Diabetes Update

Montana Diabetes Professional Conference
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University of Colorado
Barbara Davis Center

I) New Insulins
   • Prandial
   • Basal

II) Guidelines for Diabetes
   • General
   • New HbA1c goals for youth

III) Summary

A. Relationship of A1C to Risk of Microvascular Complications

Adapted with permission from Skyler JS. Endocrinol Metab Clin North Am. 1996;25:243

A. Mean HbA1c by Age Group
Type 1 Diabetes Exchange Registry (Helmsley)
C. Pre-meal Bolusing

![Graph showing blood glucose levels before, during, and after a meal.](image)

Time Post Meal (min)

<table>
<thead>
<tr>
<th>Blood Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
</tr>
<tr>
<td>125</td>
</tr>
<tr>
<td>150</td>
</tr>
<tr>
<td>175</td>
</tr>
<tr>
<td>200</td>
</tr>
<tr>
<td>225</td>
</tr>
<tr>
<td>250</td>
</tr>
</tbody>
</table>

PRE (-20)  START (0)  POST (+20)


I) Prandial Insulins

- Rapid-Acting Insulin Analogs:
  - Humalog®, NovoLog®, Apidra®
    (lispro, aspart and glulisine)
- Local Heat
- Hylenex = Hyaluronidase+RAIA
- FIAsp= Aspart
- Intra-peritoneal or Pulmonary delivery
Rapid-acting Insulin Analogs: Lispro, Aspart, and Glulisine

Similar IGF-1 activity

Insulin Aspart
- Aspartate at position B28 instead of proline

Insulin Lispro
- Positions of proline and lysine reversed at B28 and B29


Post prandial glycemic excursions with local heating

Friedman et al. JDST July 2012

Emerging Treatments and Technologies

Accelerated Insulin Pharmacokinetics and Improved Postprandial Glycemic Control in Patients With Type 1 Diabetes After Co-administration of Prandial Insulins With Hyaluronidase

- Hyaluronidase = An enzyme that deactivates Hyaluron
- Used to accelerate absorption of meds since the 1940s
- Must inject the Hyaluronidase prior to the insulin (currently)

Diabetes Care 34,696-698, 2011

Different approaches being pursued to make an Ultra-Rapid Acting insulin
rHuPH20-Hyaluronidase

- First and Only FDA Approved Human Hyaluronidase that increases dispersion and accelerates absorption of other injected drugs
- PH20 acts transiently and locally to depolymerize hyaluronan that provides barrier to fluid flow in the S/Q interstitium
- No systemic exposure to rHuPH20

Buse, Garg and Skyler, ADA, 2011

PK/GD of PH20+RHI vs. Lispro

21 Patients with T1D

Addition of PH20 to RHI Accelerates Absorption to Mimic Profile of Lispro

PK/GD of PH20+RHI vs. Lispro

Garg and Skyler, ADA, 2011

Glycemic Response (A) and Insulin Levels After 80 gm Carb Liquid Meal

- Black dashes = Lispro + Hyal.
- Solid line = Lispro
- Grey dashes = RHI + Hyal.

Hompesch et al., Diabetes Care 34:666 (2011)
Alternate Insulin Delivery Devices

- Alkermes/Lilly AIR®
- Pfizer Exubera®, Other pulmonary devices
- Aeradigm/AERx® Technosphere

Why use the pulmonary route?
Inhalation has long been used for delivery of ‘drugs’

Time-Action Profile of Inhaled Insulin with Various Systems

Data from different studies

- MannKind
- Pfizer/Aventis/Nektar
- Lilly/AIR/Alkermes
- Aerogen
- Novo Nordisk/Aradigm

GIR (glucose infusion rates mg/kg/min)

![Graph showing time-action profile of inhaled insulin with various systems.](Br J Diab Vasc Dis 2004;4:205-301)
Phase II AERx in Type 2 Diabetes Glucose Profiles

- 3 month trial/T2D
- Inhaled insulin meal vs. SC insulin 30 min. prior to meal
- Non inferiority - HbA1c values similar

Hermansen K et al. Diabetes Care 2004;27(1):162-7

Discontinuation and Readministration of Inhaled Insulin in Adults with T2DM: 3-Year FEV1 Data

Rosenstock et al. ADA 2007.

SUMMARY: Prandial Insulins

1) An ideal ultra-RAI is badly needed
2) The lack of an ultra-RAI will be a major deficit in the CL (bionic) pancreas (in relation to both hyper-and hypo-glycemia)
3) Post-meal hyperglycemia needs much more attention from diabetes care-providers (50% of HbA1c [if not more])
4) With time, the ideal ultra-RAI will become available
BASAL INSULIN
What do we still Need?

• A reliable True 24 hour Basal insulin
• Less Hypoglycemia
• Allows better glucose control (A1c)
• Less or no weight gain
• Decreased variability

Future Basal Insulins (Better?)

• Insulin Degludec-True 24 Hour Basal
• Degludec-Plus - Basal + Aspart (Ideal 2 in 1)
• Lilly Basal Insulin-Pegylated lispro
• U300 Glargine
• Sensulin (glucose-responsive insulin)
Insulin Degludec: Structure

Des(B30) LysB29(γ-Glu Ne-hexadecandioyl) human insulin

The amino acid sequence is identical to human insulin except for removal of threonine at B30. At B29, a glutamic acid spacer is attached that bridges to a 16-carbon diacid.

Insulin Degludec Association: From Formulation, Injection to Absorption

Injected Formulation

SQ depot formation

Absorption

Intra-Individual Variability- 24 Hours

Heise T et al. Diabetes 2011;60; A263
Degludec vs. Glargine in T1D Patients – Phase 3, 52 Week Study

Nocturnal Hypoglycemia

20% reduction with Degludec.

Overall Hypoglycemia

Nocturnal Hypoglycemia

10/21/2014
Degludec vs. Glargine in Type 1 Diabetes: Clamp Study
Degludec: Longer duration and less variation

Euglycemic Clamp at 100 mg/dl under steady state

Source: IN250-1875, PK/PD MD study in T1D

Macro-Vascular Events with Degludec Vs. Comparators

<table>
<thead>
<tr>
<th></th>
<th>IDeg/IDegAsp 60/60%</th>
<th>Comparators 70/30% (NPH/Asp)</th>
<th>Hazard Ratio (95% C.I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACI</td>
<td>55 (3.6)</td>
<td>37 (1.1)</td>
<td>1.3 (0.8, 2.0)</td>
</tr>
<tr>
<td>CV Death</td>
<td>12 (0.3)</td>
<td>0 (0.2)</td>
<td>1.0 (0.4, 2.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>24 (0.4)</td>
<td>9 (0.3)</td>
<td>2.0 (0.6, 6.9)</td>
</tr>
<tr>
<td>MI</td>
<td>24 (0.1)</td>
<td>9 (0.3)</td>
<td>1.5 (0.3, 6.8)</td>
</tr>
<tr>
<td>UAP</td>
<td>25 (0.4)</td>
<td>18 (0.3)</td>
<td>0.8 (0.4, 1.3)</td>
</tr>
</tbody>
</table>

FDA panel Meeting Nov, 2012

IDeg/Asp BID vs. 70/30 (NPH/Asp)
(Adults, T2D)

SUMMARY
Degludec Plus Vs. Glargine
• 30% less Nocturnal Hypoglycemia
• Insulin dose Reduced by 25%
• Lower Post-Dinner BGs
• Desirable Bed Time Glucose
• Cardiovascular risk

Basal Pegylated Lispro (Peglispro)
1) Physiologic insulin release from the pancreas to the portal vein and liver results in 40-80% extraction by the liver (= 4 to 1 hepatic vs. peripheral action).
2) SubQ insulin has equal hepatic and peripheral action.
3) Peglispro is a polyethylene glycosylated insulin which has hepatopreferential action.
4) Peglispro has less patient variability and less hypoglycemia in comparison to insulin glargine.
5) Toxicity currently unknown.

(Henry, et al. Diabetes Care 37, 2609, Sept., 2014)
Summary: Basal Insulins:

1) Degludec: close to approval in US.
2) Degludec Plus (combined with NovoLog) bid may be helpful.
3) Peglispro has potential benefits, but still need toxicity data.
4) Glucose-responsive insulins are possible for prandial and basal insulin, but in the distance.

Part II: Diabetes Guidelines

1. Initial Diagnosis
2. Pediatric
3. Cardiovascular
4. Thyroid
5. Recent change in HbA1c recommendations for children
**INITIAL DIAGNOSIS**

**Oral Glucose Tolerance Test (OGTT), Blood Sugar Values and HbA1c Values**

<table>
<thead>
<tr>
<th>Blood Sugar</th>
<th>Normal</th>
<th>Pre-Diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>≤100</td>
<td>140-200</td>
<td>≥200</td>
</tr>
<tr>
<td>2 hours after drinking the sugar load</td>
<td>90-140</td>
<td>180-260</td>
<td>≥160</td>
</tr>
<tr>
<td>HbA1c</td>
<td>&lt;6</td>
<td>5.7-6.4</td>
<td>≥6.5</td>
</tr>
<tr>
<td>mmol/L</td>
<td>≤42</td>
<td>30-46</td>
<td>≥48</td>
</tr>
</tbody>
</table>

Chase HP, Garg S. Management of Diabetes in Adults, p 9, 2013. (Available at 303-863-1200.)

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**BDC Pediatric Guidelines (7/2014)**

1. A1C targets (ADA guidelines)
   - Pediatrics (birth through 17 years) 7.5%
   - Adult (18 years and above) 7.0%

2. Glucose Targets
   - Toddler (up to 5 years of age) 80-180
   - Children, Teens (5-17 years of age) 70-150
   - Adult (18 years and older) 70-130

3. Pediatric bedtime targets
   - ≤5 years ≥130
   - >5 years ≥130

4. Each patient will have these guidelines adjusted as needed to meet individual needs.

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**Risk Factors for Cardiovascular Complications Prevention**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycemic (sugar) control</td>
<td>HbA1c below 7.0% (53 mmol/mol)</td>
</tr>
<tr>
<td></td>
<td>Preprandial glucose = 70-130 mg/dL (3.9-7.2 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>Postprandial glucose &lt; 180 mg/dL (&lt;10 mmol/L)</td>
</tr>
<tr>
<td>blood pressure</td>
<td>below 130/80 (140/80, 150/90)</td>
</tr>
<tr>
<td>tobacco use</td>
<td>don’t use</td>
</tr>
<tr>
<td>elevated total cholesterol</td>
<td>below 200 mg/dL (5.2 mmol/L)</td>
</tr>
<tr>
<td>elevated LDL cholesterol</td>
<td>below 100 mg/dL (3.2 mmol/L)</td>
</tr>
<tr>
<td>elevated (fasting) triglyceride</td>
<td>below 150 mg/dL (1.7 mmol/L)</td>
</tr>
</tbody>
</table>

Chase, HP and Garg, S. Management of Diabetes in Adults, 2013. p 111
2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol
(J. Am College of Cardiology 63, 2889-2933, 2014)

A: Heart-healthy lifestyle habits should be encouraged for all individuals.

B-2: Primary preventions of LDL-C ≥ 190 mg/dL-high intensity statin: 1B

B-3: Diabetes, ages 40-75 yrs and LDL-C, 70-189 mg/dL, use a “moderate-intensity” statin dose.
[Advised with a high-level of evidence: 1-A]

- No primary-prevention RCT data were available for individuals 21 to 39 years of age. Therefore, use clinical knowledge, experience, and skill (“the art of medicine”) to decide on statin therapy.

Screening for Thyroid

- Autoimmune, as is Type 1 Diabetes (T1D)
- Approximately 1/20 people with T1D need thyroid treatment
- Annual screening with TSH and T4 or Free T4
- Annual physical exam for enlarged thyroid
- Hashimoto’s thyroiditis may initially occur with hyperthyroidism (relatively rare in T1D)
- Thyroid autoantibodies in questionable cases
  (I rarely measure antibodies)

HbA1c: Changes in Recommendations for Youth

<table>
<thead>
<tr>
<th>ADA rational for HbA1c</th>
<th>&lt;8.5% in 0-6 yo*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;8.0% in 7-12 yo</td>
</tr>
<tr>
<td></td>
<td>&lt;7.5% in ≥ 13 yo</td>
</tr>
</tbody>
</table>

- Vulnerability to hypoglycemia
- Insulin sensitivity
- Unpredictability in dietary intake and physical activity

The ADA also notes:
- Goals should be individualized and lower goals may be reasonable based on benefit-risk assessment.
- A lower goal (<8.0%) is reasonable if it can be achieved without excessive hypoglycemia

* Clinical Practice Recommendations, 37, S51, Jan, 2014
Change in ADA Goal for HbA1c Level
(as of June, 2014)

New ADA Goal: All children with type 1 diabetes should aim for an HbA1c level <7.5%

ISPAD (Int'l Society for Pediatric and Adolescent Diabetes) has recommended <7.5% for all children for many years.

The consequences of the new recommendations are unknown

T1D Exchange (T1DX) Registry
and the Prospective Diabetes Follow-up Registry (DPV)

- T1DX: ~26,000 participants with Type 1 Diabetes (T1D) from 70 diabetes clinics across the U.S.
  - Data obtained from both medical chart review and participant questionnaires
- DPV: includes 85,439 patients with all types of diabetes from both Austria and Germany
  - Data documented locally by participating centers in electronic health record. Twice yearly, data exported for central analyses

Insulin Pump vs. MDI in Children <6yo in the T1D Registry
(Blackman, SM, Chase, HP et al, Pediatric Diabetes, pre-press, 2014)

<table>
<thead>
<tr>
<th></th>
<th>CSII</th>
<th>MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>4.9yr</td>
<td>4.9yr</td>
</tr>
<tr>
<td>Mean T1D duration</td>
<td>2yr</td>
<td>1 yr</td>
</tr>
<tr>
<td>SMBG/Day</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Mean HbA1c</td>
<td>7.9</td>
<td>8.3 (P=0.001, Adjusted)</td>
</tr>
<tr>
<td>Severe Hypoglycemia</td>
<td>12%</td>
<td>8% (P=0.20)</td>
</tr>
<tr>
<td>DKA in past 12 mo</td>
<td>10%</td>
<td>8% (P=0.58)</td>
</tr>
<tr>
<td>COM use</td>
<td>12%</td>
<td>2.9% (P=0.001)</td>
</tr>
</tbody>
</table>
Comparison of Data from Children <6yo from Both Registries
(Maahs, D, et al, Diabetes, 57, 1578, 2014)

<table>
<thead>
<tr>
<th>Median (IQR)</th>
<th>T1DX</th>
<th>GER/AUS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>4.9 (4.0, 5.5)</td>
<td>5.0 (4.1, 5.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>58%</td>
<td>33%</td>
<td>0.03</td>
</tr>
<tr>
<td>T1D duration, years</td>
<td>2.0 (1.0, 3.0)</td>
<td>1.8 (1.3, 2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI Z score</td>
<td>0.85 (0.30, 1.30)</td>
<td>0.84 (0.26, 1.44)</td>
<td>0.33</td>
</tr>
<tr>
<td>Pump Use, %</td>
<td>50%</td>
<td>74%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total daily insulin, units/kg/d</td>
<td>0.68 (0.56, 0.83)</td>
<td>0.66 (0.54, 0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% prandial insulin</td>
<td>62% (50%, 71%)</td>
<td>66% (55%, 74%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SMBG/day</td>
<td>7.0 (5.0, 9.0)</td>
<td>8.0 (6.0, 10.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CGM use, %</td>
<td>7%</td>
<td>7%</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Median HbA1c (%)

<table>
<thead>
<tr>
<th></th>
<th>T1DX</th>
<th>GER/AUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>8.2%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Pump Users</td>
<td>7.4%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Injection Users</td>
<td>7.4%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Percent with HbA1c <8.5%

<table>
<thead>
<tr>
<th></th>
<th>T1DX</th>
<th>GER/AUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>66%</td>
<td>90%</td>
</tr>
<tr>
<td>Pump Users</td>
<td>79%</td>
<td>91%</td>
</tr>
<tr>
<td>Injection Users</td>
<td>54%</td>
<td>88%</td>
</tr>
</tbody>
</table>
Percent with HbA1c <7.5%

Percent with ≥1 SH Event in Past Year

Percent with ≥1 SH Event in Past Year by HbA1c
Earliest Sequelae of Early-Onset T1D*

(Cognitive Function)

- Early-Age Diagnosis of T1D:
  Several studies have documented worse outcomes across a variety of cognitive domains, including IQ, executive function, learning and memory, and processing speed.

- Severe Hypoglycemia (Seizure or loss of consciousness)
  Many (at least 15) studies have noted poorer cognitive outcomes.

- Chronic Hyperglycemia (≥DKA)
  Fewer studies available, but associated with abnormal grey and white matter volumes, decreased processing speed and reduced verbal intelligence.

Cameron F, et al, Diabetes Care 37,1554,2014: Neurologic changes from DKA at new-onset T1D.
## Conclusions

- The data from Germany and Austria indicate that HbA1c levels of <7.5% can be frequently achieved in children with T1D <6 years old.
- Improved metabolic control of T1D in young patients decreases the risk of DKA without increasing the risk of SH.
- Sub-optimal control in young patients in the T1DX may relate to less frequent use of insulin pumps, SMBG and insulin boluses and the higher HbA1c targets in this age group that were recommended in the U.S.
- “Time will tell.”

## DIABETES UPDATE
### SUMMARY

1. A “cure” is still in the future
2. Better care and safety with technology continues
   - i) New insulins
     - prandial
     - basal
   - ii) Technologic advances
     - pumps
     - CGM
   - The “Bionic” pancreas
   - iii) Guidelines will continue to get “tighter”