Targeting the Underlying Pathophysiology of Type 2 Diabetes
Aim

Provide practical guidance on improving diabetes care through highlighting the need to:

• understand that insulin resistance and β-cell dysfunction are core defects of type 2 diabetes
• address the underlying pathophysiology
Type 2 diabetes

- Characterized by chronic hyperglycemia
- Associated with microvascular and macrovascular complications
- Generally arises from a combination of insulin resistance and β-cell dysfunction
What is insulin resistance?

• Major defect in individuals with type 2 diabetes
  
• Reduced biological response to insulin
  
• Strong predictor of type 2 diabetes
  
• Closely associated with obesity

What is $\beta$-cell dysfunction?

- Major defect in individuals with type 2 diabetes
- Reduced ability of $\beta$-cells to secrete insulin in response to hyperglycemia
Insulin resistance and β-cell dysfunction are core defects of type 2 diabetes

Genetic susceptibility, obesity, Western lifestyle

Insulin resistance

β-cell dysfunction

Type 2 diabetes

How do insulin resistance and β-cell dysfunction combine to cause type 2 diabetes?

Abnormal glucose tolerance

Hyperinsulinemia, then β-cell failure

Increased insulin resistance

Abnormal glucose tolerance

Hyperglycemia

IGT* = impaired glucose tolerance

*IGT = impaired glucose tolerance

Adapted from Type 2 Diabetes BASICS. International Diabetes Center (IDC), Minneapolis, 2000.
How is insulin resistance measured?

• Several methods exist, including:
  – continuous sampling of insulin/glucose\(^1\)
    • gold standard, but impractical for large-scale use
  – single measure of insulin/glucose\(^2\)
    • simple estimate from fasting insulin and glucose
    • useful for assessment on a larger scale

More than 80% of patients progressing to type 2 diabetes are insulin resistant

- Insulin resistant; low insulin secretion (54%)
- Insulin resistant; good insulin secretion (16%)
- Insulin sensitive; good insulin secretion (1%)
- Insulin sensitive; low insulin secretion (16%)

Insulin resistance – reduced response to circulating insulin

Insulin resistance

Liver: ↑ Glucose output
Muscle: ↓ Glucose uptake
Adipose tissue: ↓ Glucose uptake
Hyperglycemia
Overall, 75% of patients with type 2 diabetes die from cardiovascular disease.
Insulin resistance is as strong a risk factor for cardiovascular disease as smoking.
Insulin resistance is closely linked to cardiovascular disease.

- Present in > 80% of people with type 2 diabetes
- Approximately doubles the risk of a cardiac event
- Implicated in almost half of CHD events in individuals with type 2 diabetes

References:
Insulin resistance is linked to a range of cardiovascular risk factors

- Hyperglycemia
- Dyslipidemia
- Hypertension
- Damage to blood vessels
- Clotting abnormalities
- Inflammation

Atherosclerosis

~90% of people with type 2 diabetes are overweight or obese

How is β-cell function measured?

- β-cell function is difficult to measure and most methods are impractical for large-scale use\(^1\)

- Homeostasis model assessment (HOMA) provides a simple estimate of β-cell function\(^2\)

- Proinsulin:insulin ratio is sometimes used as a marker of β-cell dysfunction\(^1\)

Why does the \( \beta \)-cell fail?

Chronic hyperglycemia

Oversecretion of insulin to compensate for insulin resistance\(^1,2\)

Glucotoxicity\(^2\)

Pancreas

Lipotoxicity\(^3\)

High circulating free fatty acids

\( \beta \)-cell dysfunction


\(^3\) Finegood DT & Topp B. *Diabetes Obes Metab* 2001; 3 (Suppl. 1):S20–S27.
Glycemic control declines over time

- Median HbA$_{1c}$ (%)
- Years from randomization

Diet
- Sulfonylurea or insulin

6.2% upper limit of normal range

Loss of $\beta$-cell function occurs before diagnosis

Time from diagnosis (years)

-10 -9 -8 -7 -6 -5 -4 -3 -2 -1  1  2  3  4  5  6

\[ \begin{array}{cccccccc}
\text{Diagnosis} & \text{Up to 50\% loss}
\end{array} \]

Oral antidiabetic agents – do they target insulin resistance and β-cell dysfunction?
Barriers to achieving good glycemic control

Inadequate targeting of underlying pathophysiology
Primary sites of action of oral antidiabetic agents

α-glucosidase inhibitors
↓ Carbohydrate breakdown/absorption

Sulfonylureas/meglitinides
↑ Insulin secretion

Biguanides
↓ Glucose output
↓ Insulin resistance

Thiazolidinediones
↓ Insulin resistance

The dual action of thiazolidinediones reduces HbA$_{1c}$

Potential to prevent progression to type 2 diabetes in at-risk women

Troglitazone reduced progression to type 2 diabetes by > 50%

*Troglitazone is no longer available

Can thiazolidinediones delay progression from IGT to T2DM?

<table>
<thead>
<tr>
<th>Subjects (%)</th>
<th>Placebo</th>
<th>Rosiglitazone 8 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>IGT 100%</td>
<td>IGT 100%</td>
</tr>
<tr>
<td>Week 12</td>
<td>IGT 89%</td>
<td>IGT 100%</td>
</tr>
<tr>
<td></td>
<td>T2DM 11%</td>
<td></td>
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<tr>
<td></td>
<td>NGT 44%</td>
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</tbody>
</table>

Does decreasing insulin resistance decrease macrovascular complications?

<table>
<thead>
<tr>
<th>Sulfonylureas/insulin</th>
<th>Metformin</th>
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</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td><strong>Myocardial infarction</strong></td>
</tr>
<tr>
<td>21%</td>
<td>39%</td>
</tr>
<tr>
<td>Not significant</td>
<td>Significant</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td><strong>All-cause mortality</strong></td>
</tr>
<tr>
<td>8%</td>
<td>36%</td>
</tr>
<tr>
<td>Not significant</td>
<td>Significant</td>
</tr>
</tbody>
</table>

Insulin sensitizers reduce cardiovascular events in type 2 diabetes

How can diabetes care and outcomes be improved?

The Global Partnership recommends:

Address the underlying pathophysiology, including treatment of insulin resistance.