Review of Diabetes Therapies: Key Drivers of Disease Progression

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Diabetes Therapies and Disease Progression: Discussion Outline

• Disease progression in Type 2 diabetes
  – The role of beta cell function and insulin resistance
  – Clinical consequences of disease progression
    ▪ Glycemic control and treatment “failure”

• Specific therapies – effect on diabetes progression
  – Diabetes prevention vs. disease progression

• A Glimpse of the Future – Implications for Treatment
  – Early intervention and diabetes treatment response
  – Impact on the risk of complications
The Pathophysiology of Type 2 Diabetes

- Impaired Incretin Effect
- Insulin Resistance
- Relative Insulin Deficiency

Prediabetes and Type 2 Diabetes
Natural History of Type 2 Diabetes

Glucose (mg/dL)

Pre Diabetes (IFG, IGT)

Diabetes diagnosis

Postmeal Glucose

Fasting glucose

Relative amount

Insulin resistance

Incretin effect

β cell function

Years

Onset Diabetes

Kendall DM, Cuddihy, RM, Bergenstal RM © 2008 International Diabetes Center. All rights reserved
Diabetes Disease Progression: 
β cell Dysfunction and Early Hyperglycemia

Ferrannini E.  *J Clin Endocrinol Metab* 90: 493–500, 2005
Diabetes Disease Progression: Clinical Consequences

- Implications of disease progression
  - Progressive deterioration in glycemic control (UKPDS)
    - Increasing risk of complications
  - Stepped, failure-based therapeutic approach – delay in Rx

Clinical Impact of Diabetes Therapy

Diabetes Prevention and Disease Progression
# Diabetes Disease Progression: Impact of Specific Therapies

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<td>• Measures of fasting insulin</td>
<td>• Beta cell mass</td>
<td>• Prevent increase in FPG</td>
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<td>Metformin</td>
<td>• Stimulated insulin response</td>
<td>• Insulin content and mRNA</td>
<td>• Maintain or restore normal glucose response</td>
<td>• Stability of glycemic control</td>
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<td>• Limit need for added therapies</td>
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Diabetes Prevention Program (DPP)
Prevention of Diabetes

The DPP Research Group, *NEJM* 346:393-403, 2002
The STOP-NIDDM Study: Effect of Acarbose Therapy

Durability of Glycemic Control with Sulfonylurea Therapy

Intensive Treatment of Type 2 Diabetes: UKPDS

## Diabetes Disease Progression: Impact of Specific Therapies

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Thiazolidinediones

A Closer Look at β Cell Function and Diabetes Disease Progression
Effect of Early TZD Use on A1C

- Rosiglitazone (n=39)
- Pioglitazone (n=62)
- Control (n=71)

- 19/71 subjects with diabetes
- 3/101 subjects with diabetes

*P<0.001 vs. baseline;
† P<0.001 vs. rosiglitazone and pioglitazone

Durbin RJ. Diabetes, Obesity & Metabolism 6:280-285, 2004
DREAM: Investigation of Diabetes Prevention or Delay


![Graph showing the rate of new-onset diabetes or death over follow-up years for Placebo and Rosiglitazone groups.](image-url)

- **Rate of new-onset diabetes or death**
- **Follow-up (years)**
- **No. at risk**
  - Placebo: 2634, 2470, 2150, 1148, 177
  - Rosiglitazone: 2635, 2538, 2414, 1310, 217

- **60% RRR**
  - HR 0.40 (0.35–0.46)
  - *P* < 0.0001
ADOPT
Cumulative Incidence of Treatment Failure

Cumulative Incidence of Monotherapy Failure (%)

No. at risk
Rosiglitazone 1393 1207 1078 957 844 324
Metformin 1397 1205 1076 950 818 311
Glyburide 1337 1114 958 781 617 218

Rosi vs metformin, 32% RRR \( P<0.001 \)
Rosi vs glyburide, 63% RRR \( P<0.001 \)

Improved estimates of \( \beta \) cell function

ADOPT
Impact of Initial Therapy on A1C

*Significant difference rosiglitazone vs other treatment groups with Hochberg adjustment.
Durability of Glycemic Control with Thiazolidindiones

![Graph showing change in A1C (%)]

Incretin Based Therapy with GLP-1 Potential Impact on Disease Progression

Excess food intake

CNS: promotes satiety and reduction of appetite

Excess glucose production

Liver:
- ↓ glucagon reduces hepatic glucose output

Alpha cell:
- ↓ glucagon secretion post-meal

Beta cell:
- enhances glucose-dependent insulin secretion and β cell mass

Stomach:
- regulates gastric emptying

Impaired β-cell function

Glucagon excess

Rapid substrate delivery

Exenatide Improves Phasic Insulin Secretion in Type 2 Diabetes

Incretin Based Therapies and Disease Progression
Impact of Exenatide Over 3 Years

Change in A1c (%)

Change in Body Weight (kg)

Treatment (wk)

Baseline Weight: 99 kg

N = 217; Mean ± SE
Exenatide vs Glargine Over 1 Year
Impact on C-peptide Secretion During Hyperglycaemic Clamp

![Graph showing the impact of Exenatide vs Glargine on C-peptide secretion during hyperglycaemic clamp.](image)

- **Mean (SE):**
  - Exenatide
  - Glucose Bolus
  - Arginine Bolus

- **Time (min):**
  - 165
  - 180
  - 190
  - 210
  - 240
  - 260
  - 270
  - 290

- **Glucose 15 mM**

- **Ratio to baseline:**
  - P < 0.0001
  - 3.19
  - 1.31

Bunck M. *Diabetologia.* EASD 2007/2008
The Temporal Pattern of Weight Loss with Exenatide Therapy

Kendall DM et al. Diabetes 2008. ADA Annual Scientific Sessions
Impact of DPP-4 Inhibitor on Glycemic Control and Beta Cell Function

Nauck M. Diabetes Obes Metab, 2007; 9:195-205
## Impact of Type 2 Diabetes Therapy on Disease Progression: A Checklist

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A Glimpse of the Future: Implications for Clinical Care

- Early intervention and diabetes treatment response
  - Achieve and sustain glucose control
  - Legacy effect on risk of complications

- Therapeutic Options
  - Disease modification – targeting pathophysiologic defects
  - Sustain beta-cell responsiveness
  - Early combination therapy

- Limit factors that negatively impact treatment response
  - Hypoglycemia
  - Weight gain
  - Treatment tolerability and concordance
Clinical Implications of Disease Progression: The “Natural History” of Type 2 Diabetes

Early deterioration in glycemic control  
Drives the risk for complications

May limit later efforts at intensive glucose control?

Adapted from Prof. Stefano del Prato. EASD Commentary, Rome ITALY, 2008. With permission