The road ahead – new treatment strategies for diabetes

Shafie Kamaruddin
Consultant Physician
Friarage Hospital
South Tees NHS Foundation Trust
**OMINOUS OCTET**

- Decreased Insulin Secretion
- Increased Lipolysis
- Decreased Incretin Effect
- Increased Glucose Reabsorption
- Increased Glucagon Secretion
- Increased HGP
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction
Epidemiology of hypoglycaemia in UK

Proportion reporting at least one hypoglycaemic episode

Major hypoglycaemia

Mild hypoglycaemia

SU, sulphonylurea
The history of insulin development

- **1920**: Discovery of insulin
- **1930**: Longer acting insulins (e.g., protamine zinc)
- **1940**: Lente insulins
- **1950**: NPH insulin
- **1960**: Recombinant human insulin
- **1970**: First rapid-acting insulin analogue (lispro), followed by glulisine, aspart
- **1980**: Further rapid-acting insulin analogues (glulisine, aspart)
- **1990**: First long-acting analogue insulin glargine
- **2000**: Second long-acting analogue insulin detemir
- **2010**: Next-generation long-acting analogue insulin degludec
Cases

Options:

1) SGLT2 inhibitor

2) GLP1 agonist

3) Long acting insulin analogue
SGLT2 inhibitor
Normal renal glucose handling

Majority of glucose is reabsorbed by SGLT2 (90%)

Remaining glucose is reabsorbed by SGLT1 (10%)

Minimal to no glucose excretion

SGLT, sodium-glucose co-transporter.
A novel insulin-independent approach to remove excess glucose

Selectively inhibits SGLT2 in the renal proximal tubule
Altered Renal Glucose Control in Diabetes

Gluconeogenesis is increased in postprandial and post-absorptive states in patients with T2D

- Renal contribution to hyperglycemia
- 3-fold increase relative to patients without diabetes

Glucose reabsorption

- Increased SGLT2 expression and activity in renal epithelial cells from patients with diabetes vs normoglycemic individuals

Increased Excretion Threshold and Increased Glucose Reabsorption Exacerbates Hyperglycemia in Type 2 Diabetes (cont)

Increased Excretion Threshold and Increased Glucose Reabsorption Exacerbates Hyperglycemia in Type 2 Diabetes (cont)

Increased Excretion Threshold and Increased Glucose Reabsorption Exacerbates Hyperglycemia in Type 2 Diabetes (cont.)

SGLT2 Inhibitors Lower Renal Threshold for Glucose Excretion

![Graph showing the effect of SGLT2 inhibition on urinary glucose excretion compared to different plasma glucose levels in T2D and healthy individuals.]

SGLT2 inhibitor

• Dapagliflozin
  • 10mg
• Canagliflozin
  • 100mg, 300mg

- HbA1c reduction ~ 1%
- Weight loss ~ 3kg

• Caution:
  • Hypoglycaemia
    • SU, insulin
  • GU infection
  • Efficacy
    • eGFR>60
  • Dehydration
    • Elderly
    • Loop diuretic
    • Intercurrent illness
I have a pt who is 48 with T2DM having spent a long time on antipsychotic medication.

- HbA1c; 6.4% Mar, 7.9% Sep, 8.4% Oct
- She can’t tolerate metformin so takes gliclazide 160mg bd and vildagliptin 100mg od.
- There are no microvascular or macrovascular complications. I think we might be seeing the start of loss of pancreatic islet cell function.
- She is not heavy enough for a GLP-1 mimetic. Insulin could pose some problems as she is quite isolated.
- I have considered a SGLT-2 inhibitor and would like advice on prescribing with her other diabetes meds – do I need to reduce the gliclazide and or the gliptin?
Options

a)  Stop Vildagliptin + start GLP1 agonist + Gliclazide 80mg bd

b)  Start basal insulin od + gliclazide 160mg bd + vildagliptin 100mg od

c)  Start SGLT2 inhibitor + gliclazide 160mg bd + vildagliptin 100mg od

d)  Start SGLT2 inhibitor + gliclazide 80mg bd + vildagliptin 100mg od

e)  Start Pioglitazone 15mg + gliclazide 160mg bd + vildagliptin 100mg od
GLP1 agonist
Physiology of GLP-1 when secreted in response to food ingestion

- **Neural pathway**
  - Food ingestion → 
  - 10-15% of secreted amount leaves liver → 
  - 25% reaches liver → 
  - Liver

- **Endocrine pathway**
  - GLP-1 secretion → 
  - 100% secreted → 
  - Villus → 
  - L-cell → 
  - DPP-IV breakdown → 
  - Half-life for intact GLP-1 in plasma is 1–2 min

**Physiological effect:**
- ↓ Appetite
- ↓ Gastric motility & emptying
- ↑ Insulin
- ↓ Glucagon

Adapted from Holst J. *Physiol Rev* 2007; 87:1409-39.
The contribution of postprandial glucose to the glycaemic burden HbA1c <8%
Choice of GLP-1 receptor agonist: short acting versus long acting

The pharmacological profile and half-life of a GLP-1 receptor agonist influences its effects on postprandial and basal (fasting) glycaemia.

**SHORT ACTING**
GLP-1 receptor agonists
eg. Lixisenatide OD, Exenatide BD

**LONG ACTING**
GLP-1 receptor agonists
eg. Liraglutide OD, Exenatide OW

<table>
<thead>
<tr>
<th>Effect on FPG</th>
<th>Effect on PPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
<td>▼</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effect on FPG</th>
<th>Effect on PPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose
PPG = postprandial glucose

Fineman MS et al. Diabetes Obes Metab 2012;14:675-88
Case

65 year old man

- Semi-retired HGV driver
- 2 year history of T2DM
- HbA1c 10 %
- BMI 36 kgm²
- CKD 3, HTN, OA
- Laser eye treatment 2 weeks ago
- Under investigation for angina

Meds:

- Metformin 1gm bd
- Gliclazide 80mg bd
- Sitagliptin 100mg od
- Lisinopril 20mg od
- Simvastatin 40mg od
Options

a) Start twice daily premix insulin + Metformin

b) Continue with Metformin & Sitagliptin + increase Gliclazide to 160mg bd

c) Start Exenatide LAR OW + Metformin

d) Start basal insulin only + Metformin + Sitagliptin

e) Start basal insulin + Metformin + Sitagliptin and in 4 months if not meeting HbA1c target (<7.5%) to switch sitagliptin to Lixisenatide and continue with Metformin & basal insulin
Long acting insulin analogue
Why develop insulin analogues?

Hypoglycaemic events per patient-year

- Insulin A
- Insulin B

HbA$_{1c}$ (%)
Balancing glycaemic control vs risk of hypoglycaemia
How far have we come?

Rate of progression of retinopathy (per 100 patient-years)

Rate of severe hypoglycaemia (per 100 patient-years)

 Clinician’s dilemma

Rate of hypoglycaemia (events/100 patient-years)

Insulin analogues reduce hypoglycaemia even at high HbA$_1c$ levels

Confirmed hypoglycaemia threshold <3.6 mmol/L

Mullins et al. *Clin Ther* 2007;29;1607–19

Hypoglycaemia rate
Retinopathy risk
NPH insulin
Insulin glargine
Issues with existing insulin therapy

• Basal
  • Significant inter patient variability & day to day variability
  • Analogues such glargine and determir still has small peaks (4-10 hours)
  • 24 hour cover is not sustained especially when using smaller dose

• Bolus
  • Mismatch between insulin action and glucose absorption
  • Difficult to estimate insulin to carbohydrate ratios
Hypoglycaemic unawareness

• Hypoglycaemia unawareness is observed in at least 25% of people with type 1 diabetes and 10% of those with type 2.¹

• After 20-30 years duration of diabetes more than 50% of patients will display hypoglycaemic unawareness.¹

• This diminished ability to perceive the onset of hypoglycaemia is associated, in patients with type 1 diabetes, with²
  – twice the usual frequency of mild hypoglycaemia
  – up to a six fold greater incidence of severe hypoglycaemia

• In patients with type 2 diabetes, hypoglycaemic unawareness is associated with up to a 9-fold higher rate of major hypoglycaemia.³

Major hypoglycaemia occurs more frequently during sleep

- 36% of major episodes that occurred while awake had no warning signs
- 43% of all major episodes occurred between midnight and 08:00 am

216 participants with T1DM reported 714 episodes of major hypoglycaemia, the majority of which occurred during sleep. Major hypoglycaemia was defined as blood glucose <2.8 mmol/L requiring third-party assistance.

DCCT, Diabetes Control and Complications Trial

Insulin degludec: immediately after injection

Insulin degludec injected

Phenol from the vehicle diffuses quickly, and insulin degludec links up via single side-chain contacts

Soluble multi-hexamer chains assemble as s.c. depot

Insulin degludec: slow release following injection

Zinc diffuses slowly causing individual hexamers to disassemble, releasing monomers

Monomers are absorbed from the depot into the circulation

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

<table>
<thead>
<tr>
<th>Insulin degludec</th>
<th>Insulin glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 U/kg</td>
<td>0.4 U/kg</td>
</tr>
<tr>
<td>0.6 U/kg</td>
<td>0.6 U/kg</td>
</tr>
<tr>
<td>0.8 U/kg</td>
<td>0.8 U/kg</td>
</tr>
<tr>
<td><strong>Half-life (hours)</strong></td>
<td><strong>Mean half-life</strong></td>
</tr>
<tr>
<td>25.9</td>
<td><strong>25.4</strong></td>
</tr>
<tr>
<td>27.0</td>
<td></td>
</tr>
<tr>
<td>23.9</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td>14.0</td>
</tr>
<tr>
<td></td>
<td><strong>12.5</strong></td>
</tr>
</tbody>
</table>

*Insulin glargine was undetectable after 48 hours.

Results from patients with type 1 diabetes (T1D).

IDeg, insulin degludec; IGlar, insulin glargine.

Heise et al. Diabetologia 2011;54(Suppl. 1):S425
Flat time-action profile in type 1 diabetes at steady state

<table>
<thead>
<tr>
<th>Dose level</th>
<th>$\text{AUC}_{\text{GIR,0–12h}}$</th>
<th>$\text{AUC}_{\text{GIR,12–24h}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 U/kg</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Insulin degludec = 0.4 U/kg
Heise *et al.* *Diabetologia* 2011;54(Suppl. 1):S425
Basal–bolus in T1DM: confirmed nocturnal hypoglycaemia

Comparisons: estimates adjusted for multiple covariates


IDeg: 4.41 events/PYE
IGlar: 5.86 events/PYE

25% lower rate with IDeg, $p=0.021$
Case

• 35 yr old man
• T1DM since 2 years old
• HbA1c 9%
• Variable shifts – Tesco
• Loss driving license
  • 3 episode of severe hypo
    • 2x nocturnal
• BG testing at least twice/day
• Retionopathy & microalbuminuria

• Meds:
• Novorapid
  • CHO counting using expert meter
• Glargine 24 units nocte
  • Variable compliance
Options

a) Split glargine twice daily

b) Refer for insulin pump therapy

c) Refer for structured type 1 education eg. DAFNE

d) Switch glargine to degludec

e) Switch glargine to degludec & refer for type 1 structured education programme
Take home messages

• SGLT2 inhibitor
  • HbA1c reduction ~ 1%
  • Weight loss
  • Caution risk of dehydration

• GLP1 agonist
  • HbA1c thresholds
  • Short acting vs long acting

• Long acting insulin analogues
  • Hypoglycaemia – especially nocturnal