Effective Use of Insulin in the Primary Care Practice: Insulin Therapy Initiation, Intensification, and the Utilization of Non-insulin Therapies with Insulin

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T2DM and Need for Insulin

UKPDS: at 6 years, more than 50% of patients need insulin to reach target (FPG ≤6.0 mmol/L)

When To Start Insulin in T2DM

- When combination oral/injectable agents become inadequate
- Unacceptable side effects of other agents
- Patient with advanced hepatic or renal disease
- Special circumstances (eg, steroids, infection, pregnancy)
- Patient with hyperglycemia in the hospital
- “Severely” uncontrolled diabetes*

*Defined as FPG >250 mg/dL, random glucose >300 mg/dL, A1C >10%, ketonuria, or symptomatic (polyuria, polydipsia, and weight loss) by ADA 2009 Consensus Statement.

After glucose is controlled, oral agents can be added and insulin withdrawn if preferred.


FDA-approved Insulins for Subcutaneous Injection

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Insulin Pharmacokinetics

Rypins S, J Fam Pract. 2007;56(suppl 1):S1-S12.
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**Insulin Therapy in T2DM**

<table>
<thead>
<tr>
<th>Complexity</th>
<th>Basal Insulin only</th>
<th>1 mealtime insulin(a)</th>
<th>2 mealtime insulin(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: (a) Includes an analog or a new insulin. (b) Includes a full dose of intermediate-acting insulin included with a short-acting insulin. (c) Lipids, adipose, or glucagon peak acting medication. (d) 75%/25% or 50%/50% NPH/regular mix, or 75%/25% regular mix.

**Physiologic Insulin Secretion**

- **Basal**
- **Prandial**

- **Breakfast**
- **Lunch**
- **Dinner**

**Basal Only Insulin Therapy**

- Long (glargine, detemir)

**Treat-to-Target Trial**

- **Change of FPG over 24 Weeks**
  - Glargine: 117, 130 mg/dL

- **Change of A1C over 24 Weeks**

- **Hypothetical Barriers to Insulin Use**

  **Patient Barriers**
  - Fear of injections
  - Fear of hypoglycemia
  - Fear of weight gain
  - Insulin need = "severe diabetes"

  **Solutions**
  - Improved comfort & convenience
  - Severe hypoglycemia rare
  - Weight gain seen with most Rx
  - Glucose lowering is the KEY

  **Provider Barriers**
  - Insulin is athropgenic
  - Concerns over starting, and follow-up of insulin
  - Complexity of use, adjustments

  **Solutions**
  - NOI – DIGAMI, UKPDS, DCCT
  - Improved devices, insulin – use of patient self-management education
  - Simplify regimens, dosing
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**Patient- vs Physician-adjusted Basal Insulin**

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Baseline</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-adjusted</td>
<td>8.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Physician-adjusted</td>
<td>8.9</td>
<td>7.9</td>
</tr>
</tbody>
</table>

**Incidence of Hypoglycemia**

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Patient-adjusted</th>
<th>Physician-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>2.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>29.7</td>
<td>30.5</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>41</td>
<td>32</td>
</tr>
</tbody>
</table>

Patients can be safely instructed to adjust their insulin dose. (Davies M, et al. Diabetes Care. 2005;28:1282-1288.)

**Premixed (Biphasic) Insulin Analogues**

- Premixed insulins:
  - 75% insulin lispro protamine suspension/25% insulin lispro injection
  - 50% insulin lispro protamine suspension/50% insulin lispro injection
  - 70% insulin aspart protamine suspension/30% insulin aspart injection
  - 70% human insulin isophane suspension/30% human insulin injection
  - 70% NPH, human insulin isophane suspension/30% regular, human insulin injection

- Premixed insulin may be appropriate:
  - When basal/bolus cannot be used
  - For those with regular lifestyles who eat similar amounts at similar times each day (similar total calories and similar content for carbohydrate/fat/protein)
  - Those who wish only 2 injections/day

**The INITIATE Trial: A Comparison of Basal Insulin and Biphasic Insulin Analog Therapy**

- N: 233 patients with T2DM
- A1C >8% (insulin-naive)
- OAD failures on MET ≥1000 mg/dL
- Target FPG: 80-110 mg/dL

**The 1-2-3 Study: Dosing of Biphasic Insulin**

- Phase 1: 68 subjects
  - Twice Daily
  - 28 completed
  - A1C ≤6.5%
  - Pre-dinner × 16 wks
  - Start with 12 U at dinner
  - Add 3 U at bedtime if FPG >110

- Phase 2: 25 subjects
  - Thrice Daily
  - 25 completed
  - A1C ≤6.5%
  - Pre-breakfast & dinner × 16 wks
  - Add 6 U at breakfast if FPG >110

- Phase 3: 100 subjects
  - Daily
  - 21 completed
  - If A1C >6.5%, go to thrice daily

**The INITIATE Trial: Biphasic Insulin Analog Therapy Resulted in Greater Reductions in A1C than Basal Insulin Analog Therapy**

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Baseline</th>
<th>20 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic insulin aspart twice daily</td>
<td>9.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Insulin glargine once daily</td>
<td>5.9</td>
<td>7.4</td>
</tr>
</tbody>
</table>

**When Is Basal Alone Not Enough?**

- When A1C values are still not at target AND...
  - Basal insulin dose titrated to 0.4-0.6 units/kg/day
  - Fasting BG levels at or approaching target
  - Post-prandial BG values remain above target

**How to Intensify Using the Basal Plus Approach**

- Choose the "target" meal to initiate prandial coverage:
  - Breakfast or the largest meal of the day
- Start 4-6 units of a rapid-acting insulin analog:
  - 10-15 minutes before the meal
- Adjust prandial insulin dose based on:
  - 2-3 h PPG → target <180 mg/dL
  - Next pre-prandial or HS BG → target <130 mg/dL
- If A1C remains above target add 2nd prandial dose:
  - Usually need about 8-12 units of prandial insulin to cover meal(s)

**Requirements of Multi-dose Insulin Therapy**

- Requires understanding of insulin action:
  - Basal-bolus therapy – generally 50% basal/50% bolus
- Critical role of patient education:
  - Nutrition education – Carbohydrate counting
  - Understand insulin action times, dosing
  - Emphasize need for frequent monitoring
- Pattern control:
  - Daily insulin adjustments, modification based on BG patterns
  - Correlation factor – what does an extra unit do for me?
  - Impact of exercise

**Simple Algorithm for Basal-bolus Approach**

<table>
<thead>
<tr>
<th>Insulin Glargine Adjustments: Both Groups</th>
<th>Insulin Glulisine Adjustments: Simple Algorithm Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of last 3-day fasting SMBG mg/dL</td>
<td>Adjustment</td>
</tr>
<tr>
<td>&lt;180 mg/dL</td>
<td>Increase 6 units</td>
</tr>
<tr>
<td>140-180 mg/dL</td>
<td>Increase 4 units</td>
</tr>
<tr>
<td>120-140 mg/dL</td>
<td>Increase 2 units</td>
</tr>
<tr>
<td>95-120 mg/dL</td>
<td>No change</td>
</tr>
<tr>
<td>&lt;95 mg/dL</td>
<td>Decrease by the same number of units as the insulin dose</td>
</tr>
</tbody>
</table>

**Mimicking Physiologic Insulin Secretion: Basal-bolus Insulin Therapy**

- Endogenous insulin
  - Basal insulin
  - Bolus insulin

**Simple vs Complex Algorithm for Basal-bolus Approach**

- 273 intent-to-treat patients where randomized to either a simple algorithm or a complex algorithm
- A1C was measured after 24 weeks

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Δ from BL A1C</th>
<th>% reaching A1C &lt;7.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>-1.46</td>
<td>73.2</td>
</tr>
<tr>
<td>Complex</td>
<td>-1.59</td>
<td>69.2</td>
</tr>
</tbody>
</table>

There were no significant differences in A1C reduction or A1C goal attainment found between the two groups

**Hypoglycemia Management**

- At-risk patients: Ask about symptomatic and asymptomatic hypoglycemia at each encounter
- Personalized treatment glucose 15-20 g
  - After 15 min of treatment, repeat if hypoglycemia continues (per SMBG)
  - When SMBG normal, patient should consume meal or snacks to prevent recurrence

**Hypoglycemia unawareness or episode of severe hypoglycemia**

- Familiarize treatment regimen
- Insulin-treated patients: set glycemic targets for several weeks to partially reverse hypoglycemia unawareness and reduce recurrence

**Low or declining cognition**

- Continuously assess cognitive function with increased vigilance for hypoglycemia
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**Summary of Comparative Insulin Trials**

- Any insulin will lower glucose and A1C; the more injections, the better titration, and the higher the dose, the better the control.
- All insulin use results in weight gain and increases the risk of hypoglycemia.
- Generally, insulin analogs reduce the incidence of hypoglycemia over human insulins but generally do not result in better overall glycemic control.
- Insulin strategies that include prandial dosing (e.g., basal-bolus; premixed) will generally reduce A1C to a greater extent than basal-only, but at the expense of more weight gain, hypoglycemia.

**Strategies for Insulin Selection**

- Convenience (once daily vs twice or three times daily)
- Proven safety:
  - Analogs – ORIGIN study showed low hypoglycemic risk, no adverse CV effects, and no cancer risk
  - NPH – a little more hypoglycemic risk than analogs
- Cost:
  - NPH $;
  - Analogs $$$$$
- Insurance coverage:
  - Analogs – coverage varies and may require prior authorization

**Potential Non-insulin Therapies To be Combined with Insulin**

- Metformin
- TZDs
- Pramlintide
- DPP-4 inhibitors
- SGLT2 inhibitors
- GLP-1 receptor agonists

**Metformin Plus Insulin: A1C Reduction**

- Table showing percentage reduction in A1C with different combinations of Metformin and Insulin.
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### SGLT2 Inhibitors Plus Insulin

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Background Therapy</th>
<th>Intervention</th>
<th>Δ From BL</th>
<th>A1C (%)</th>
<th>Δ From BL</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devarahanti D et al</td>
<td>28 days</td>
<td>Insulin + 1 OAD</td>
<td>100 mg canagliflozin QD</td>
<td>-0.73</td>
<td>-0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>300 mg canagliflozin BID</td>
<td>-0.92</td>
<td>-1.19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Not considered statistically significant.


### GLP-1 RA Plus Insulin

**Promotes satiety and reduces appetite**

**β cells: Enhance glucose-dependent insulin secretion**

Liver: ↓ glucagon reduces hepatic glucose output

Stomach: Helps regulate gastric emptying

**GLP-1 RA + Insulin Options**

- Dist, exercise, weight loss, oral agents
  - + GLP-1 RA
  - + Insulin

- Dist, exercise, weight loss, oral agents
  - + Insulin
  - + GLP-1 RA

### Potential Benefits of Combining GLP-1-based Therapies with Insulin

**GLP-1-based therapies**

- Insulin secretion (glucose-dependent)
- β cell preservation
- Glucagon secretion (glucose-dependent)
- Risk of hypoglycemia
- Body weight
- PPG levels
- Energy intake
- Safety
- GI tract motility

**Basal insulin therapy**

- Insulin levels (insulin supplementation)
- β cell rest
- Corrects glucotoxicity

- Relaxes endogenous prandial insulin response
- Moderate risk of hypoglycemia
- Weight gain
- FPG levels

### Insulin/GLP-1 Combos

- Dist, exercise, weight loss, oral agents
  - + GLP-1 RA + Insulin

### Exenatide Added to Basal Glargine

- Screening
- Randomization
- Study End

- 5 μg EXE
- 10 μg EXE

- Insulin Glargine + OADs
- Insulin Glargine + OADs + PLB BID
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Exenatide Added to Basal Glargine

Exenatide Added to Basal Glargine: Side Effects

MET + LIRA + Insulin Detemir

Liraglutide with Basal Insulin Over 38 Weeks

Insulin Degludec + Liraglutide Combination

Inclusion criteria:
- T2DM
- Insulin-naïve, treated with metformin + pioglitazone
- A1C 10-10.9%
- BMI 25-40 kg/m²
- Age 18-80 years

Patients with T2DM (n=163)

Mean Fasting PG | Dose Change
---|---
<72 | Med-Low
72-100 | Low
>100 | High

*Patient algorithm: Eligible for and Eligible for DM2 or T2DM, age 40-75 years. Base J. Presented at the 75th American Diabetes Association Scientific Sessions, June 25, 2019, Chicago, IL.
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**IDeg + LIRA Combination: Glycemia**

<table>
<thead>
<tr>
<th>A1C Over Time</th>
<th>FPG Over Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (weeks)</td>
<td>Time (weeks)</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>FPG (mg/dL)</td>
</tr>
<tr>
<td>LIRA (n=414)</td>
<td>LIRA (n=414)</td>
</tr>
<tr>
<td>8.5</td>
<td>153</td>
</tr>
<tr>
<td>8.0</td>
<td>135</td>
</tr>
<tr>
<td>7.5</td>
<td>117</td>
</tr>
<tr>
<td>7.0</td>
<td>99</td>
</tr>
<tr>
<td>6.5</td>
<td>82</td>
</tr>
<tr>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>∆A1C</td>
<td>∆FPG</td>
</tr>
<tr>
<td>-1.28%</td>
<td>32 mg/dL</td>
</tr>
<tr>
<td>EOT</td>
<td>131 mg/dL</td>
</tr>
</tbody>
</table>

Mean values (±SEM) based on FAS and LOCF-imputed data.

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ADA/EASD A1C target <7.0%. AACE A1C target ≤6.5%.

**IDeg + LIRA Combination: Body Weight and Hypoglycemia**

<table>
<thead>
<tr>
<th>Change in Body Weight Over Time</th>
<th>Confirmed Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (weeks)</td>
<td>Time (weeks)</td>
</tr>
<tr>
<td>Change in Body Weight Over Time (kg)</td>
<td>LIRA (n=414)</td>
</tr>
<tr>
<td>LIRA (n=414)</td>
<td>0.0</td>
</tr>
<tr>
<td>IDeg (n=413)</td>
<td>-2.44 kg P=.0001</td>
</tr>
<tr>
<td>IDeg+LIRA (n=833)</td>
<td>-2.22 kg P=.0001</td>
</tr>
<tr>
<td>Mean values based on SAS.</td>
<td>Rate ratio: 0.68 P=.002</td>
</tr>
<tr>
<td>Estimated rate ratio and P-values are from a negative binomial model.</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions**

- In patients with T2DM, treating the multiple defects (insulin resistance plus insulin deficiency) can improve A1C levels
- Options include adding metformin, DPP-4 inhibitors, GLP-1 RAs, pramlintide, TZDs and potentially SGLT2 inhibitors
- Must adjust the dose of insulin in order to avoid hypoglycemia when adding some of the non-insulin agents