Diabetes in Pediatrics: Advances in Treatment and Technologies

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Pediatric Endocrinology
July 9, 2019
Objectives

• Evaluate children presenting with new onset diabetes mellitus
• Describe recent advances in insulin pump therapy
• Explore how continuous glucose monitors are used in diabetes management
Types of Diabetes Mellitus

- **Type 1A**: Immune-mediated
- **Type 1B**: Insulin-deficient, not autoimmune
- **Type 2**: Combined insulin resistance and insulin secretory deficiency

- **Secondary**: Cystic fibrosis; pancreatitis; endocrinopathies (e.g. Cushing syndrome, acromegaly); drug-induced (e.g. glucocorticoids)
- **Gestational**: First recognized/onset during pregnancy
- **Monogenic**: Maturity-onset diabetes of the young (MODY); insulin signaling defects; insulin gene mutations
Criteria for Diagnosis of Diabetes Mellitus (Non-Pregnant Individuals)

Plasma glucose $\geq 200$ mg/dl at any time plus classic symptoms such as increased urination (*polyuria*), increased thirst (*polydipsia*), and weight loss

or

Fasting plasma glucose $\geq 126$ mg/dl (fasting $\geq 8$ hours after last meal)

or

2-hour plasma glucose $\geq 200$ mg/dl during an oral glucose tolerance test (75 g)

or

Hemoglobin A1c $\geq 6.5\%$
Type 1 Diabetes in Youth
Diagnosis of Type 1 Diabetes

• Clinical features
  • Polydipsia, polyuria, polyphagia, weight loss
  • Absence of signs of insulin resistance (acanthosis nigricans)*
  • Age, ethnicity, family history

• Glucose/A1C criteria

• Presence of antibodies
  • GAD
  • Insulin
  • Islet cell
  • Zinc transporter 8
Epidemiology of Type 1 Diabetes

• Most commonly presents in childhood
  • 25% of cases are diagnosed after age 18 years

• About 1 in every 400 children and adolescents has diabetes
  • One of the most common chronic diseases in childhood
  • On the rise
Type 1 Diabetes Management

**Insulin Dosing**
- Traditional regimen
  - NPH/Fast-acting insulin
  - Set meal times and carbohydrate counts

- Multiple Daily Injections (MDI)
  - Basal/Bolus
  - Carbohydrate counting

- Insulin Pump Therapy
  - Basal/Bolus
  - Carbohydrate counting
Insulin Regimens

Conventional

MDI (multiple daily injections)
Insulin Administration
Insulin Regimens

CSII = insulin pump
(Continuous Subcutaneous Insulin Infusion)
Insulin Pumps (CSII)
Insulin Pump Infusion Sites
Infusion Set Insertion
Insulin Pump Therapy

• Basal/bolus regimen
  • Basal dosing is achieved with fast-acting insulin

**Upside:**

• Allows for more finite dosing
  • As little as 0.01 units!
• Basal rates allow for more physiologic dosing
  • Variability, especially overnight

**Downside:**

• Not “automatic”
  • Insulin pumps can be dangerous if the user is not vigilant
• Requires high frequency of blood glucose monitoring
Insulin Pump Initiation

**Who is eligible?**
- Diagnosis of type 1 diabetes
- Any length of diagnosis
- Any age*

**What is required?**
- Insurance coverage
- Education
- Patient interest/acceptance
Type 1 Diabetes Management

**Blood Glucose Monitoring**

Required:

- Prior to administration of fast-acting insulin
- Before and after exercise
- When feeling ill
- With signs/symptoms of hypoglycemia or hyperglycemia
Blood Glucose and A1C Goals

**American Diabetes Association Recommendation**

- A1C goal of < 7.5% is recommended across all pediatric age groups

<table>
<thead>
<tr>
<th>Before Meals</th>
<th>Bedtime/Overnight</th>
<th>A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-130 mg/dl</td>
<td>90-150 mg/dl</td>
<td>&lt; 7.5%</td>
</tr>
</tbody>
</table>

- A lower goal (< 7%) is recommended for adults (≥18 years) and for youth if it can be achieved without excessive hypoglycemia.
Why does glucose control matter?

Short-term diabetes complications:
• Severe hypoglycemia
• Diabetic ketoacidosis

Long-term diabetes complications:
• Retinopathy
• Nephropathy
• Neuropathy
• Cardiovascular disease
History of Glucose Monitoring

A physician looking at a container of urine, using his senses of sight, touch, hearing, smell and taste to make a diagnosis.

Clinitest was introduced by Ames in 1945, and utilised a copper reagent tablet that contained all the reagents required for a urine glucose test.
Glucometers Through the Years

Wikipedia
Modern Blood Glucose Monitors
Blood Glucose Meters

**Upside**
- Real-time capillary glucose measurement
- Fast results < 5 seconds

**Downside**
- Industry-accepted MARD (mean absolute relative difference) of 15%
- Pain
- Cost
  - Meters can be provided
  - Strips are often $1 each
- Adherence (it’s a challenge!)
Continuous Glucose Monitor (CGM)

Dexcom G6
SMALL WEARABLE SENSOR
Continuous Glucose Monitor (CGM)

https://www.youtube.com/watch?v=dBOgdsfeM-A
Continuous Glucose Monitor

Freestyle Libre
Continuous Glucose Monitor

Medtronic Guardian with 670G pump
Continuous Glucose Monitors

**Upside**
- MARD (Mean absolute relative difference) of 9%
- Virtually painless
- Continuous data
- Alarms for low and high blood sugar thresholds*
- Glucose trends/predictions
- Ability to share real-time data*

**Downside**
- Cost
  - 1 month of sensors: $349 for Dexcom, $120+ for Libre
  - Receiver (1 time cost): $365 for Dexcom, $70 for Libre
  - 2 transmitters (6 months of use): $475 for Dexcom
- Discomfort of wearing device
Impact of CGM use on glycemic control over time

- Minimal: CGM 0-5 days/week at 3 and 6 months
- Inconsistent: CGM 6-7 days/week at either 3 or 6 months
- Consistent: CGM 6-7 days/week at both 3 and 6 months
CJM Initiation

Who is eligible?
• Patients with type 1 or type 2 diabetes
• Age
  • Dexcom 2+ years
  • Freestyle Libre 18+ years
  • Metronic Guardian 14-75 years

What is required?
• Insurance coverage
• +/- education
• Patient interest

Nick Jonas, singer/heartthrob
Continuous glucose monitors in action
3.3 year old girl with T1DM for 2.5 years
3.3 year old girl with T1DM for 2.5 years
14.5 year old boy with T1DM for 7 years

<table>
<thead>
<tr>
<th>Glucose Management Indicator</th>
<th>Average glucose (CGM)</th>
<th>Standard deviation (CGM)</th>
<th>Hypoglycemia risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>%</strong></td>
<td><strong>mg/dL</strong></td>
<td><strong>mg/dL</strong></td>
<td><strong>%</strong></td>
</tr>
<tr>
<td>9.2</td>
<td>244</td>
<td>83</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

**Top Patterns**

- Best glucose day was May 27, 2019.
- Blood sugars were in the target range about 48% of the day.

This graph shows your data averaged over 14 days.
14.5 year old boy with T1DM for 7 years
How can we improve glycemic control?

Automation!
Closing the Loop: The Artificial Pancreas

- Glucagon
- Continuous Glucose Monitor
- Insulin Pump
Realizing the Artificial Pancreas

- Landmark paper in NEJM in June 2014: outpatient use of bionic pancreas
- Two random-order, crossover studies comparing glycemic control with a bihormonal bionic pancreas vs an insulin pump for 5 days in 20 adults and 32 teens with T1DM

- Devices:
  - iPhone 4S: ran control algorithm connected with a Dexcom G4 CGM custom hardware interface
  - Dexcom continuous glucose monitor
  - Two T:slim insulin pumps containing insulin and glucagon
    - Glucagon changed every 24 hours

Russell, et al. NEJM, 2014
The Beacon Hill/Summer Camp Studies

http://sites.bu.edu/bioncpancreas/clinical-trials/
Beacon Hill Study

- Patients allowed to go about life as usual during the day
  - Restaurants, gym; alcohol somewhat limited
- Monitored in hotel room overnight

- Patients asked to announce meal size as “typical”, “more than usual”, “less than typical”, or “a small bite”
- Asked to label as “breakfast”, “lunch”, or “dinner”

- System initialized with the patient’s weight only
  - No prior insulin doses or settings were entered
  - System “learned” the patient after 24 hours

Russell, et al. NEJM, 2014
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adults †</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>20</td>
<td>32</td>
</tr>
<tr>
<td>Sex  —  no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Age (range) — yr</td>
<td>40±16 (21–75)</td>
<td>16±3 (12–20)</td>
</tr>
<tr>
<td>Weight (range) — kg</td>
<td>74±10 (50–94)</td>
<td>69±18 (41–128)</td>
</tr>
<tr>
<td>Body-mass index (range)‡</td>
<td>25±3 (18–33)</td>
<td>24±5 (17–45)</td>
</tr>
<tr>
<td>Diabetes duration (range) — yr</td>
<td>24±11 (5–45)</td>
<td>9±5 (1–18)</td>
</tr>
<tr>
<td>Daily insulin dose (range) — U/kg</td>
<td>0.50±0.11 (0.33–0.76)</td>
<td>0.80±0.18 (0.43–1.25)</td>
</tr>
<tr>
<td>Glycated hemoglobin (range) — %</td>
<td>7.1±0.8 (6.0–8.6)</td>
<td>8.2±1.0 (5.6–11.6)</td>
</tr>
<tr>
<td>Estimated average glucose level (range) — mg/dl§</td>
<td>158±23 (125–200)</td>
<td>189±30 (114–286)</td>
</tr>
</tbody>
</table>
A Mean Glucose Levels in Adults

B Mean Glucose Levels in Adolescents

1% <70 mg/dl
5% <70 mg/dl
10% <70 mg/dl
Results

• In the two studies, the bionic pancreas reduced mean levels of blood glucose, as compared with insulin-pump therapy
  • Even though approximately 75% of the patients had better glycemic control at baseline than national averages!

• During the bionic-pancreas period, all the patients had a mean glucose level of less than 154 mg/dl on continuous monitoring
  • A level that corresponds to an A1C of ≤ 7%

• Most notable improvements overnight

Russell, et al. NEJM, 2014
Home Use of an Artificial Beta Cell in Type 1 Diabetes

- Insulin only
- Children overnight
- Adults day/night

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Study Participants at Baseline.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Sex — no. (%)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Age — yr</td>
</tr>
<tr>
<td>Weight — kg</td>
</tr>
<tr>
<td>BMI†</td>
</tr>
<tr>
<td>BMI z score</td>
</tr>
<tr>
<td>Duration of diabetes — yr</td>
</tr>
<tr>
<td>Duration of pump use — yr</td>
</tr>
<tr>
<td>Total daily insulin dose — U/kg/day</td>
</tr>
<tr>
<td>Glycated hemoglobin at screening</td>
</tr>
<tr>
<td>Percent</td>
</tr>
<tr>
<td>Millimoles per mole of non-glycated hemoglobin</td>
</tr>
</tbody>
</table>

Thabit, et al. NEJM, 2015
Overnight mean sensor glucose levels

**A** Adults

<table>
<thead>
<tr>
<th>Mean Sensor Glucose (mg/dl)</th>
<th>Control</th>
<th>Closed Loop</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**B** Children and Adolescents

<table>
<thead>
<tr>
<th>Mean Sensor Glucose (mg/dl)</th>
<th>Control</th>
<th>Closed Loop</th>
</tr>
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<tbody>
<tr>
<td>1%</td>
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<tr>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thabit, et al. NEJM, 2015
Hybrid Closed-Loop Systems

• In 2016, the Medtronic 670G became the world’s first hybrid closed-loop artificial pancreas device to be approved by the FDA

**Overview:**

• Insulin-only algorithm
• Integrated with Medtronic CGM
  • Requires 2 calibrations/day (often more)
• Background/basal insulin automatically adjusts for low and high glucose
• User must bolus for carbohydrates
Hybrid Closed-Loop Systems

- In June 2018, the Tandem T:slim X2 pump released the Basal IQ update

**Overview:**
- Insulin-only algorithm
- Integrated with a Dexcom CGM
  - Requires no calibrations
  - Background/basal insulin automatically adjusts for low glucose
    - Algorithm for high glucose to be released mid-2019
- User must bolus for carbohydrates
Bionic Pancreas Update

• In September 2018, the FDA granted an investigational device exemption to allow recruitment for home-based studies
  • Will test insulin-only configuration of bionic pancreas system

• Multi-arm, crossover clinical trial

• Adults with type 1 diabetes
  • Massachusetts General Hospital
  • Stanford University

• Children aged 6-17 years with type 1 diabetes
  • Nemours Children’s Health System
  • Barbara Davis Center for Diabetes at the University of Colorado
  • Stanford University
Artificial Pancreas System

• Beta Bionics plans to enter pivotal trials with its final iLet design in 2019 and expects to launch its first product in 2020.
Glucagon
Current Glucagon Kit
Nasal Glucagon

• Developed by Lilly
  • Submitted to the FDA in 2018; FDA delays decision in May 2019
• Eliminates need for reconstitution, subsequently decreasing error and time to treatment
Soluble Glucagon

Dasiglucagon

- Developed in Denmark
- A soluble glucagon formula that can be used in insulin pumps
  - Also being developed in a rescue pen
- Phase II clinical trial recently wrapped up

Xerisol

- Developed in Chicago, received “Orphan Drug Designation” from FDA for treatment of hypoglycemia in patients who have just undergone bariatric surgery
  - Rescue Pen (single-dose)
  - Glucagon Mini-Dosing (multiple, small doses)
  - Pumpable glucagon
Artificial Pancreas Limitations

• Pump
  • Device malfunction leading to severe hypoglycemia or ketosis

• CGM
  • Loss of connectivity
  • Lag time
  • Reduced measurement accuracy during first days of use; influenced by skin temperature, pressure, movement
  • Error margin increases during rapid glucose swings and extremes

• Insulin
  • Fast-acting insulin is still slower than endogenous delivery
  • Insulin sensitivity varies with skin temperature, physical activity
  • Location of cannula, local fibrous tissue formation
Hurdles to progress
Closing the loop: patients and families are moving faster than the device companies and FDA.
Cost of Insulin

For millions of people with diabetes, including all individuals living with type 1 diabetes, access to insulin is a literal matter of life and death. There is no day off and no medication that can be substituted for insulin. No individual in need of this life-saving medication should ever go without it due to prohibitive cost.

The American Diabetes Association calls on Congress to help increase transparency among all entities in the insulin supply chain to identify the reasons for the dramatic increases in insulin prices and to take action to ensure that all people who use insulin have affordable access to the insulin they need.
Other challenges to progress

• Patient use/outlook

• FDA
  • The FDA has been working together with diabetes patient groups, diabetes care providers, medical device manufacturers, and researchers to advance the development of an artificial pancreas

• Financial coverage
  • Study funding
  • Devices – public versus private health insurance coverage
  • Glucagon
  • Insulin
What can you do?

Support your patients and families with type 1 diabetes!

• Applaud their hard work
• Encourage use of psychology services
• Educate them about the existence and benefits of diabetes technology
• Connect them with social/case workers for help with coverage
• Remind them of how far we’ve come and assure them their future with T1D is bright
Type 2 Diabetes in Youth
Percentage of young adults with diabetes developing complications from the disease

- **Type 2 Diabetes**
- **Type 1 Diabetes**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Type 2 Diabetes</th>
<th>Type 1 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney Disease</td>
<td>19.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Eye Disease</td>
<td>9.1</td>
<td>5.6</td>
</tr>
<tr>
<td>Nerve Disease</td>
<td>17.7</td>
<td>8.5</td>
</tr>
<tr>
<td>Cardiovascular Neuropathy</td>
<td>15.7</td>
<td>14.4</td>
</tr>
<tr>
<td>Arterial Stiffness</td>
<td>47.4</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.6</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Risk factors for heart disease

Source: "Association of type 1 diabetes vs. type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood," *Journal of the American Medical Association*, Feb. 28, 2017

Credit: NIH/NIDDK
• Combination of obesity, genetics, hormonal milieu, incretins and/or their effect, and metabolic alterations
  → Contribute to deteriorating β-cell function

• Background of insulin resistance
  → Culminating in prediabetes and type 2 diabetes
Who to screen: risk based screening for Type 2 DM or prediabetes

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Overweight (BMI &gt; 85th percentile for age and sex, weight for height &gt; 85th percentile, or weight &gt; 120% of ideal for height). A</td>
</tr>
<tr>
<td>- Maternal history of diabetes or GDM during the child’s gestation. A</td>
</tr>
<tr>
<td>- Family history of type 2 diabetes in first- or second-degree relative. A</td>
</tr>
<tr>
<td>- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander). A</td>
</tr>
<tr>
<td>- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight). B</td>
</tr>
</tbody>
</table>

*Persons aged < 18 years.

If tests are normal, repeat testing at a minimum of 3-year intervals or more frequently if BMI is increasing

Arslanian et al, Diabetes Care 2018
Treatment of Type 2 diabetes

• Only a minority of youth with type 2 diabetes are on lifestyle management alone
  • Often inadequate for achieving and maintaining optimal glycemic control and BMI improvement
  • In most cases, the addition of pharmacologic intervention early in the disease is warranted

→ Initiate pharmacologic therapy, in addition to lifestyle therapy, at diagnosis of type 2 diabetes
New-Onset Diabetes in Overweight Youth
Initiate lifestyle management and diabetes education

- **A1C <8.5%**
  - No acidosis or ketosis
  - Metformin PO b.i.d.
  - Titrate up to 2,000 mg per day as tolerated

- **A1C ≥8.5%**
  - No acidosis with or without ketosis
  - Basal Insulin: start at 0.5 units/kg/day and escalate every 2–3 days based on meter glucose
  - Metformin
  - Titrate up to 2,000 mg per day as tolerated

- **Acidosis and/or DKA and/or HHNK**
  - Manage DKA or HHNK
  - I.V. insulin until acidosis resolves, then subcutaneous, as for type 1 diabetes until antibodies are known

---

**Pancreatic autoantibodies**

- **NEGATIVE**
  - Continue metformin
  - Wean insulin guided by meter glucose values

  - **A1C goals not met**
    - Initiate add-on insulin or continue insulin therapy—basal insulin to maximum 1.5 unit/kg/day

  - **A1C goals not met**

- **POSITIVE**
  - Continue or initiate MDI insulin or pump therapy, as for type 1 diabetes

  - **Consider other drug therapy**
    - Liraglutide
Liraglutide in Children and Adolescents with Type 2 Diabetes


FDA NEWS RELEASE

FDA approves new treatment for pediatric patients with type 2 diabetes

For Immediate Release:  June 17, 2019
Metabolic surgery for Type 2 DM in youth

- Considered for the treatment of adolescents with type 2 diabetes who are markedly obese (BMI > 35 kg/m$^2$) and who have serious comorbidities despite lifestyle and pharmacologic intervention.

- Performed only by an experienced surgeon working as part of a well-organized and engaged multidisciplinary team:
  - Surgeon, endocrinologist, nutritionist, behavioral health specialist, and nurse.
Surgery versus Medical Therapy in Type 2 DM

• 93 severely obese adolescents with type 2 diabetes
  • 30 surgical treatment
  • 63 medical management

• HbA$_{1c}$ and mean BMI decreased in 30 patients who underwent surgical treatment and increased in 63 patients who received medical treatment at 2-year follow-up

• Significant improvements in blood pressure, dyslipidemia, and kidney function were observed in the patients treated surgically but not in those treated medically

Inge, TH, et al. *JAMA Pediatrics* 2018
Follow-up of teens with Type 2 DM

Mean Percent Change in Body Mass Index (BMI) Over Time

BMI was calculated as weight in kilograms divided by height in meters squared. Error bars indicate 95% CIs. Teen-LABS indicates Teen-Longitudinal Assessment of Bariatric Surgery; TODAY, Treatment Options of Type 2 Diabetes in Adolescents and Youth.

Inge, TH, et al. JAMA Pediatrics 2018
Inge, TH, et al. JAMA Pediatrics 2018

Bariatric surgery

Medical management

HbA1c range
- Normal (<5.7%)
- Prediabetes (5.7-6.5%)
- Diabetes (≥6.5%)

Participants, %

Baseline 6 mo 1 y 2 y

Teen-LABS

Study Point

Baseline 6 mo 1 y 2 y

TODAY
Type 2 Diabetes

• **Always rule out type 1 diabetes**
  • Diabetes autoimmune panel

• Clinical presentation can vary widely
  • Asymptomatic to DKA

• Start medical management: high risk of complications

• New treatment approved in children > 10 years: liraglutide (GLP-1 agonist)

• Bariatric surgery
Which of the following is indicative of a diagnosis of diabetes mellitus?
A. Random blood sugar ≥ 140 mg/dL
B. Fasting blood sugar ≥ 110 mg/dL
C. Hemoglobin A1c ≥ 6.5%
D. 2-hour plasma glucose ≥ 145 mg/dL after oral glucose tolerance test
Which of the following is indicative of a diagnosis of diabetes mellitus?

A. Random blood sugar $\geq 140$ mg/dL
B. Fasting blood sugar $\geq 110$ mg/dL
C. Hemoglobin A1c $\geq 6.5\%$
D. 2-hour plasma glucose $\geq 145$ mg/dL after oral glucose tolerance test
Which of the following is indicative of a diagnosis of diabetes mellitus?

A. Random blood sugar ≥ 140 mg/dL 200 mg/dL
B. Fasting blood sugar ≥ 110 mg/dL 126 mg/dL
C. Hemoglobin A1c ≥ 6.5%
D. 2-hour plasma glucose ≥ 145 mg/dL after oral glucose tolerance test 200 mg/dL
One benefit of continuous glucose monitor use is:

A. Continuous insulin infusion
B. Low and high glucose threshold alarms
C. Glucagon treatment for hypoglycemia
D. Reduced insulin requirements
One benefits of continuous glucose monitor use is:
A. Continuous insulin infusion
B. Low and high glucose threshold alarms
C. Glucagon treatment for hypoglycemia
D. Reduced insulin requirements
Closed-loop insulin pumps

A. Integrate continuous glucose monitor and insulin pump technologies
B. Are implanted under the skin for 3-6 months at a time
C. Reduce hyperglycemia and increase hypoglycemia frequency
D. Are only used at night
Closed-loop insulin pumps

A. Integrate continuous glucose monitor and insulin pump technologies

B. Are implanted under the skin for 3-6 months at a time

C. Reduce hyperglycemia and increase hypoglycemia frequency

D. Are only used at night
Questions?

MOST EXPENSIVE LIQUIDS

- chanel no 5
- cobra venom
- human blood
- black ink
- scorpion venom
- mercury
- insulin

https://beyondtype1.org

Lisa Swartz Topor, MD, MMSc
lisa_swartz_topor@brown.edu
• **Metformin**

  Metformin is the preferred drug for initial treatment of type 2 diabetes in adults and youth. In the TODAY study, 48.3% of youth with type 2 diabetes who were enrolled, with less than 2 years (median 8 months) of diabetes duration, maintained adequate glycemic control (A1C <8.0%) on metformin alone for up to 6 years (104). However, youth were more likely than adults to require additional pharmacologic treatment to meet glycemic targets, with the other 51.7% of youth on metformin requiring insulin by 4 years, with a median time to treatment failure of 11.8 months.
Treatment of Type 2 DM in Youth

• Incidentally diagnosed or metabolically stable patients (A1C <8.5% and asymptomatic), metformin is the initial pharmacologic treatment of choice if renal function is normal

• Youth with marked hyperglycemia (blood glucose ≥250 mg/dL, A1C ≥8.5%) who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with basal insulin while metformin is initiated and titrated

• In patients with ketosis/ketoacidosis, treatment with subcutaneous or intravenous insulin should be initiated to rapidly correct the hyperglycemia and the metabolic derangement
  • Once acidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued

• In patients initially treated with insulin and metformin who are meeting glucose targets based on home blood glucose monitoring, insulin can be tapered over 2–6 weeks by decreasing the insulin dose 10–30% every few days

• If the glycemic target is no longer met using metformin alone, or if contraindications or intolerable side effects of metformin develop, basal insulin therapy should be initiated

Arslanian et al, Diabetes Care 2018
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Teen-LABS (n = 30)</th>
<th>TODAY (n = 63)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, y</td>
<td>16.9 (1.3)</td>
<td>15.3 (1.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>21 (70)</td>
<td>28 (44)</td>
<td>.03</td>
</tr>
<tr>
<td>Race/ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>18 (66)</td>
<td>45 (71)</td>
<td>.06</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>9 (30)</td>
<td>18 (29)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic multirace</td>
<td>2 (7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hispanic white</td>
<td>1 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Surgical procedure, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>23 (77)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Adjustable gastric banding</td>
<td>1 (3)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sleeve gastrectomy</td>
<td>6 (20)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.6 (9.3)</td>
<td>170.3 (7.8)</td>
<td>.37</td>
</tr>
<tr>
<td>Weight, median (IQR), cm</td>
<td>145.2 (134.2-176.6)</td>
<td>116.3 (107.6-126.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI</td>
<td>54.4 (9.5)</td>
<td>40.5 (4.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>51.7 (7.2)</td>
<td>38.9 (6.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>151.4 (16.6)</td>
<td>121.2 (13.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128.8 (12.3)</td>
<td>118.5 (11.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75.6 (11.6)</td>
<td>70.4 (8.7)</td>
<td>.02</td>
</tr>
<tr>
<td>Blood pressure medication use, No. (%)</td>
<td>17 (57)</td>
<td>8 (13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.8 (1.9)</td>
<td>6.2 (1.0)</td>
<td>.15</td>
</tr>
<tr>
<td>Total cholesterol level, mg/dL</td>
<td>172.3 (29.7)</td>
<td>146.7 (27.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-C level, mg/dL</td>
<td>101.8 (26.3)</td>
<td>83.3 (23.1)</td>
<td>.001</td>
</tr>
<tr>
<td>HDL-C level, mg/dL</td>
<td>40.1 (9.9)</td>
<td>38.5 (8.5)</td>
<td>.44</td>
</tr>
<tr>
<td>Fasting triglyceride level, median (IQR), mg/dL</td>
<td>152.7 (111.0-197.0)</td>
<td>132.0 (76.0-150.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lipid-lowering medication use, No. (%)</td>
<td>3 (10.0)</td>
<td>0</td>
<td>.03</td>
</tr>
<tr>
<td>Elevated urine albumin-creatinine ratio, No. (%)</td>
<td>8 (27)</td>
<td>13 (21)</td>
<td>.54</td>
</tr>
<tr>
<td>Fasting glucose level, median (IQR), mg/dL</td>
<td>105.0 (90.0-148.0)</td>
<td>116.0 (100.0-138.0)</td>
<td>.59</td>
</tr>
<tr>
<td>Fasting insulin level, median (IQR), µU/mL</td>
<td>42.1 (21.3-67.1)</td>
<td>32.2 (22.6-54.0)</td>
<td>.14</td>
</tr>
<tr>
<td>eGFR</td>
<td>110.0 (29.8)</td>
<td>109.3 (24.7)</td>
<td>.91</td>
</tr>
</tbody>
</table>

Inge, TH, et al. *JAMA Pediatrics* 2018
2016 report, two cohorts of youth with T1DM

(A) Solid black bar represents CGM users. Solid white bar represents non-CGM users

(B) Mean HbA1c by insulin delivery method and CGM use within each registry in 2016. BGM, blood glucose monitoring; CGM, continuous glucose monitoring or intermittent flash glucose monitoring.

*P-values compared with the reference group of pump + CGM
• Role of genetics/epigenetics: often a strong family history of type 2 diabetes
• Maternal obesity and GDM contribute to obesity and type 2 diabetes in youth
• Age of onset of type 2 diabetes was younger in those exposed to diabetes during gestation.

Arslanian et al, Diabetes Care 2018
Comparison of Surgical and Medical Therapy in Type 2 DM in Adolescents

• Secondary analysis of data collected by the Teen–Longitudinal Assessment of Bariatric Surgery (Teen-LABS) and Treatment Options of Type 2 Diabetes in Adolescents and Youth (TODAY) studies
  • Teen-LABS participants underwent a primary bariatric surgical procedure
  • TODAY participants were randomized to receive metformin alone or in combination with rosiglitazone or an intensive lifestyle intervention; insulin therapy was given in cases of progression of disease

Inge, TH, et al. JAMA Pediatrics 2018