SRI LANKA MEDICAL ASSOCIATION OF NORTH AMERICA
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PRESENTS

SLMANA EAST CHARITY BALL
ANNUAL GENERAL MEETING &
SCIENTIFIC SESSIONS
ON NOVEMBER 12TH, 2011

NEW YORK HILTON AND TOWERS
1335 Avenue of The Americas New York, NY
Targeting the Incretins System: Can it Improve Our Ability to Treat Type 2 Diabetes?

Darshi Sunderam, MD
Chief of Endocrinology
East Orange General Hospital
Age-adjusted Percentage of US Adults Who Were Obese or Had Diagnosed Diabetes

Obesity (BMI ≥30 kg/m²)

<table>
<thead>
<tr>
<th>Year</th>
<th>No Data</th>
<th>&lt;14.0%</th>
<th>14.0-17.9%</th>
<th>18.0-21.9%</th>
<th>22.0-25.9%</th>
<th>&gt;26.0%</th>
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<tbody>
<tr>
<td>1994</td>
<td>No Data</td>
<td>&lt;4.5%</td>
<td>4.5-5.9%</td>
<td>6.0-7.4%</td>
<td>7.5-8.9%</td>
<td>&gt;9.0%</td>
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<td>2000</td>
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<td>2007</td>
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Diabetes

<table>
<thead>
<tr>
<th>Year</th>
<th>No Data</th>
<th>&lt;4.5%</th>
<th>4.5-5.9%</th>
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<td>2007</td>
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</table>

Diabetes is **Costly**

$132 Billion for Total Excess U.S. Cost Attributable to Diabetes in 2002

**Costs in Millions of Dollars**

- **Indirect Costs**: $39,180
- **Medication and Supplies**: $17,516
- **Outpatient Care**: $20,130
- **Institutional Care**: $54,215

and **Deadly**

- **New Cases** – 4,100
- **Amputations** – 230 (**60% of non-traumatic amputations annually**)
- **Blindness** – 55 (**#1 cause**)
- **Kidney Failure** – 120 (**#1 cause**)
- **Deaths** – 810 - **>60% due to CVD**

*Derived from NIDDK, National Diabetes Statistics fact sheet. HHS, NIH, 2005.*
ADA Criteria for the Diagnosis of Diabetes
Diabetes Care, January 2010; 33:S62-S69

• HbA1C ≥6.5%  **OR**

• FPG ≥126 mg/dl. Fasting is defined as no caloric intake for at least 8 h  **OR**

• 2-h plasma glucose ≥200 mg/dl using 75 g glucose load  **OR**

• Random plasma glucose ≥200 mg/dl with classic symptoms of hyperglycemia or hyperglycemic crisis
Change in Nomenclature and Testing

Pre-diabetes = Increased Risk for Diabetes

- HbA1C of 5.7–6.4%
- FPG 100 mg/dl to 125 mg/dl
- 2-h 75-g OGTT 140 mg/dl to 199 mg/dl
Goal of HbA1C

What is Safe?

- Lower HbA1C decreases microvascular complications DM1 and DM2

- But, is tight control dangerous in type 2 diabetes with cardiovascular risks?
Pathophysiology
Natural History of Type 2 Diabetes

Years from diagnosis

Progressive β-Cell Failure

β-Cell function
Incretin Defect

Insulin resistance
Insulin secretion

Post-Meal glucose
Fasting glucose

Pre-diabetes
Pre-diabetes
Type 2 diabetes

β-Cell Dysfunction Begins 10 Years Prior to Diagnosis of Type 2 Diabetes

Diagram showing the decline in β-cell function over 10 years prior to the diagnosis of Type 2 Diabetes (T2DM) compared to Impaired Glucose Tolerance (IGT). The timeline is marked from -12 to 2 years before diagnosis.
Introduction to Incretin Therapy in T2DM
Functional Definition of an Incretin

- Hormone(s) released during food ingestion
- Augment insulin secretion at physiologic concentrations
- Insulinotrophic effects are glucose dependent

**Intestinal Secretion of Insulin**
Measuring the Incretin Effect: OGTT and Matched IV Infusion

Key Characteristics of Incretin Hormones Differ in Patients with Type 2 Diabetes

**GIP**

- No defect in GIP secretion
- Defective GIP response

**GLP-1**

- Reduced GLP-1 secretion
- Preserved GLP-1 response

References:

The Incretin Effect in Type 2 Diabetes
GLP-1: Effects in Humans

GLP-1 is secreted from L-cells of the jejunum and ileum.

- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying

Long-term effects in animal models:
- Increase of β-cell mass and improved β-cell function
- Improves insulin sensitivity
- Leads to a reduction of food intake

After food ingestion...

Drucker. Mol Endocrinol. 2003
GLP-1 Secretion and Metabolism

Mixed meal eaten

GLP-1 released into bloodstream and rapidly degraded by DPP-4

Remaining GLP-1 enters pancreas

Remaining GLP-1 affects other systems

• >50% of secreted GLP-1 is degraded before it reaches the general circulation
• Stimulates insulin secretion
  • Suppresses glucagon secretion
• Slows gastric emptying
• Enhances satiety and reduces food intake

Incretin-Based Therapy

GLP-1 Analog / Agonist
- Resistant to DPP4 Action
- Prolonged Duration of Action

DPP4 Inhibitor
- Prevents Native GLP-1 Breakdown
- Prolongs Duration of Action of Native GLP-1
Therapeutic Effect of GLP-1 in People with Type 2 Diabetes

- Glucose (mmol/l)
  - GLP-1 infusion
  - GLP-1 vs Saline

- C-peptide (nmol/l)
  - GLP-1 infusion
  - GLP-1 vs Saline

- Glucagon (pmol/l)
  - GLP-1 infusion
  - GLP-1 vs Saline

*P<0.05

Nauck et al. Diabetologia. 1993
Available Incretin Agents and Their Effect on A1C and Glucose Levels
GLP-1 enhancement

GLP-1 secretion is impaired in Type 2 diabetes
Natural GLP-1 has extremely short half-life

Add GLP-1 analogues with longer half-life:
• Exenatide (Byetta)
• Liraglutide (Victoza)
• Exenatide QW (Bydurion)

Injectables

Block DPP-4, the enzyme that degrades GLP-1:
• Sitagliptin (Januvia)
• Saxagliptin (Onglyza)
• Vildagliptin (Tradjenta)

Oral agents

# GLP-1 Agent Therapy

## Glycemic Effects

<table>
<thead>
<tr>
<th>GLP-1 Agents</th>
<th>A1C %</th>
<th>FPG (mg/dL)</th>
<th>PPBG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>↓ 0.8</td>
<td>↓ 10.25</td>
<td>↓ 126</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>↓ 1.0</td>
<td>↓ 26.44</td>
<td></td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>↓ 1.5</td>
<td>↓ 42</td>
<td></td>
</tr>
</tbody>
</table>

References:
- [Laneu D, Diabetes Care 2008; 31:2194-200](#)
- [Mauri M, Diabetes Med 2009; 29:784-90](#)
- [Rusn M, Lancet 2009; 374:39-47](#)
## GLP-1 Agent Therapy

### Weight Effects

<table>
<thead>
<tr>
<th>GLP-1 Agents</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>↓ 1.6 5.3</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>↓ 0.4 6.2</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>↓ 2.3 3.7</td>
</tr>
</tbody>
</table>

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References:
- Buse J, Diabetes Care 2004; 27:2628-35
- Kendall D, Diabetes Care 2006; 29:1083-91
- Delahanty R, Diabetes Care 2005; 28:1092-100
- Drucker D, Lancet 2003;372:1240-1250
- Diamant M, Lancet 2010; 375:2234-43
- Bengoechea E, Lancet 2010; 376:431-9
- Mane M, Diabetes Med 2009; 26:268-78
- Nauck M, Diabetes Care 2009; 32:84-90
- Cumber A, Lancet 2009; 373:473-81
- Zinman B, Diabetes Care 2009; 32:1594-30
Exenatide Therapy for 3 Years
Cardio-Metabolic Effects

Type 2 Diabetes Subjects (21%)
3 Year Open Label Extension: Exenatide vs Placebo

Chol LDL HDL TG SBP DBP

+24.1%

5.5% 6.9% 3.5 mm 3.3 mm

C/W Placebo

P <.0001 <.0001 <.0001 .0003 .006 <.0001

Klonoff CD, Curr Med Res Opin 2008;24:275-286
Incretin Mimetic Drugs: Safety Issues – CV Events

- Meta-analysis of 12 randomized, controlled trials
  - 12-52 weeks duration
  - Exenatide (5-10 µg bid) vs comparator (placebo or insulin)
- Patient characteristics at baseline (mean)
  - Age 56 y; BMI = 31-32 kg/m²; A1C = 8.3%-8.4%

<table>
<thead>
<tr>
<th></th>
<th>Exenatide (n=2279)</th>
<th>Comparator (n=1629)</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>1063 patient-years</td>
<td>780 patient-years</td>
<td></td>
</tr>
<tr>
<td>CV event incidence (unadjusted)</td>
<td>2.0%</td>
<td>2.6%</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>(0.46-1.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure-adjusted incidence (per 1000 patient-years)</td>
<td>43.7</td>
<td>54.4</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.53-1.22)</td>
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</tbody>
</table>

# DPP4 Therapy

## Glycemic and Weight Effects

<table>
<thead>
<tr>
<th>DPP4 Inhibitors</th>
<th>A1C (%)</th>
<th>FPG (mg/dl)</th>
<th>PPBG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>↓ 0.5 1.0</td>
<td>↓ 15 25</td>
<td>↓ 36 54</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>↓ 0.5 0.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DPP4 Inhibitors</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>No $\Delta$</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>No $\Delta$</td>
</tr>
</tbody>
</table>

Goldstein B, Diabetes Care 2007; 30:1979-87
Nauck M, Diab Obsess Metab 2007; 9:194-205
Wischull T, Diabetes Obsess Metab 2010; 12:161-77
Acute Pancreatitis
Exenatide and Sitagliptin

Retrospective Cohort Study, Claims Database (786,656 Patients)

Exenatide vs Sitagliptin vs Diabetes Controls

Pancreatitis
Exenatide
HR 0.9 (0.6, 1.3)
Sitagliptin
HR 1.0 (0.7, 1.3)

Kaplan-Meier Estimate

Days to Pancreatitis

P = 0.992

Garb R, Diabetes Care 2010; 33:2349-54
Liraglutide and Medullary Thyroid Cancer

![Graph showing calcitonin levels over time for Liraglutide 1.2 mg, Liraglutide 1.8 mg, Liraglutide 2.4 mg, Liraglutide 3.0 mg, Orlistat, and Placebo.]

- **Calcitonin**

  - Upper normal range males (8.4 ng/L)
  - Upper normal range females (5.0 ng/L)

The Journal of Clinical Endocrinology & Metabolism

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Comparison of GLP-1 Receptor Agonists and DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Effects/parameters</th>
<th>GLP-1 receptor agonists</th>
<th>DPP-4 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Subcutaneous injection</td>
<td>Oral</td>
</tr>
<tr>
<td>Dosim/timing of administration</td>
<td>Once or twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>Enhanced</td>
<td>Enhanced</td>
</tr>
<tr>
<td>Fc reduction</td>
<td>% to %</td>
<td>% to %</td>
</tr>
<tr>
<td>Osprandial hyperglycemia</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Glicagon secretion</td>
<td>Suppressed</td>
<td>Suppressed</td>
</tr>
<tr>
<td>Body weight</td>
<td>Reduced</td>
<td>Eutral</td>
</tr>
<tr>
<td>Appetite</td>
<td>Suppressed</td>
<td>No effect</td>
</tr>
<tr>
<td>Abstric emptying</td>
<td>Lowed significantly</td>
<td>No effect</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Low rates</td>
<td>Low rates</td>
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<tr>
<td>'s</td>
<td>Nausea, diarrhea</td>
<td>No significant 's</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Improved (with weight loss)</td>
<td>No consistent change</td>
</tr>
</tbody>
</table>
**Tier 1: Well-validated core therapies**

**At Diagnosis:**
- Lifestyle + Metformin

**STEP 1**
- Lifestyle + Metformin
- Lifestyle + Metformin + Basal insulin

**STEP 2**
- Lifestyle + Metformin + Sulfonylurea
- Lifestyle + Metformin + Intensive insulin

**STEP 3**
- Lifestyle + Metformin + Intensive insulin

**Tier 2: Less well validated therapies**

**Lifestyle + Metformin + Pioglitazone**
- No hypoglycemia
- Edema/CHF
- Bone loss

**Lifestyle + Metformin + GLP-1 agonist**
- No hypoglycemia
- Weight loss
- Nausea/vomiting

**Lifestyle + Metformin + Pioglitazone + Sulfonylurea**

**Lifestyle + Metformin + Basal insulin**

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Summary

• Type 2 diabetes is a progressive disease with multiple pathogenic defects.
• Therapeutic approaches based on pathophysiology with multiple agents early in the disease state.
• GLP-1 increases insulin secretion, decreases glucagon secretion in a glucose dependent manner.
• GLP-1 has an effect on beta cell, liver, alpha cell, gut and brain.
• GLP-1 analogs provide long acting activity.
  – Improve glycaemia with weight loss.
  – Reduce blood pressure with improved lipid profile.
• DPP-4 inhibitors prolong activity of native GLP-1.
  – Improve glycaemia and weight neutral.
• GLP-1 analogs and DPP-4 inhibitors are effective alone and in combination with oral agents or with insulin.
Remember

- Multiple pathogenic abnormalities
- Early diagnosis only % of beta cell function is left
- Early diagnosis and aggressive treatment
- Protect remaining beta cells
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