Case 4

History

- Age: 58
- Type 2 diabetes duration: 10 years
- Co-morbid conditions: Hypertension, hypercholesterolemia
- Ex-smoker (quit 5 years ago)
- He is able to manage once daily basal insulin therapy and is willing to add more injections

Current treatment:
Insulin glargine 36 IU at bedtime, metformin 1g bid and SGLT2 inhibitor

*Hypothetical patient profile.*
Case 4

Physical examination

- BP: 148/94 mmHg
- Pulse: 78 bpm
- BMI: 25 kg/m²
- Weight: 70kg
- No signs of heart failure
Investigations:

- SMBG, values in mmol/L (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>Pre-lunch</th>
<th>Pre-dinner</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.7 (103)</td>
<td>7.7 (139)</td>
<td>9.0 (162)</td>
<td>8.5 (153)</td>
</tr>
</tbody>
</table>

- HBA1c: 10.0 %
- ECG normal
- Total cholesterol: 5.0 mmol/L (194 mg/dL)
- LDL cholesterol: 3.1 mmol/L (120 mg/dL)
- HDL cholesterol: 1.2 mmol/L (46 mmol/dL)
- TG: 1.8 mmol/L (159 mg/dL)
Meal pattern as seen in the patient diary:

<table>
<thead>
<tr>
<th>Day</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Tea-time</th>
<th>Dinner</th>
<th>Supper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>Fried noodles</td>
<td>-</td>
<td>2 toast bread with jam</td>
<td>Rice with chicken curry</td>
<td>Hot drink</td>
</tr>
<tr>
<td>Tuesday</td>
<td>Sandwich</td>
<td>Vermicelli soup</td>
<td>Coffee &amp; Biscuits</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Wednesday</td>
<td>Yogurt</td>
<td>Soup and salads</td>
<td>Coffee &amp; biscuits</td>
<td>Fried noodles</td>
<td>Hot drink</td>
</tr>
<tr>
<td>Thursday</td>
<td>Fried rice</td>
<td>Pasta</td>
<td>Sandwich</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Friday</td>
<td>Rice with beef</td>
<td>-</td>
<td>Coffee and sandwich</td>
<td>Stake</td>
<td>-</td>
</tr>
<tr>
<td>Saturday</td>
<td>Sandwich</td>
<td>Fried rice</td>
<td>Cakes</td>
<td>Pasta</td>
<td>Hot drink</td>
</tr>
<tr>
<td>Sunday</td>
<td>Cereals</td>
<td>Fried noodles</td>
<td>Biscuits</td>
<td>Rice with beef</td>
<td>Hot drink</td>
</tr>
</tbody>
</table>
Why choose the stepwise basal-bolus intensification approach for Mr. Ahmed?

- Irregular meal-times & lifestyle of patient
- Higher education level and able to institute multiple injections
- Achieve tighter glycaemic control
- More advance disease or duration of diabetes

Glargine plus mealtime lispro
Practical suggestions when managing patients like Mr. Ahmed

Counselling tips for starting patients on the Humalog self-titration algorithm are:

- Review the benefits of using the titration tool with patients
- Continue as usual on diet and exercise (carbohydrate counting not needed as shown in the study†)
- Add 1 Humalog injection at largest meal and proceed with stepwise titration
- Review proper injection techniques, etc.

For many T2DM patients failing to achieve glycaemic control on basal insulin alone:

Stepwise addition of Humalog to insulin glargine provides incremental improvements in glycaemia.

Hypoglycaemia and weight gain are potential adverse events that patients need to be aware about.

Insulin intensification can be made practical through application of simple patient tools.
MANAGEMENT OF HYPERGLYCEMIA with Insulin Lispro

INSULIN LISPRO (rDNA origin)
Rapid Acting Insulin Analogues
Structure of Rapid-acting Insulin Analogues

Insulin Monomers
This is the active form of Insulin that circulates in blood and binds to the insulin receptor

Insulin Hexamers
Composed of 6 monomers
These are the storage form of insulin both in the β-cell and in insulin vials

Insulin analogues are associated with:

- Less hypoglycemia\(^1,2\)
- Less weight gain\(^1,2\)
- Lower HbA1c\(^1,2\)
- Better PPG and FPG control\(^1,2\)

HbA1c = glycated hemoglobin  
PPG = post-prandial plasma glucose  
FPG = fasting plasma glucose

With Insulin Lispro, 2-hour PPG excursions were:

53%*

lower

Compared with Regular Human Insulin

Hypoglycemia Rates
Lower nocturnal hypoglycemic episodes\(^1\) and rates \(^2,3\)

Mean number of episodes/patient/30 days

- Regular Human Insulin: 0.73
- Rapid-Acting Analogue Insulin Lispro (Humalog®): 0.47

*36%*\(^*\) difference

Insulin lispro has significantly lower nocturnal hypoglycemia episodes compared with Regular Human Insulin (p<0.001)

Rates of symptomatic nocturnal hypoglycemia per patient-year [mean (SD)]

- Insulin Glulisine: 12.8
- Insulin Aspart: 9.66
- Insulin Lispro: 9.48

Insulin lispro has significantly lower nocturnal hypoglycemia episodes compared with Insulin Glulisine (p<0.001)

Findings from a randomized crossover study considered to be of clinical importance, showed Insulin Lispro* to have:

1. **More rapid absorption**
   \[(P=0.01)\]

2. **Faster peak concentration**
   \[(P=0.01)\]

3. **Faster reduction from peak to 50% maximum concentration**
   \[(P=0.01)\]

*compared to Insulin Aspart

Insulin Lispro (rDNA) origin (Humalog®) offers excellent pharmacodynamic properties similar to other rapid-acting insulins for a wide range of patients.1

Insulin Lispro (rDNA origin) [Humalog®]
HbA1c Reduction

Reduces HbA1c of patients with T1DM and T2DM (on CSII and MDI):

**Greater reduction of HbA1c**
-0.62% ± 0.13%

Compared with REGULAR HUMAN INSULIN (using CSII for T1DM)

**Non-inferior efficacious reduction of HbA1c**

NIM< 0.4%
95% CI (-0.002, 0.210)

Compared with INSULIN ASPART (using CSII for T2DM)

**Efficacious glycemic control with similar HbA1c reductions**

NIM< 0.4%
95% CI (-0.09, 0.10)

Compared with INSULIN GLULISINE (using MDI for T1DM)

CSII = Continuous Subcutaneous Insulin Infusion, MDI = Multiple Daily Injections; NIM = Non-inferiority margin

Structure of Rapid-acting Insulin Analogues

(1) Insulin lispro (rDNA origin) [Humalog®][Package Insert]; Eli Lilly and Company, 2015
(2) Insulin aspart (NovoLog®)[Package Insert]; Novo Nordisk, 2015
(3) Insulin glulisine (Apidra®)[Package Insert]; Sanofi, 2008
Time-action Profile of Rapid-acting Insulin Lispro versus Regular Human Insulin

Insulin lispro: serum insulin levels (ng/mL) after subcutaneous injection in healthy volunteers (n=10)

Insulin Lispro (rDNA origin) [Humalog®]

First insulin analog &
First rapid-acting analog developed
and commercialized\(^1\)

Mimic pattern of endogenous
pancreatic insulin secretion\(^1\)

Indicated for normal glucose control
for patients requiring insulin\(^2\)

---

2. Insulin Lispro (Humalog Kwikpen 100U/ml) Package Insert, Philippines. PV8110PLP.
Basal Insulin Is Sometimes Not Enough for Patients to Reach Their HbA$_{1c}$ Goal of $<7\%$

- Percentage of patients above target HbA$_{1c}$ ($<7\%$) after 6 months of therapy with once-daily insulin glargine.
Basal-plus Regimen Options for Simpler Insulin Intensification in Patients With Type 2 Diabetes Mellitus
Table of Contents

• Initiating and intensifying insulin therapy
  – Delays in initiating and intensifying insulin therapy
  – Patient and provider barriers to insulin therapy
  – Selecting insulin regimen for intensification
  – Clinical guidelines
  – Considerations for choosing an insulin regimen

• Basal-plus insulin regimens
  – Proof-of-concept studies
  – Basal-plus vs. basal-bolus regimens studies
  – Basal-plus insulin regimens studies
  – Choosing meal for first prandial injection
  – Insulin titration approach
  – Summary and conclusions

• AUTONOMY study
Importance of Glycemic Control to Prevent Diabetic Complications

- Maintaining glycemic control over long term is associated with prevention of microvascular and possibly cardiovascular complications in T2DM\textsuperscript{1-3}
- Stepwise therapy intensification is usually required to maintain glycemic control as T2DM progresses\textsuperscript{3,4}
- Modelling studies suggest increased risk of diabetes-related complications and higher costs with delayed treatment intensification to maintain glycemic control\textsuperscript{5,6}

4. Garber AJ et al. Endocr Pract 2016;22;84-113
5. Goodall G et al. BMC Endocr Disord 2009;9:19
Barriers to Initiating or Intensifying Insulin Therapy

**Patient Barriers**
- Complexity and burden of administration\(^1\)
- Fear of side effects (eg, weight gain, hypoglycemia)\(^1\)
- Fear of injections\(^1\)
- Perceived lack of diabetes control\(^2\)
- Fear diabetes is worsening\(^1,2,3\)
- Self-blame\(^2\)
- Perception of personal failure\(^3\)
- Coping difficulties\(^2\)

**Health Care Provider Barriers**
- Lack of experience with insulins\(^1,4\)
- Lack of time or support resources for patient education\(^1,4\)
- Perception that intensifying therapy is too difficult or complex\(^1,4\)
- Belief that regimens are too complicated for patients\(^1,5\)
- Unclear guidelines\(^1,4\)

---

3. Grant RW *Diab Educ* 2011;37:78-84
Overcoming Barriers to Insulin Therapy: Recommendations From ADA and EASD

• Emphasize patient-centered care with shared decision making\(^1\)
  – Treatment decisions should be made with patients and reflect their preferences, needs, and values

• Consider treatment-related barriers to patient adherence\(^2\)
  – Regimen complexity\(^1,2\) and flexibility\(^2,3\)
  – Patients’ financial resources and treatment cost\(^1,2\)
  – Patients’ attitudes and expected treatment efforts\(^1,2\)

• Avoid overly burdensome regimens\(^1\)
  – Simplifying complex treatment regimens may improve adherence\(^2,4,5\)

• Provide patients with an algorithm for self-titrating insulin doses based on SMBG\(^3\)

\(^1\) Inzucchi SE et al. *Diabetes Care* 2015;38:140-9
\(^3\) American Diabetes Association. *Diabetes Care* 2017;40(Suppl 1):S64-74
\(^5\) Garber AJ et al. *Endocr Pract* 2016;22;84-113
# Guidelines for Initiating and Intensifying Insulin Therapy

<table>
<thead>
<tr>
<th>Insulin Regimen</th>
<th>Insulin Initiation vs. Intensification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>Initiation&lt;sup&gt;1-5&lt;/sup&gt;</td>
<td>Basal insulin analogs or NPH insulin injected once or twice daily&lt;sup&gt;1-5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Basal-plus</td>
<td>Initiation and intensification&lt;sup&gt;a,1-3&lt;/sup&gt;</td>
<td>Basal insulin plus stepwise&lt;sup&gt;a&lt;/sup&gt; addition of 1-3 daily injections of rapid-acting insulin&lt;sup&gt;1-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Basal-bolus</td>
<td>Intensification&lt;sup&gt;1,4,5&lt;/sup&gt;</td>
<td>Basal insulin plus injections of rapid-acting insulin at every meal&lt;sup&gt;1,4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Premixed</td>
<td>Initiation&lt;sup&gt;4,5&lt;/sup&gt; or intensification&lt;sup&gt;2-5&lt;/sup&gt;</td>
<td>Once to thrice-daily injection of premixed biphasic insulin analogs&lt;sup&gt;2-5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>The stepwise approach for intensifying insulin therapy is recommended by the AACE/ACE, ADA, and EASD<sup>1-3</sup>

- AACE=American Association of Clinical Endocrinologists; ACE=American College of Endocrinology; ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes

Similar Efficacy With Basal-bolus and Premixed Insulin Regimens

• Two observational studies showed similar glycemic control with premixed and basal-bolus insulin regimens
  – TREAT: In this 24-month observational study mean change in HbA1c from baseline was -2.6% for premixed and -2.7% for basal-bolus
  – CREDIT: In this 4-year observational study mean change in HbA1c from baseline was -2.1% for premixed and -1.9% for basal-bolus

• Two meta-analyses of RCTs demonstrated similar efficacy and hypoglycemia rates between premixed and basal-bolus regimens for reducing HbA1c in patients initiating and intensifying insulin therapy

CREDIT=Cardiovascular Risk Evaluation in people with type 2 Diabetes on Insulin Therapy; RCT=randomized controlled trials; TREAT=TREATment factors and costs associated with insulin therapy in patients with type 2 diabetes

• Giugliano D et al. Endocrine 2016;51:417-28
Costs Associated With Insulin Therapy

- Costs of insulin therapy include insulin and costs associated with SMBG\(^1\)
- Intensive SMBG with a basal-bolus regimen has been associated with sustained reductions in HbA1c\(^2,3\)
  - ADA recommends SMBG >3 times daily for patients taking multiple doses of daily insulin
- Patients taking multiple insulin doses per day test only about once a day in real-life conditions\(^2\)
- Increased cost for basal-bolus regimens due to more intensive SMBG\(^1\) may also limit their use in some countries

Basal Bolus Intensification
For many T2DM patients failing to achieve glycemic control on basal insulin alone:

- Stepwise addition of Humalog to insulin glargine provides incremental improvements in glycemia.
- Hypoglycemia and weight gain are potential adverse events that patients need to be aware about.
- Insulin intensification can be made practical through application of simple patient tools.