, after boluses, and overnight
Vintage Blood Glucose Meters

DextroStix (Ames), 1965

Reflomat (Boehringer-Mannheim), 1974
Traditional Glucose Meters on the Market
Mobile Phone-based Glucose Testing

• Some systems allow glucose-checking and data management generated directly from a phone

• Other systems pair glucose meter with a mobile phone for a data sync
Glucose Meters for the Blind

Glucose meters that have:

• Speech output
• Capillary traction
• No need for test strip coding
Glucose Monitoring Apps

Several apps for both Android and iOS are available to facilitate data tracking, trending, and communication with providers.

- BG Monitor
- BlueLoop
- OnTrack Diabetes

- Some studies suggest positive results using mobile phone-based interventions for diabetes control
- Apps specific for the needs of minorities with diabetes are needed
When Finger-stick Testing Is More Reliable Than A1C Measurement

- Several anemias due to low Hb values (e.g., sickle cell, hemolytic)
- CKD on erythropoietin-analogue therapies
- Pregnancy
- Splenectomy
- Some ethnic groups

CKD=chronic kidney disease

Accuracy of Glucose Meters

• FDA guidance (non-binding):
  • +/- 15% for OTC self-monitoring devices
  • +/- 10% for clinical use meters

Acceptable to measure only as low as 50mg/dL for self-monitoring devices

• 2013 ISO Standards:
  95% of blood glucose results
  • Below 100 mg/dL need to be within 15 mg/dL of reference
  • Above 100 mg/dL need to be within 15% of reference

At least 30% of glucose meters do not meet ISO 2013 standards!

ISO = International Organization for Standardization; FDA = Food and Drug Administration; OTC = over-the-counter

FDA draft guidance issued January 2014
Does Monitoring Lead To Better Outcomes?

- SMBG provides treatment guidance and feedback to patients with type 1 and 2 diabetes
- Several studies suggest a relationship between more frequent monitoring and improved glucose control
- Increased frequency of monitoring reduces hypoglycemia in patients with type 1 and 2 diabetes
- There are ongoing trials on the effect of SMBG on provider and patient outcomes in non-insulin patients with type 2 diabetes

SMBG = Self-Monitoring of Blood Glucose

Are There Needle-free Glucose Meters?

- **Glucowatch Biographer:**
  - Released in 2002
  - Needed 3 hour ‘warm-up period’
  - Skin irritation
  - Discontinued by manufacturer

In development:
- **Temporary sensor “tattoo”**
  - Tested in 7 patients at UCSD
- **“Smart” Contact Lens Project**