Incretin therapies (DPP4-inhibitors, GLP-1 agonists) and Insulin products

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Objectives / Areas to be Covered

• Differences and advantages/weaknesses of different synthetic insulin formulations.
• Clinical contexts where one form of insulin therapy may be superior to another.
• Multisystems biology of injected GLP1 agonists. (including role of DPPIV agonists)
• Synergy and convenience of dual insulin-GLP1 injected therapies.
INSULINS
<table>
<thead>
<tr>
<th></th>
<th>Onset after SC injection (h)</th>
<th>Time to peak effect (h) *</th>
<th>Duration of action (h) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Aspart, Recombinant</td>
<td>0.5–1</td>
<td>1–2</td>
<td></td>
</tr>
<tr>
<td>Insulin Lispro, Recombinant</td>
<td>0.5–1</td>
<td>1–2</td>
<td>3–5</td>
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<tr>
<td>Insulin Glulisine</td>
<td>0.5–1</td>
<td>1–2</td>
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<tr>
<td>Insulin Human Regular</td>
<td>0.75–1</td>
<td>2–4</td>
<td>5–8</td>
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<tr>
<td>Insulin Human Isophane (NPH)</td>
<td>1–2</td>
<td>6–12</td>
<td>12–18</td>
</tr>
<tr>
<td>Insulin Human Isophane (NPH)/Insulin Human Regular</td>
<td>1–2</td>
<td>2–8</td>
<td>18–24</td>
</tr>
<tr>
<td>Insulin Aspart Protamine, Recombinant/Insulin Aspart, Recombinant</td>
<td>0.5–1</td>
<td>2–8</td>
<td>18–24</td>
</tr>
<tr>
<td>Insulin Lispro Protamine, Recombinant/Insulin Lispro, Recombinant</td>
<td>0.5–1</td>
<td>2–8</td>
<td>18–24</td>
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<tr>
<td>Insulin Degludec</td>
<td>8–10</td>
<td>36–42</td>
<td></td>
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<tr>
<td>Insulin Detemir</td>
<td>8–10</td>
<td>6–24</td>
<td></td>
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<tr>
<td>Insulin Glargine, Recombinant</td>
<td>8–10</td>
<td>11–24</td>
<td></td>
</tr>
<tr>
<td>Insulin Degludec/Insulin Aspart, Recombinant</td>
<td>0.5–1.0</td>
<td>8–10</td>
<td>36–42</td>
</tr>
</tbody>
</table>
Synthetic Insulins: Current Designs

Polymerization Control

Acylation/Lipid Partitioning (Fatty Acid Modification)
Basal-Bolus Multidose Insulin Tx
Basal-Bolus Multidose Insulin Tx via Insulin Pump
Short-Acting Insulins
Long-Acting Insulins

![Graph showing the glucose infusion rates (GIR) of different long-acting insulins over time. The graph compares NPH insulin (12–16h), Insulin glargine U100 (~24h), Insulin detemir (~20–24h), Insulin glargine U300 (~32h), and Insulin degludec U100 and U200 (~42h).](Nature Reviews | Endocrinology)
Long-acting insulins not equivalent

**Half-life of insulin degludec is twice as long as that of insulin glargine**

![Graph showing half-life comparison between IDeg and IGlar.]

<table>
<thead>
<tr>
<th>Time since injection (hours)</th>
<th>IDeg 0.8 U/kg</th>
<th>IGlar 0.8 U/kg</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
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<tr>
<td>24</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>48</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>72</td>
<td>10</td>
<td>10</td>
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<tr>
<td>96</td>
<td>5</td>
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<tr>
<td>120</td>
<td>2</td>
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</table>

<table>
<thead>
<tr>
<th>Insulin concentration (%) of maximum</th>
<th>IDeg 0.8 U/kg</th>
<th>IGlar 0.8 U/kg</th>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
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<td>96</td>
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<tr>
<td>120</td>
<td>2</td>
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</tbody>
</table>

<table>
<thead>
<tr>
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<th>IDeg 0.4 U/kg</th>
<th>IDeg 0.6 U/kg</th>
<th>IDeg 0.8 U/kg</th>
<th>IGlar 0.4 U/kg</th>
<th>IGlar 0.6 U/kg</th>
<th>IGlar 0.8 U/kg</th>
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<tr>
<td>0.4 U/kg</td>
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<td>27.0</td>
<td>23.6</td>
<td>11.5</td>
<td>12.9</td>
<td>11.9</td>
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<td>0.6 U/kg</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0.8 U/kg</td>
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<td></td>
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<tr>
<td>0.4 U/kg</td>
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<td></td>
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<td>11.5</td>
<td>12.9</td>
<td>11.9</td>
</tr>
<tr>
<td>0.6 U/kg</td>
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<td>0.8 U/kg</td>
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<tr>
<td>0.4 U/kg</td>
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<td>0.8 U/kg</td>
<td></td>
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<td></td>
<td></td>
<td>25.4</td>
</tr>
</tbody>
</table>

*Insulin glargine was undetectable after 48 hours
Results from 58 patients with T1D
IDeg, insulin degludec; IGlar, insulin glargine
Long-acting insulins not equivalent

Degludec exhibits less pharmacodynamic variability than glargine

Heise, T. et al. ADA 2011 Abstract 960-P
Long-acting insulins not equivalent

Switch 1 & 2 Trials

Switch 1:
501 T1DM patients. Degludec vs. Glargine.
Outcome: **Severe Hypoglycemia**
- Glargine 17%
- Degludec 10%

Switch 2:
721 T2DM patients. Degludec vs. Glargine
Outcome: **Nocturnal Hypoglycemia**
- Glargine 14.7%
- Degludec 9.7%
Outcome: **Severe Hypoglycemia**
- Glargine 2.4%
- Degludec 1.6%

JAMA. 2017;318(1):33-44; 45-56
When to start injected insulin?

No-Brainers:

- Type 1 diabetes (long and short-acting – multidose insulin)
- Recent Hyperglycemic Emergency: DKA or NKHOC
- Features of Type 1 diabetes: Polyuria/polydipsia/weight loss
- Antibody-positive diabetics progressively failing oral medications (LADA)

Goals:

Prevent DKA or dangerous hyperglycemia, reduce glucotoxicity
When to start injected insulin?

Timing is everything:

Old thinking:
- FPG > 250 mg/dg or random BG > 300 mg/dL
- HbA1c > 10%
- Start Long-Acting Insulin

New thinking:
- HbA1c and glucose triggers are unclear – even high A1c patients respond to SGLT2 inhibitor and GLP-1 agonists
- Consider patients ability to make behavioral change with addition of new next-generation medicines
- Patients with increasing or stalled HbA1c on Metformin plus 1-2 other oral meds, and who are not candidates for SGLT2 inhibitor or GLP1 agonist.
- Failing Metformin + SGLT2 + GLP1
- Mealtime insulin may be more important than long-acting insulin
Is insulin a one-way trip in T2DM?

No.

First-Phase Insulin Secretion is acutely Inhibited by hyperglycemia ...
... and can be recovered once glucose is controlled

... likely true for insulin-sensitivity as well
Getting a grip on insulin-treated patients

CGM is a powerful problem-solving tool for patients and practices.
Clinical contexts & insulin therapy

DIP/Gestational DM: Short acting insulins, NPH and Levemir

Financial stress: Regular insulin qAC; NPH at dinnertime
70/30 Mix Insulin twice daily

Compliance issue: 70/30 Mix Insulin twice daily

Cognitive issues: Avoid pump.
70/30 – Simple, few variables

Fragile patients with care: Lantus/Toujeo/Tresiba + Short acting insulin

Recurrent hypoglycemia: Tresiba

Smart/motivated: Lantus/Toujeo + Rapid Insulin qAC/HS
Carbohydrate counting preferred
Alternative: insulin pump w/ CGM
Synthetic Insulins: Ultra Fast-Acting Insulin
Synthetic Insulins:
Ultra Fast-Acting Insulin
Synthetic Insulins: Ultra Fast-Acting Insulin

*FiAsp:* Peaks in about 15 minutes; 1 hr duration of action
Synthetic Insulins: Next Gen Tech
Synthetic Insulins: Next Gen Tech

Insulin-PBA-F = Insulin-phenylboronic acid

Insulin-PBA-F (Partitions to Fat)

Glucose-Activated Switch

“off”

Glucose

“on”

Insulin-PBA-F-Glucose (Released from Fat)

Insulin-PBA-F = Insulin-phenylboronic acid
Synthetic Insulins: Next Gen Tech

![Graph showing blood glucose levels over time after a glucose challenge. The graph compares different types of insulins: Long-acting Insulin, Ins-PBA-F, and “smart” insulin against Healthy controls. The x-axis represents time in hours, and the y-axis represents blood glucose levels in mg/dL. The graph highlights how each type of insulin responds differently to a glucose challenge.](image-url)
Synthetic Insulins: Next Gen Tech

Smart Patch
Polymer containing insulin-loaded vesicles is sensitive to hydrogen peroxide (H$_2$O$_2$)

Impregnated with glucose oxidase: generates H$_2$O$_2$ in presence of glucose

H$_2$O$_2$ creates holes in vesicles that release insulin into subcutaneous space
Incretin Therapies
Biology
Incretin Biology

Nauck et al., Diabetologia 1986; 29:46-52
Incretin Biology

The Incretin Effect in Subjects Without and With Type 2 Diabetes

Control Subjects (n=8)

Patients With Type 2 Diabetes (n=14)

The incretin effect is diminished in type 2 diabetes.

Incretin Biology

- Incretins: GLP-1, GIP
- Stimulate insulin release
- Inhibit glucagon release
- Lowering of blood glucose
- DPP-4 enzyme inactivates incretins
- DPP-4 inhibitors (drugs) block DPP-4
Bariatric surgery is incretin therapy

![Diagram A](#)

GLP-1 Total (pmol/L)

- Pre-Surgery
- Post-Surgery
- Controls

Time (min)

0 15 30 45 60 75 90 105 120 135 150 165 180

![Diagram B](#)

GIP (pg/mL)

Time (min)

0 15 30 45 60 75 90 105 120 135 150 165 180

![Diagram C](#)

GLP-1 Active (pmol/L)

Time (min)

0 15 30 45 60 75 90 105 120 135 150 165 180

![Diagram D](#)

Incretin Effect on Insulin (%)

Controls
Pre-Surgery
Post-Surgery

Diabetes Care 2007 Jul; 30(7): 1709-1716
GLP1-specific actions
DPP-IV sits at a metabolic nexus

DPP-IV

Active forms

GLP-1
GLP-2
GIP
PACAP
NPY
PYY

Inactive forms

Liver lipid

DPIV inhibitor

GLP-1
GLP-2
GIP
PACAP
NPY
PYY

Pancreas

Glycemic control

Liver

Appetite

Gastric emptying
Incretin Therapies
DPP-IV Inhibitors
DPP-IV inhibitors: Safe, CV benefit, well-tolerated, weight neutral...and lower glucose

<table>
<thead>
<tr>
<th>Table 1. Abstracts on Diabetes Studies With DPP-4 Inhibitors</th>
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<tr>
<td><strong>TECOS</strong></td>
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<td><strong>MEDICATION</strong></td>
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<tr>
<td><strong># OF PATIENTS</strong></td>
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<tr>
<td><strong>HISTORY</strong></td>
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<td><strong>STUDY DESIGN</strong></td>
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<td><strong>PRIMARY OUTCOME</strong></td>
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<tr>
<td><strong>RESULTS</strong></td>
</tr>
<tr>
<td><strong>ADDITIONAL BENEFITS/RISKS</strong></td>
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GLP1 Agonists
Current GLP-1 Agonist Landscape

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Dosing Schedule</th>
<th>Mixing Required</th>
<th>Pre-injection waiting time</th>
<th>Dosing</th>
<th>Smallest Needle Size</th>
<th>Needles included</th>
<th>Use with basal insulin</th>
<th>Auto Injector</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byetta</td>
<td>Exenatide</td>
<td>BID</td>
<td>No</td>
<td>None</td>
<td>5mcg, 10mcg</td>
<td>32 gauge, 4mm needle</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Bydureon Kit</td>
<td>Exenatide extended release</td>
<td>QW</td>
<td>Yes</td>
<td>None</td>
<td>2mg</td>
<td>23-gauge, 8mm needle</td>
<td>Yes</td>
<td>No Currently studies are evaluating</td>
<td>No</td>
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<td>Bydureon Pen</td>
<td>Exenatide extended release</td>
<td>QW</td>
<td>Yes</td>
<td>None</td>
<td>2mg</td>
<td>23-gauge, 8mm needle</td>
<td>Yes</td>
<td>No Currently studies are evaluating</td>
<td>No</td>
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<tr>
<td>Tanzeum</td>
<td>Albiglutide</td>
<td>QW</td>
<td>Yes</td>
<td>15-30 minutes</td>
<td>30mg, 50mg</td>
<td>5mm 29-gauge thin-walled needle</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Trulicity</td>
<td>Dulaglutide</td>
<td>QW</td>
<td>No</td>
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<td>0.75mg, 1.5mg</td>
<td>Built in to device 29g</td>
<td>Yes part of device</td>
<td>No Currently studies are evaluating</td>
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<td>Victoza</td>
<td>Liraglutide</td>
<td>QD</td>
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<td>32 gauge, 4mm needle</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

- Lower A1c from 1.0 to 1.8%, depending on clinical context.
- Not shown: Saxenda, Liraglutide 3 mg – approved for obesity indication only – remarkable ability to prevent conversion from prediabetes to diabetes; 80% relative risk reduction. Under-prescribed due to cost.
- Short acting – tend to have more impact on body weight adiposity
- Long acting – more well tolerated; better compliance

Not included: Adlyxin (lixisenatide)
GLP-1 agonist Risks vs. Benefits

Benefits
• Weight loss – can be very significant (Saxenda safe and effective for 3 years)
• Low risk of hypoglycemia
• Improves beta cell function
• Cardiovascular protection: decreased BP, increased cardiac glucose uptake, decreased vascular inflammation, increased myocardial viability

Side effects
• Black box warning: Follicular C-cell hyperplasia in rats (no MTC effect ever detected in humans)
• GI Symptoms: Nausea/vomiting – usually transient
• Pancreatitis – may increase risk
• Injection site reactions
• Avoid concurrent DPP-IV inhibitor or sulfonylurea
Previously mentioned LEADER Trial

**Primary Outcome**

<table>
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<tr>
<th>Patients with an Event (%)</th>
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<tbody>
<tr>
<td>100</td>
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<tr>
<td>90</td>
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<tr>
<td>80</td>
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<td>20</td>
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<tr>
<td>10</td>
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<td>0</td>
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</tbody>
</table>

- **Placebo**
- **Liraglutide**

**Hazard ratio, 0.87 (95% CI, 0.78–0.97)**

- **P<0.001 for noninferiority**
- **P=0.01 for superiority**

**Months since Randomization**

0 6 12 18 24 30 36 42 48 54
When/why start a GLP1 agonist?

When:
- As soon as possible, and continue if tolerated. Cost is primary barrier.

Why:
- Obesity, progressive weight gain on insulin, synergy with SGLT2.
- Some patients can be weaned off insulin.
Dual insulin-GLP1 injected therapies
Clinical contexts: dual insulin-GLP1 therapy

Conceptual Underpinnings
• Insulin causes weight gain.
• GLP1 agonists may offset weight gain.
• GLP1 agonists may enhance insulin action through effects to delay gastric emptying, decrease glucagon secretion, and increase blood flow to muscle.
• Fixed ratio of Insulin to GLP1 agonist; primarily dosed according to insulin units.
• Capable of titration by patients at home (cruise-control) based on AM BG

Available agents
• Xultophy -- Degludec insulin 100U/ml and Liraglutide 3.6 mg/mL (daily)
• Soliqua– Glargine 100U/ml and Lixisenatide 33 mcg/mL (daily)
Long-acting insulin and GLP-1 Agonists Synergize in T2DM

DUAL II Study:
Weight loss 2.7 kg with IDegLira vs. 0 kg with Degludec alone
Parting Thoughts
Dealing with Payors: Step Therapy Requirements
One Approach to Step Therapy

Metformin +/- SU → Metformin +/- SU + DPP-IV (gliptin) → Metformin +/- SU + DPP-IV (gliptin) + Pioglitazone

Alternate insulin regimens:
- Single meal fixed dose insulin
- 70/30 insulin AM and Dinner

Metformin +/− SU

Metformin +/− SU + DPP-IV (gliptin)

Metformin +/− SU + DPP-IV (gliptin) + Pioglitazone

Metformin +/− SU + DPP-IV (gliptin) + Pioglitazone + SGLT2 Inhibitor

Metformin +/− SU + DPP-IV (gliptin) + Pioglitazone + SGLT2 Inhibitor + GLP1 Agonist

Metformin +/− SU + DPP-IV (gliptin) + Pioglitazone + SGLT2 Inhibitor + GLP1 Agonist

Metformin (d/c DPP-IV & SU) + Long Acting Insulin (d/c DPP-IV & SU)

Metformin (d/c DPP-IV & SU) + Long Acting Insulin (d/c DPP-IV & SU) + Pioglitazone (d/c Pioglitazone)
Questions?