Type 2 diabetes: Overcoming multifaceted pathophysiology and barriers to glycaemic control

Learning objectives

You will learn:

- The difficulties associated with achieving sustained glycaemic control in patients with type 2 diabetes mellitus
- The barriers to treatment adherence posed by different diabetes therapies
- The basis of a pathophysiology-based, individualised approach for diabetes management
- Considerations for selecting a targeted combined treatment regimen and the use of a fixed-ratio combination therapy.

Unmet needs relating to the management of type 2 diabetes

In patients with type 2 diabetes mellitus (T2DM), early intensification of therapy to achieve good glycaemic control reduces the risk of both micro- and macrovascular complications. In the UK Prospective Diabetes Study (UKPDS), each 1% reduction in HbA1c was associated with a reduction in risk of 21% for any endpoint related to diabetes, 21% for diabetes-related death, 14% for myocardial infarction and 37% for any microvascular complications, with no threshold of risk observed for any endpoint.1 However, even with insulin-based regimens it is difficult to achieve sustained glycaemic control, and in everyday clinical practice glycaemic control is notoriously poor.2,3 Recent data from primary health care clinics and tertiary referral centres in South Africa indicate that the average HbA1c is around 8-9% and approximately 15% of patients achieve glycaemic targets.4-7 The 2020 CDC Diabetes Statistics Report showed that even in the USA approximately 50% of T2DM patients have HbA1c >7% and around 20% of 18-44-year-olds have HbA1c >9%.8 Diabetes treatments themselves are associated with adverse effects that reduce both compliance with and adherence to therapy, providing a barrier to achieving target HbA1c.
Hypoglycaemia and weight gain in particular are a problem, especially with the sulphonylureas and insulin. Considering that most patients with T2DM are already overweight or obese, further weight gain is both psychologically and physiologically undesirable. Treatment-related hypoglycaemic events are costly and reduce both prescription of appropriate therapy and adherence to the prescribed regimen. In an internet survey of 1 250 physicians in specialist and primary care clinics, 88% reported that many insulin-treated patients do not have adequate glucose control, but 75% admitted they do not treat as aggressively as they would like to because of concerns about hypoglycaemia.

Furthermore, complex treatment regimens reduce adherence and injected insulin regimens are viewed by patients, although sometimes unrealistically so, as highly burdensome. Specific concerns are that insulin injections may be inconvenient, will interfere with daily living and expose them to social stigma. Among a sample of 1 530 insulin-treated patients, one-third reported insulin omission/non-adherence on at least one day in the last month, with an average of 3.3 days. Number of injections required, having to take insulin at prescribed times and difficulty in adjusting doses were among the most frequent reasons patients cited for dissatisfaction with insulin therapy.

A pathophysiology-based approach to diabetes management

In contrast to the traditional algorithmic guideline approach that promotes sequential addition of antidiabetic agents as the preceding treatment regimen fails to maintain glycaemic control (‘treat to failure’), recent guidelines advocate a ‘pathophysiological’ approach using initial combination therapy with agents with complementary mechanisms of action known to correct established pathophysiological defects in T2DM. Within this latter approach, the choice of antidiabetic agents is individualised, taking into account the patient’s general health status and associated medical disorders, including age, body weight and micro- and macrovascular complications.

The interrelationship between the multiple pathophysiological mechanisms underlying diabetes is complex. At the centre is the failing pancreatic β-cell, which is common to all forms of diabetes mellitus. In addition, hepatic insulin resistance causes glucose overproduction during the basal state, despite fasting hyperinsulinaemia and impaired suppression of hepatic glucose production by insulin. Insulin resistance in muscle causes impaired glucose uptake after carbohydrate ingestion, which results in postprandial hyperglycaemia. In addition to genetic predisposition, obesity and physical inactivity, which are insulin-resistant states, place stress on the β-cells to compensate for insulin resistance by increasing insulin secretion. However, ultimately this is not sustainable and progressive β-cell failure ensues, leading to rising levels of fasting plasma glucose (FPG) and development of overt diabetes. As well as this pivotal ‘triumvirate’ of β-cell failure and hepatic and peripheral insulin resistance, at least eight other pathophysiological abnormalities contribute to glucose intolerance in T2DM:

- Insulin resistance in adipocytes causes loss of normal insulin-mediated lipolysis, leading to elevation of plasma free fatty acids and accumulation of intracellular toxic lipid metabolites in liver, muscle and β-cells, which, in turn, worsens insulin resistance and β-cell failure and apoptosis;
- Impaired secretion of glucagon-like peptide (GLP)-1 and severe β-cell resistance to the stimulatory effect of GLP-1 and glucose-dependent insulinotrophic polypeptide reduce the incretin effect;
- Increased glucagon secretion by α-cells and enhanced hepatic sensitivity to glucagon cause increased hepatic glucose production and impair suppression of hepatic glucose production by insulin;
- Upregulation of sodium glucose co-transporter (SGLT)-2 protein in the kidney causes enhanced glucose reabsorption by the renal tubules, further contributing to elevated plasma glucose;
- Resistance of the central nervous system to the anorectic effect of insulin and altered neurosynaptic hormone secretion contribute to appetite dysregulation, weight gain and insulin resistance in the liver and muscle;
- Systemic low-grade inflammation (at least in part caused by loss of the incretin effect) increases endoplasmic and metabolic stress.
Recent guidelines advocate a ‘pathophysiological’ approach using initial combination therapy with agents with complementary mechanisms of action known to correct established pathophysiological defects in T2DM.

- Changes in the gut microbiota may be instrumental in development of, and relationship between, T2DM and obesity;
- Decreased amylin levels, consequent on β-cell dysfunction, lead to accelerated gastric emptying and increased glucose absorption in the small intestine. Because the incretins slow gastric emptying, the resulting increases in postprandial glucose may be exacerbated by the loss of the incretin effect.

These 11 pathophysiological pathways have been dubbed ‘The Egregious 11’ (Figure 1).

Selecting a combined treatment regimen

The ideal treatment approach to T2DM would be one that uses the least number of medications possible to target the greatest number of these mediating pathophysiological pathways active in an individual patient (Table 1). Notably, combination therapy containing insulin degludec and a GLP-1 receptor agonist (GLP-1RA) addresses 10 out of 11 of these pathways. At present, the only available therapy for T2DM that directly addresses renal tubular glucose absorption are the SGLT-2 inhibitors (SGLT-2is), which are also associated with important improvements in renal function over the longer term. Because it is central to the pathophysiology of T2DM, treatment should not be potentially detrimental to the long-term integrity of the β-cell. Sulphonylureas and glinides are associated with increased risk of hypoglycaemia, weight gain and β-cell exhaustion, are best avoided.

Additional considerations when selecting a treatment regimen are its ability to achieve and sustain blood glucose target levels, associated risks for adverse events (primarily avoidance of hypoglycaemia and weight gain), and potential to reduce diabetes-related cardiovascular morbidity and mortality (Table 2). Of all the current treatment options for T2DM, only two, the SGLT-2is and GLP-1RAs (in particular liraglutide), have so far been shown to improve cardiovascular outcomes (in patients with and without established cardiovascular disease). Both also have a low risk of hypoglycaemia and promote weight loss. Consequently, they are recommended as second-line agents of choice in patients with T2DM and cardiovascular risk and where there are compelling reasons to avoid hypoglycaemia and/or weight gain (Table 3).
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The ideal treatment approach to T2DM would be one that uses the least number of medications possible to target the greatest number of these mediating pathophysiological pathways active in an individual patient.

Table 1. Targeted treatments for the multiple pathophysiological pathways in T2DM15

<table>
<thead>
<tr>
<th>Pathophysiological pathway</th>
<th>Metformin</th>
<th>SU</th>
<th>DPP-4i</th>
<th>SGLT-2i</th>
<th>GLP-1RA</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic β-cells</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓*</td>
</tr>
<tr>
<td>Incretin effect</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Pancreatic α-cell</td>
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<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin resistance: adipose</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Insulin resistance: muscle</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin resistance: liver</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon/biome</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune dysregulation/inflammation</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach/small intestine</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DPP-4i: dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT-2i: sodium glucose co-transporter-2 inhibitor; SU: sulphonylurea
*Pancreas-sparing

Table 2. Summary of key benefits and risks associated with diabetes treatments20-23

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Metformin</th>
<th>SU</th>
<th>DPP-4i</th>
<th>SGLT-2i</th>
<th>GLP-1RA (liraglutide)</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postprandial glucose lowering</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Fasting glucose lowering</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Cardiovascular benefit: ASCVD</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>✓</td>
<td>✓</td>
<td>↔</td>
</tr>
<tr>
<td>Cardiovascular benefit: Heart failure</td>
<td>↔</td>
<td>↔</td>
<td>!</td>
<td>✓</td>
<td>✓ / ↔</td>
<td>↔</td>
</tr>
<tr>
<td>Renal benefit</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>✓</td>
<td>✓ / ↔</td>
<td>✓ / ↔</td>
</tr>
<tr>
<td>Adverse effects/risks</td>
<td>↔</td>
<td>++/++</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>++/+++</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>↔</td>
<td>++/+</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Weight change</td>
<td>↓</td>
<td>↑+</td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
<td>↑+</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>++</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>++</td>
</tr>
</tbody>
</table>

a. Basal insulin; b. Basal bolus regimens; c. Basal insulin and basal bolus regimens
↔ ↔ Neutral; ↓ Decrease; ↑ Increase; + Mild; ++ Moderate; +++ Marked/Severe; !: Potential risk
ASCVD: Atherosclerotic cardiovascular disease; DPP-4i: dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT-2i: sodium glucose co-transporter-2 inhibitor; SU: sulphonylurea
Type 2 diabetes: Overcoming multifaceted pathophysiology and barriers to glycaemic control

Fixed-ratio combination therapy with IDegLira

IDegLira is a fixed-ratio combination of the ultralong-acting, once-daily basal insulin analogue, degludec (IDeg), and the GLP-1RA, liraglutide, addresses 10 of the 11 T2DM pathophysiological pathways. Each dose step of IDegLira contains 1 unit IDeg and 0.036mg liraglutide, with recommended starting doses of 10 dose steps for patients uncontrolled on oral antihyperglycaemic drugs (OADs) and 16 dose steps for those uncontrolled on basal insulin or GLP-1RA. 

IDeg and liraglutide have both complementary and synergistic actions. IDeg differs from other basal insulins in that, after injection, it forms a depot of multihexamers from which monomers slowly and continuously dissociate, providing a constant and stable blood glucose-lowering profile over each 24-hour dosing interval. The day-to-day pharmacodynamic variability of IDeg is approximately 40% lower than that associated with insulin glargine (IGlar), conferring a significantly lower risk of overall and nocturnal hypoglycaemia. In combination with liraglutide, the basal insulin provides potent reduction of FPG, while the glucose-dependent mechanism of action of the GLP-1RA reduces postprandial excursions. In addition, clinical trials have shown that combining IDeg with liraglutide further reduces the risk of adverse effects and regimen complexity that might affect adherence to therapy (Figure 2). It is administered once a day in a single pen device and is simple to titrate based on the average of three fasting blood glucose measurements. In comparison with alternative insulin regimens, this reduces both the number of daily injections and finger pricks required for self-monitoring of blood glucose. In the DUAL clinical trial programme, IDegLira has been extensively studied across a diverse spectrum of T2DM patients, including those with inadequate glycaemic control with OADs, maximum dose GLP-1RA (plus OADs) or basal insulin (Table 4).
Type 2 diabetes: Overcoming multifaceted pathophysiology and barriers to glycaemic control

IDegLira is a fixed-ratio combination of the ultralong-acting, once-daily basal insulin analogue, degludec (IDeg), and the GLP-1RA, liraglutide, which, in combination with metformin, addresses 10 of the 11 T2DM pathophysiological pathways.

Table 4. Summary of clinical studies of IDegLira

<table>
<thead>
<tr>
<th>Trial</th>
<th>HbA1c (%)</th>
<th>Body weight (change from baseline, kg)</th>
<th>Hypoglycaemia (events/subject-year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Study end</td>
<td>Change</td>
</tr>
<tr>
<td>Add to OAD(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUAL I ext.27</td>
<td>8.3</td>
<td>6.4</td>
<td>−1.9</td>
</tr>
<tr>
<td>DUAL IV22</td>
<td>7.9</td>
<td>6.4</td>
<td>−1.5</td>
</tr>
<tr>
<td>DUAL VI133</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1WT</td>
<td>8.2</td>
<td>6.1</td>
<td>−2.0</td>
</tr>
<tr>
<td>2WT</td>
<td>8.1</td>
<td>6.0</td>
<td>−2.0</td>
</tr>
<tr>
<td>DUAL VIII10</td>
<td>8.4</td>
<td>6.4</td>
<td>−1.99</td>
</tr>
<tr>
<td>DUAL IX14</td>
<td>8.2</td>
<td>6.3</td>
<td>−1.9</td>
</tr>
<tr>
<td>GLP-1RA switch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUAL III15</td>
<td>7.8</td>
<td>6.4</td>
<td>−1.3</td>
</tr>
<tr>
<td>Basal insulin switch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUAL II28</td>
<td>8.7</td>
<td>6.9</td>
<td>−1.9</td>
</tr>
<tr>
<td>DUAL V29</td>
<td>8.4</td>
<td>6.6</td>
<td>−1.8</td>
</tr>
<tr>
<td>DUAL VII131</td>
<td>8.2</td>
<td>6.7</td>
<td>−1.5</td>
</tr>
</tbody>
</table>

1WT: Dose titration once a week; 2WT: Dose titration twice a week.

The DUAL VIII study compared IDegLira with IGlar U100 in insulin-naïve patients.30 Those treated with IDegLira had a significantly longer time until dose intensification was required and fewer patients in the IDegLira group needed treatment intensification over 104 treatment weeks than those in the IGlar U100 group. In comparison with IGlar, significantly more patients receiving IDegLira achieved HbA1c <7% with no hypoglycaemia and no weight gain.

Figure 2. Rationale for combining a GLP-1RA and basal insulin in one pen.
In the DUAL VII study, IDegLira was compared with a basal bolus regimen of IGlar plus insulin aspart in patients who had been uncontrolled on basal insulin. Overall, after 26 weeks of treatment, the mean HbA₁c was 6.7% in both groups. However, in the IDegLira group, this was achieved with less than half the total daily insulin dose required in the basal bolus group (40.4 units vs 84.1 units; P<0.0001), with no weight gain (-0.9kg vs +2.9kg; p<0.0001) and 92% lower rate of nocturnal severe or blood glucose-confirmed symptomatic hypoglycaemia (rate ratio 0.08; p<0.0001). Furthermore, significantly more patients in the IDegLira group achieved HbA₁c with no hypoglycaemia and no weight gain (38.2% vs 6.4%; odds ratio 10.39; 95%CI 5.76; 18.75).

These therapeutic advantages of IDegLira, combined with the greater acceptability of once-daily dosing in one pen, independent of meals and requiring only one blood glucose measurement a day, offers significant benefits over alternative therapies for patients who require intensification of their diabetes treatment.

IDegLira: Place in therapy

Patients who may be suitable candidates for treatment with IDegLira include those who require intensification of therapy while:

1. Receiving only OADs, who are unlikely to achieve glycaemic goals with a GLP-1RA alone (e.g. HbA₁c >9%), to avoid hypoglycaemia and weight gain;
2. Not achieving glycaemic goals on basal insulin. Switching to the fixed-ratio combination may improve HbA₁c and weight while maintaining a low risk of hypoglycaemia.

Conclusion

Recognition of the complex and multifaceted pathways that play a role in the pathophysiology of T2DM highlights the importance of a carefully considered and individualised approach to diabetes management. In addition, one must remain cognisant of the factors that contribute to poor adherence and reluctance on the part of clinicians and patients to intensify therapy. Simple regimens containing agents with complementary actions, with a low risk of hypoglycaemia, weight gain and other side effects may help to overcome some of these barriers. In clinical trials, IDegLira improved glycaemic control, with a low risk of hypoglycaemia and gastrointestinal side effects, and a neutral or favourable effect on body weight. The single daily injection and easy titration schedule might improve convenience and therefore significantly improve adherence to therapy and treatment outcomes.

Key learnings

- For the T2DM patient, it is difficult to achieve sustained glycaemic control
- Diabetes treatments themselves are associated with adverse effects that reduce compliance and adherence to therapy; complex treatment regimens further reduce adherence
- Recent guidelines advocate initial combination therapy individualised to use agents with complementary mechanisms of action known to correct established pathophysiological defects in T2DM
- Ideally, the least number of medications should be used to target the greatest number of pathophysiological defects
- Current evidence on the benefits of fixed-ratio combination therapy, IDegLira, in combination with metformin; and which patients may be suitable candidates for this treatment.
References

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Type 2 diabetes: Overcoming multifaceted pathophysiology and barriers to glycaemic control


