The Evolution of Insulin Therapy: Solutions to Treatment and Access Challenges in 2021

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Dualities

• Research Support: Medtronic, Insulet, Beta Bionics
• Consulting: Abbott, Bigfoot
Dogs 92 and 409, blood and urine glucose, August 11, 1921
Insulin was discovered in 1921 by Fred Banting and Charles Best. In a generous gesture that unfortunately didn't start a trend, they sold the patent for a dollar so that cheap insulin would quickly become available. It worked like a charm: within two years, Eli Lilly had sold 60 million units of its purified extract of pig and cow pancreas.

Von Wartberg, L: Diabetes Health, May 23. 2007
Insulin Toronto
Iletin, Eli Lilly, 1920s

Initial insulin from Lilly: potency varied up to 25% per lot; the development of isoelectric precipitation led to a purer and more potent animal insulin, decreasing variation between lots to 10%

The History of NPH Insulin

• Hagedorn and Krogh obtained the rights for insulin from Banting and Best in 1923 to form Nordisk Insulinlaboratorium, a non-profit company.

• Hagedorn and Jenssen discovered that the effects of injected insulin could be prolonged by the addition of protamine obtained from the semen of river trout.

• Insulin added to the protamine, pH brought to 7.0, and protomine zinc insulin was introduced in 1936 (24-36 hours).

• 1946: crystals of protamine formed and when mixed with insulin formed NPH, introduced in 1950.

• Shortly afterwards Eli Lilly introduced an NPH insulin.
Insulins: 1950s – 1970s

• 1951: addition of zinc at different concentrations without protamine: semi-lente, lente, ultralente insulins

T1D: 1950s-1960s: with longer-acting insulins most with T1D treated with one shot/day assessed with urine glucose testing

1960s-1970s: Jackson and Guthrie advocate for twice daily injections to better control T1D

Pre-1970s insulin: thousands of impurities per pmol/L; resulted in allergies and lipoatrophy; 1974-purified insulins at 1 pmol/L
1982: Human Insulin
The Introduction of Insulin Analogues

- 2001 glargine, 2005 detemir, 2015 degludec
Basal Insulin

• Basal insulin results in suppressing glucose from the liver
Basal Insulins

• Not all the same!
• NPH-occasionally used for severe dawn phenomenon, morning steroids
• Glargine (Lantus, Basaglar, Semglee): most common used basal insulin
• U-300 glargine (Toujeo)
• Degludec (Tresiba)
Understanding Insulin Durations of Action (Kinetics)

- Pharmacokinetics (PK): Can be measured by measuring insulin levels
- Pharmacodynamics (PD): the time course of the effect on blood glucose concentration.

PD: Insulin is injected, and insulin is infused ("glucose infusion rate") to measure the physiologic action of the injected insulin.
Each Basal Insulin Has Different Kinetic Properties!

U100 glargine vs. Degludec/U300 glargine

• Degludec: consistently less hypoglycemia
• U300 glargine: some but not all studies with less hypoglycemia
• Bottom line: Degludec and U300 glargine are better basal insulins than U100 glargine; some insurances don’t cover degludec/U300 glargine but as a rule of thumb if you can get them, you should
Basal Insulin

• The primary role of endogenous basal insulin secretion is to fine tune lipolysis and hepatic glucose production in the fasting state, especially overnight, while maintaining sufficient glucose for brain function

• Goal of *exogenous insulin* with severe insulin deficiency
  • Attempts to recreate constant, low levels of insulin overnight and between meals which with the correct dose will maintain euglycemia for 24 hours in the fasting state
What is the Correct Dose of Basal Insulin?

• Traditional Teaching: 50% basal/50% prandial (T1D, isocaloric diet)
How to Dose Basal Insulin?

• BeAM factor = bedtime glucose – AM glucose
• A + BeAM factor: bedtime glucose is higher than AM glucose
  • For example, mean HS BG = 200, mean FBG = 100, BeAM = 100
• A – BeAM factor: bedtime glucose is lower than AM glucose
  • For example, mean HS BG = 120, mean FBG = 180, BeAM = -60

“Fix the fasting first” is problematic if one doesn’t know the bedtime glucose level
BeAM in T2D

- Adding basal insulin in T2D (N = 1401 and 553)

BeAM increased to 60 mg/dL due to lower FBG without change in HS BG

BMJ Open Diabetes Res Care 2016;4:1-8
BeAM in T2D: Basal Insulin Only

In T2D with basal insulin alone, it appears a BeAM level > 60 mg/dL is associated with A1C levels > 7%. Should the goal in T2D on basal insulin be a BeAM < 60 mg/dL?
Case 1

• 63 y/o man with T2D
• Started insulin over 10 years ago
• Now unable to afford analogue insulin-using HS NPH and ac Reg; had to stop SGLT2 inhibitor due to cost, still taking metformin. Unable to afford CGM
• Last A1C 8.2%
Case 1

What do you want to do?  
Role of ac dinner R overnight?  
NPH in AM?  
Biggest issue: size of dinner
Understanding Prandial Vs. Basal Insulin

- Prandial insulin
  - After eating, 70% of the glucose is taken up by skeletal muscle
The basic principles of bolus insulin therapy are identical for pumps or multiple injections.
What Is *Duration of Action* of Our Current Rapid-Acting Analogues?

A) 2 hours
B) 3 hours  Given in the typical doses of 0.1-0.2 units per injection
C) 4 hours
D) 5 hours
E) 6 hours
Serum insulin levels (ng/mL)

Time (hours)

Lispro vs Regular (PK)

Diabetes 43: 396-402, 1994
Glucodynamic Principles (Analogue Pearl): Prandial Insulin: not as rapid acting as we thought.

Diabetes Care 1999;22:1501-1506
Pearls for Bolus Insulin

• LAG TIME:
  • Time between giving mealtime insulin and eating meal
Timing (lag time) of Rapid-Acting Analog Insulin Injection Alters PPG in Type 1 Diabetes Mellitus

Practice Pearls: Prandial Replacement

• Keep simple!
• No need for “carb counting” in T2D
• Small/Medium/Large doses for each meal usually works fine
• Correction dose: can use sensitivity factor or simply “add X units if above 200 mg/dL before eating”
  • ISF: trial and error, most with T2D 1 unit/30 mg/dL
• Premix a reasonable option for those without severe insulin deficiency and those less sophisticated
• **CGM should be considered for each patient receiving insulin!**
Case 2: 48 y/o woman with T2D, receiving metformin, glipizide, liraglutide, and 55 units of bedtime glargine; what to do now?

**SMBG Results**

<table>
<thead>
<tr>
<th>Fasting mg/dL</th>
<th>Lunch mg/dL</th>
<th>Supper mg/dL</th>
<th>Bedtime mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>111</td>
<td></td>
<td>210</td>
<td>245</td>
</tr>
<tr>
<td>106</td>
<td>135</td>
<td>185</td>
<td>234</td>
</tr>
<tr>
<td>110</td>
<td></td>
<td>142</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td>126</td>
<td>198</td>
<td>256</td>
</tr>
</tbody>
</table>
Next Steps

• Add pre-dinner lispro: 5 for small, 8 for medium, 10 for large meals
• Add 1 unit/30 mg/dL at and pre-meal above 150 mg/dL, above 200 mg/dL at bedtime
• Decrease glargine by 10 units
• Write in logbook
# Home blood glucose monitoring results

<table>
<thead>
<tr>
<th>Fasting (mg/dL)</th>
<th>Lunch (mg/dL)</th>
<th>Supper (mg/dL)</th>
<th>Bedtime (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>98</td>
<td>177 (8 +2)</td>
<td>198</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(meal + correction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>127</td>
<td>(8 + 0) (no correction dose as no SMBG)</td>
<td>235 (2 units + usual glargine)</td>
</tr>
<tr>
<td>108</td>
<td>193 (10 + 2)</td>
<td>244 (2 units + usual glargine)</td>
<td></td>
</tr>
<tr>
<td>91</td>
<td>175 (8 + 1)</td>
<td>252 (2 units + usual glargine)</td>
<td></td>
</tr>
</tbody>
</table>

Now what?
Banting and Macleod felt it was unethical for doctors to profit from a discovery that would save lives. The insulin patent was sold from the University of Toronto for a mere $1. They wanted everyone who needed their medication to be able to afford it.
“What is the commonest cause of death in a child with diabetes? The answer—from a global perspective—is lack of access to insulin. Families in the poorest parts of the world must make a choice between insulin for one child or starvation for the rest. The issue is an emotional one. How could it be otherwise?”

At This 100th Anniversary of the Discovery of Insulin, How Do We Do with the Insulin Access at a Global Level?

- WHO global action plan for the prevention and control of non-communicable diseases, 2013-2020
- Target: “an 80% availability of the affordable basic technologies and essential medicines, including generics, required to treat major non-communicable diseases in both public and private facilities.”

How do we do?
Not Very Well

• The average availability was 56% in the public sector (17–100%) and 39% in the private sector (0–95%) of low/mid income countries.

Only 2/15 in private, 6/15 in public sectors meet the WHO target

Lancet Diabetes Endocrinol 2016;4:275-85
And it Got Worse: Insulin Rationing from the T1International 2018 Survey (IDF 2019)

- 1478 respondents in 90 countries
- Globally: 18% ration due to cost
- US: 26% ration (N=627) compared to 6% of the other high-income countries (N=525 respondents)
- Low- and mid-income countries: 10.9% insulin rationing (N=256)
Who would have thought low- and mid-income countries made the 2020 WHO target for insulin access written in 2013, yet the US has twice as much insulin access challenges than the poorest countries in the world.
The Fundamental Problem

• Even in low- and mid-income countries, the ability to ship insulin under proper conditions is expensive
• Most countries negotiate price with the insulin company - not in the US

US DKA Rates, 2009-2015

Diabetes Care 2020;43:1057–1064
The Good News in the US

• During pandemic, cheaper (and sometimes free) insulins available from all 3 insulin manufacturers
• Still, not all patients know about the availability of cheaper insulin

Facebook posting by a nurse, August, 2020
Where to Find Less Expensive Insulin
(especially during the pandemic)

• Novocare.com
• Lillycares.com
• Sanofipatientconnection.com
• Human insulin (NPH, Reg, and 70/30) available at Walmart for $25/vial
Conclusions

• Basal = liver; bolus = muscle
• PD is the more important insulin kinetic
• Pay attention to BeAM score when dosing basal insulin
• Keep prandial dosing simple!
• Insulin is expensive but more accessible during the pandemic
• CGM should be offered to all receiving insulin
THANKS!