Current Strategies for Managing Type 2 Diabetes

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Division of Endocrinology and Molecular Medicine
• Disclosures: None

• Objectives:
  – Review current data relating glycemic control to complications
  – Review current ADA treatment goals
  – Review the landscape of antidiabetic therapies
National Diabetes Fact Sheet

- Total: 24 million - 7.9% of population
- 95% have type 2 diabetes
- Increase of 3 million in past 2 yrs
- Undiagnosed: 6 million
- Over age 60: 24% of population
- Ethnic disparities: NA 17%, AA12%, W 6.6%
- Prediabetes: 57 million: at least 33% predicted to ultimately develop diabetes
Kentucky Diabetes: “Geographic Diversity”
Diabetes: The Toll of Complications

• Complications of diabetes are a major cause of mortality and morbidity
  – >224,000 deaths
  – 82,000 amputations
  – >44,000 develop kidney failure
  – 12,000-24,000 become blind

• Cost in 2002: >$132 billion

• Prevalence of Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Prevalence in Diabetes</th>
<th>Prevalence in Non-Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>9.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>CHF</td>
<td>7.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.6%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

• Macrovascular

• Microvascular

<table>
<thead>
<tr>
<th>Complication</th>
<th>Prevalence in Diabetes</th>
<th>Prevalence in Non-Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney disease</td>
<td>27.8%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Eye disease</td>
<td>18.9%</td>
<td>N/A</td>
</tr>
<tr>
<td>Foot problems</td>
<td>22.9%</td>
<td>10%</td>
</tr>
</tbody>
</table>


AACE 2007
Sugar Rationing Reduces Diabetes Mortality Index

Figure 2–1 Diabetes mortality indices for England and Wales (1938 was used as the base year). With food rationing during both world wars there was a dramatic drop in the diabetes mortality index. There was a parallel drop in the amount of sugar consumed (dashed line) during the wars. [Source: Drash A. Influence of the level of nutrition on diabetes mellitus; world-wide dietary and ethnic factors in evaluation of the disease. In Gardner LI, Amacher P (eds): Endocrine Aspects of Malnutrition. Santa Ynez, CA: Kroc Foundation, 1973, pp. 257–287. With permission.]
2,000 Calories!!!

No one goes home hungry from The Cheesecake Factory®!
## It’s Not All About Food

<table>
<thead>
<tr>
<th>Activity</th>
<th>Calories Burned</th>
<th>Activity</th>
<th>Calories Burned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ride elevator</td>
<td>3</td>
<td>Take Stairs</td>
<td>20</td>
</tr>
<tr>
<td>Go to Car Wash</td>
<td>35</td>
<td>Wash Car</td>
<td>110</td>
</tr>
<tr>
<td>Order Take-out</td>
<td>0</td>
<td>Cook Meal</td>
<td>70</td>
</tr>
<tr>
<td>Play video game</td>
<td>50</td>
<td>Play Basketball</td>
<td>280</td>
</tr>
<tr>
<td>Riding mower</td>
<td>80</td>
<td>Power mower</td>
<td>200</td>
</tr>
</tbody>
</table>
Natural History of T2DM and Complications

**Post-meal glucose**

**Fasting glucose**

**PG 200 mg/dL**

**PG 126 mg/dL**

**Meets ADA diagnostic criteria for T2DM**

**Macrovascular disease risk**

**Microvascular disease risk**

**Insulin resistance (IR)**

**Beta-cell Function**

**Time (years)**

# Good Glycemic Control Reduces Incidence of Complications

<table>
<thead>
<tr>
<th>A1C</th>
<th>DCCT</th>
<th>Kumamoto</th>
<th>UKPDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 vs. 7%</td>
<td>9 vs. 7%</td>
<td>8 vs. 7%</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>63%</td>
<td>69%</td>
<td>17-21%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>54%</td>
<td>70%</td>
<td>24-33%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>60%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Macrovascular disease</td>
<td>–</td>
<td>–</td>
<td>16%*</td>
</tr>
</tbody>
</table>

* p = 0.052

MACROVASCULAR DISEASE*

Heart attack

Stroke

PVD (Amputation)

*accounts for ~80% of all mortality in T2DM
Steno-2 Study*
Multifactorial Intervention and Cardiovascular Disease Outcomes

- Study population: 160 patients with type 2 diabetes and albuminuria
- Intensive intervention: behavior modification and targeted pharmacologic therapy for
  - Hyperglycemia
  - Hypertension
  - Dyslipidemia
  - Microalbuminuria
  - Secondary prevention of CVD with aspirin
- Primary end point: death from cardiovascular causes, nonfatal MI, nonfatal stroke, revascularization, and amputation (composite measure). Mean follow-up 7.8 years

*From Steno Diabetes Center, Copenhagen.
Steno-2 Study Primary Composite End Point: Death From CV Causes, Nonfatal MI, CABG, PCI, Nonfatal Stroke, Amputation or Surgery for PVD

<table>
<thead>
<tr>
<th>Follow-up (Months)</th>
<th>Conventional therapy</th>
<th>Intensive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>24</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>36</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>48</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>60</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>72</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>84</td>
<td>70</td>
<td>35</td>
</tr>
<tr>
<td>96</td>
<td>80</td>
<td>40</td>
</tr>
</tbody>
</table>

Risk reduction ↓ 53% (27%–76%) P=0.008

Conventional therapy unadjusted event rate 44%
Intensive therapy unadjusted event rate 24%

Intensive Glycemic Control and CVD

• ADVANCE: A1c 6.5% : no effect on CVD
• ACCORD: : A1c 6.4%: 10% decr in nonfatal MI, but 35% incr in CV death due to MI/CHF * (Journal Club August)
• VA DT:A1c 6.9%: no diff in CV deaths, but severe hypoglycemia predictive of CV events (RSG “protective”)
ADA Glycemic Recommendations for Adults with Diabetes

- A1c < 7%
- Preprandial glucose: 70-130 mg/dl
- Peak postprandial glucose: < 180 mg/dl
- A1c primary target for glycemic control
- Individualize goals based on duration of dm, pregnancy, age, comorbid conditions, hypoglycemic unawareness, individual pt considerations
- Postprandial glucose may be targeted if A1c goal not met despite reaching preprandial goals
ADA Standards: 2010

• A1c <7%
• Blood pressure <130/80
• LDL cholesterol < 100 mg/dl
• Triglycerides < 150 mg/dl
• HDL cholesterol > 40 mg/dl
• Aspirin 81 mg men>50, women>60 with 1 add'l risk factor
• Statin Rx if >40yrs regardless of cholesterol with one other risk factor or any age with CVD

DiabCare 2010;33supp1:S32
# ADA Goals for T1DM by Age Grp

<table>
<thead>
<tr>
<th>Values by Age</th>
<th>BGs premeal</th>
<th>BGs HS/overnite</th>
<th>A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6</td>
<td>100-180</td>
<td>110-200</td>
<td>&gt;7.5, but &lt;8.5</td>
</tr>
<tr>
<td>6-12</td>
<td>90-180</td>
<td>100-180</td>
<td>&lt;8</td>
</tr>
<tr>
<td>13-19</td>
<td>90-130</td>
<td>90-150</td>
<td>&gt;7.5</td>
</tr>
</tbody>
</table>

*DiabCare 2010;33supp1:S40*
UKPDS: Epidemiological Analysis by HbA$_{1c}$ Categories

- Any endpoint related to diabetes

Rates of Severe Hypoglycemia Increase as A1C Levels Decrease in Patients With Diabetes

- Major barrier to intensive diabetes management
Survival as a Function of A1c


Figure 1: Adjusted hazard ratios for all-cause mortality by HbA1c deciles in people given oral combination and insulin-based therapies. Two proportional hazards models were used, with the HbA1c base case scenario. Vertical error bars show 95% CIs, horizontal bars show HbA1c range. Red line=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B).
Hypoglycemic Episodes and Risk of Dementia

- Cohort study of 16,000 T2DM pts mean age 65
- 8% had at least 1 episode of hypoglycemia
- Number of episodes increased 2000-2002
- 13.5% had 3 or more episodes
- Older, AA, insulin Rx, HTN, Stroke, CKD all associated
- 11% had dementia with a mean f/u of 3.8 yrs
- HR for dementia 1.68, 2.15, 2.6 based on 1, 2, or 3 hypoglycemic events; 2.4% incr risk per yr

Whitmer. 2009. JAMA;301:1565-1572
Both FPG and PPG Contribute to Elevated A1C Levels

Adapted from Del Prato S. Int J Obes Relat Metab Disord. 2002;26:S9–S17. Permission pending.
FBG and PPG Contributions to A1c

Figure 3—Relative contributions of post-prandial (□) and fasting (■) hyperglycemia (%) to the overall diurnal hyperglycemia over quintiles of HbA1c. a, significant difference was observed between fasting and post-prandial plasma glucose (paired t test); b, significantly different from all other quintiles (ANOVA); c, significantly different from quintile 5 (ANOVA).
estimated Average Glucose: eAG
ADA recommends reporting A1c results to pts as eAG

- A1C 6% ~126 mg/dL  7.0 mmol/l
- A1C 7% ~154 mg/dL  7.8 mmol/l
- A1C 8% ~183 mg/dL  10.1 mmol/l
- A1C 9% ~212 mg/dL  11.8 mmol/l
- A1C 10% ~240 mg/dL  13.4 mmol/l
- A1C 11% ~270 mg/dL  15 mmol/l
- A1C 12% ~300 mg/dL  16.7 mmol/l

- Formula: 28.7 X A1c – 46.7 = eAG
- Calculator:
  http://professional.diabetes.org/GlucoseCalculator.aspx
The Landscape of Glucose Altering Medications

- 8 Classes of Oral Meds: SU, metformin, glinides, TZDs, glucosidase inhibitors, DPP-4 inhibitors, colesevelan, bromocriptine
- 3 Classes of injectables: insulin (including 19 products), GLP-1 agonists, amylin analog
- Hypoglycemia and weight gain are common side effects of the most frequently used drugs except metformin (which carries multiple precautions and has a significant GI side effect profile)
Oral Agents for Type 2 Diabetes: Primary Sites of Action

- **Pancreas**
  - Sulfonylureas
  - Repaglinide
  - Nateglinide
  - DPP4

- **Liver**
  - Metformin
  - DPP4
  - TZDs

- **Gut**
  - Acarbose
  - Miglitol
  - Colesevelam
  - Metformin

- **Muscle**
  - Rosiglitazone
  - Pioglitazone
  - Metformin

Hyperglycemia

- Impaired Insulin Secretion = Insulin Deficiency
- ↑ Hepatic Glucose Production
- ↓ Glucose Uptake = Insulin Resistance

Carbohydrate Metabolism

Primary Sites of Action

Oral Agents for Type 2 Diabetes:
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/d)</th>
<th>↓ in HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide XL</td>
<td>5-20</td>
<td>1.8%</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>8</td>
<td>1.9%</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>12</td>
<td>1.8%</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>360</td>
<td>.9%</td>
</tr>
<tr>
<td>Metformin</td>
<td>2000</td>
<td>1.8%</td>
</tr>
<tr>
<td>Acarbose</td>
<td>300</td>
<td>.74%</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>8</td>
<td>1.55%</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>45</td>
<td>1.5%</td>
</tr>
</tbody>
</table>
Meta-analysis of OADs and A1c

• Analysis of 61 studies including 26,000 subjects randomized to drug or placebo
• Average A1c lowering 0.5-1.25%
• SUs and TZDs lowered A1c 1-1.25%
• A 1% higher baseline A1c predicted a 0.5% greater decline after 6 months
• Benefit is clear within 4-6 months
• No effect of diabetes duration on effect

Sherifali. Diabetes Care. published online June 8, 2010
Baseline A1c and Efficacy of OA’s
Decreasing A1c reductions with lower Baseline A1c

Bloomgarden, Z Diabetes Care 2006;29:2137
### Side Effects of Oral Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide XL</td>
<td>Hypoglycemia 1+Wt gain1+</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Hypoglycemia 4+Wt gain2+</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Hypoglycemia 2+Wt gain1+</td>
</tr>
<tr>
<td>Repaglinide/Nateglinide</td>
<td>Hypoglycemia 1+</td>
</tr>
<tr>
<td>Metformin</td>
<td>GI 2+ Lactic Acidosis 1+</td>
</tr>
<tr>
<td>Acarbose/Miglitol</td>
<td>GI 3+</td>
</tr>
<tr>
<td>Rosi/Pioglitazone</td>
<td>Weight gain 3+ Edema 2+</td>
</tr>
</tbody>
</table>
Rosiglitazone and CV Events

- “RSG associated with significant increase in MI and increased death rate from CV disease” Nissen. NEJM 2007; 356:2457
- 86/15,565 had MI with RSG; 72/12,282 had MI in control
- 39 CV deaths with RSG; 22 in control
- Predominately men with poor glycemic control (A1c> 8%)
- Pooled analysis of many short-term trials not powered to assess CV outcomes which were not defined or adjudicated
- FDA has added a “black box” warning regarding CHF for both RSG and PIO
ADA/EASD Algorithm 2008

Tier 1: Well-validated core therapies

At diagnosis:
Lifestyle + Metformin

STEP 1

Lifestyle + Metformin + Basal insulin

Lifestyle + Metformin + Sulfonylurea

STEP 2

Lifestyle + Metformin + Intensive insulin

STEP 3

Tier 2: Less well validated therapies

Lifestyle + Metformin + Pioglitazone

No hypoglycemia
Oedema/CHF
Bone loss

Lifestyle + Metformin + GLP-1 agonist

No hypoglycemia
Weight loss
Nausea/vomiting

Figure 2—Algorithm for the metabolic management of type 2 diabetes; Reinforce lifestyle interventions at every visit and check A1C every 3 months until A1C is <7% and then at least every 6 months. The interventions should be changed if A1C is ≥7%. aSulfonylureas other than glybenclamide (glyburide) or chlorpropamide. bInsufficient clinical use to be confident regarding safety. See text box, entitled TITRATION OF METFORMIN. See Fig. 1 for initiation and adjustment of insulin. CHF, congestive heart failure.
**A1C 6.5 – 7.5%**

**Monotherapy**
- **MET** or **DPP4**
- **GLP-1** or **TZD** or **AGI**

**Dual Therapy**
- **MET** or **GLP-1** or **DPP4**
- **TZD**
- **Glinide** or **SU**
- **Colestevamel**

**Triple Therapy**
- **MET** or **GLP-1** or **DPP4**
- **TZD**
- **Glinide** or **SU**

**A1C 7.6 – 9.0%**

**Dual Therapy**
- **MET** or **GLP-1** or **DPP4**
- **TZD**
- **SU** or **Glinide**

**Triple Therapy**
- **MET** or **GLP-1** or **DPP4**
- **TZD**
- **SU**

**A1C > 9.0%**

**Drug Naive**
- **INSULIN** ± Other Agent(s)

**Under Treatment**
- **INSULIN** ± Other Agent(s)

- **Symptoms**
- **No Symptoms**

- **May not be appropriate for all patients**
- **For patients with diabetes and A1C < 6.5%, pharmacologic Rx may be considered**
- **If A1C goal not achieved safely**
- **Preferred initial agent**
  1. DPP4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG
  2. TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)
  3. AGI if ↑ PPG
  4. Glinide if ↑ PPG or SU if ↑ FPG
  5. Low-dose secretagogue recommended
  6. a) Discontinue insulin secretagogue with multidose insulin
     b) Can use pramlintide with prandial insulin
  7. Decrease secretagogue by 50% when added to GLP-1 or DPP-4
  8. If A1C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution
  9. If A1C > 8.5%, in patients on Dual Therapy, insulin should be considered

Available at [www.aace.com/pub](http://www.aace.com/pub)
Insulin Regimens for T2DM

- Basal add-on to orals
- Premixed add-on to orals (human vs analog)
- Basal plus (one bolus with largest meal)
- Basal-bolus (MDI)
- Insulin pump
Correcting Fasting Hyperglycemia…

• *Is Usually the First Task*

…then, *Tackle Postprandial Hyperglycemia if A1C still >7%!*

## Basal Insulins

Control hepatic gluconeogenesis

<table>
<thead>
<tr>
<th></th>
<th>PEAK</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nph</td>
<td>4-8 hrs</td>
<td>8-20 hrs</td>
</tr>
<tr>
<td>Glargine (Lantus)</td>
<td>No peak</td>
<td>18-24 hrs</td>
</tr>
<tr>
<td>Detemir (Levemir)</td>
<td>Relatively flat</td>
<td>12-24 hrs</td>
</tr>
</tbody>
</table>
# Rapid-acting Insulins

## Prandial/correction

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Peak Time</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>2-4 hrs</td>
<td>5-8hrs</td>
</tr>
<tr>
<td>Lispro (Humalog)</td>
<td>1-1.5 hr</td>
<td>&lt;5 hr</td>
</tr>
<tr>
<td>Aspart (Novolog)</td>
<td>1-1.5 hr</td>
<td>&lt;5 hr</td>
</tr>
<tr>
<td>Glulisine (Apidra)</td>
<td>1-1.5 hr</td>
<td>&lt;5 hr</td>
</tr>
</tbody>
</table>
Premixed Insulins

- **Humulin/Novolin 70/30**: 70% Nph/30% Regular
- **Humulin 50/50**: 50% Nph/50% Regular
- **Novolog 70/30**: 70% protAsp/30% Asp
- **Humalog 75/25**: 75% protLis/25% Lis
- **Humalog 50/50**: 50% protLis/50% Lis
Insulin Profiles

- Lispro/aspart/glulisine (peak 1-2 hr, duration 4-5 hr)
- Regular (peak 2-4 hr, duration 6-10 hr)
- NPH (peak 4-8 hr, duration 10-20 hr)
- Glargine/detemir (~24 hr)

In Medical Management of Type 1 Diabetes, ADA, 2005
Mimicking Physiology: Basal and Prandial Insulin Coverage With Basal Analog and Rapid Analog

Breakfast  Lunch  Dinner

4:00  8:00  12:00  16:00  20:00  24:00  4:00  8:00

Plasma Insulin

Rapid analog 1, 2, or 3/d as needed

PLUS

Basal analog 1/day
Prandial Insulins: Analogs

- Analogs (lispro/aspart/glulisine) have shorter duration of action and less postprandial hypoglycemia; can be given just prior to meal or when meal over
- Patients on higher fat meal will have late hyperglycemia
- Patients with gastroparesis may have hypoglycemia
- Ideally should be dosed according to quantity of carbohydrate ingested, but can be started at .05-.1 Units/kg/meal
**Prandial Analog Insulin**

- CHOgm intake/carbohydrate insulin ratio (CIR)
- C:I ratio= 500 / TDI (total daily insulin)
- Estimated TDI = BW (lb) / 4
- Common C/I ratio: 1u/5-15 gms CHO
- Correction Dose = 1700 / TDI = ___ mg/dl BG reduced by 1u reduced rapid insulin
- Ideal BG rise post meal is 30 – 60 mg
- Typical Correction/Supplemental insulin(CF) range 1 u/25-50 BG mg/dl > 150
Prandial Insulins: Regular

- Regular insulin should be given 30 minutes prior to a meal (same as a premixed NPH/Reg)
- May cause late post-meal hypoglycemia
- May be more appropriate for high fat-mixed meals or for patients with gastroparesis
Insulin Analogs vs Nph/Regular Insulins

- More “physiologic”: match basal/bolus needs
- Less hypoglycemia
- Less weight gain
- Improved glycemic control
Basal Insulin Dosing

- Start with 10 Units at bedtime for NPH/detemir/glargine (or anytime with detemir/glargine)
- Can titrate every 3-7 days in increments of 2-4 Units until FBS <120
- Average daily dose in Treat to Target Trial was 45-50 units after 10 weeks
- Dose usually 0.3-0.4 Units/kg
- Lean may need only 0.2 Units/kg
- Obese may need 0.5 Units/kg
- Evaluate overnight effect: HS BGs > 200: need PM prandial insulin!
Basal vs Premix Insulin in T2DM

• Retrospective observational analysis of 4500 pts showed lower A1c values at 3, 6, 9, 12 mos post-initiation in analog premix pt vs basal alone. 
  Sun, P. 
  Diabetologia 2005; 48: 3

• Open label observational study of 100 T2DM pts using an analog pre-mix showed 77% achieved an A1c < 7% with 1, 2, or 3 injections daily Garber, A. 
  Diab Ob Metab 2006; 8: 58

• Multi-center treat to target study of 233 T2DM pts comparing basal analog vs bid premix analog showed 40% achieved A1c < 7% with basal vs 66% reached A1c < 7% with premix. 
  Raskin, P. Diab Care 2005; 28: 260
Basal vs Premixed Insulin

- Lower A1c values at 3, 6, 9, 12 mos post-initiation in analog premix pt vs basal alone. Sun, P. Diabetologia 2005;48:3
- Analog pre-mix showed 77% achieved an A1c < 7% with 1, 2, or 3 injections daily Garber, A. Diab Ob Metab 2006; 8:58
- Asp 70/30 efficacy superior to basal detemir with more weight gain and hypoglycemia Holman NEJM 2007;357:1716
- (lispro 75/25) compared to glargine resulted in lower A1c, more weight gain, higher overall rates of hypoglycemia, but less nocturnal hypoglycemia Buse Diabetes Care 2009;32:1007
Add-on Bolus Therapy to Basal

- Add Prandial insulin if A1c remains elevated or daytime BG’s elevated despite FBS < 120
- Sulfonylureas may no longer be effective
- Metformin and/or TZD’s should be continued
- Start by adding rapid analog or regular with largest meal
- Bolus dose: 10% of basal dose
- Basal dose: reduce by 10%
  - Example: basal 50 units converts to 45 units with 5 unit meal bolus
- Adjust meal bolus based on post-prandial glucose levels
- Add meal bolus doses based on SMBG data

U-500 Insulin

- Used in patients with severe insulin resistance, requiring > 200 units /day
- Available only as Regular insulin
- Pharmacokinetic peak similar to NPH (8-12 hrs) and duration up to 24 hrs
- Typically used BID: breakfast and supper but pts requiring higher doses can inject TID with meals
- Not combined with other insulins
- Pts use U-100 syringes: Dosing is in milliliters: Example Rx: *Regular insulin U-500, 150 units, inject 0.3 ml SQ 3 times daily with meals*

The Incretin Effect in Subjects without and with Type 2 Diabetes

Control Subjects (n=8)

Patients With Type 2 Diabetes (n=14)

The incretin effect is diminished in type 2 diabetes.

GLP-1 Effects in Humans
Understanding the Natural Role of Incretins

GLP-1 secreted upon the ingestion of food

Promotes satiety and reduces appetite

↓ Beta-cell workload

Alpha cells: ↓ Postprandial glucagon secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Stomach: Helps regulate gastric emptying

Beta cells:
Enhances glucose-dependent insulin secretion

↓ Beta-cell response

Beta cells: Enhances glucose-dependent insulin secretion

Adapted from Nauck MA, et al. Diabetologia. 1996;39:1546-1553
Adapted from Drucker DJ. Diabetes. 1998;47:159-169
The Beginning

- **Exenatide**
  - Synthetic version of salivary protein found in the Gila monster
  - More than 50% overlap with human GLP-1
    - Binds to known human GLP-1 receptors on beta cells (*in vitro*)
    - Resistant to DPP-IV inactivation
  - Following injection, exenatide is measurable in plasma for up to 10 hours

## Exenatide Mimics Many Properties of GLP-1

<table>
<thead>
<tr>
<th></th>
<th>GLP-1</th>
<th>Exenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>↑ Glucose-dependent insulin secretion</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>↓ Glucagon secretion</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>↓ Hepatic glucose output</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Regulates gastric emptying</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>↓ Rate of nutrient absorption</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>↓ Food intake</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>↓ Plasma glucose acutely to near-normal levels</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Resistant to DPP-IV degradation</strong></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Duration in plasma following a subcutaneous (SC) injection</strong></td>
<td>Short</td>
<td>Long</td>
</tr>
</tbody>
</table>

See Important Safety Information included in this presentation
Exenatide (BYETTA®)

- Approved for use as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking
  - Metformin (MET)
  - Sulfonylurea (SFU)
  - TZD
  - A combination of MET & SFU or MET & TZD

But have not achieved adequate glycemic control
Liraglutide (Victoza®)

- Liraglutide is a QD analog of GLP-1
- 52 week monotherapy trial comparing glimepiride to LRG
- Baseline A1c 8.3±1.1%
- 51% achieved A1c < 7%
- Wt loss (5lb) , less hypoglycemia(8vs24%), nausea 29%
- Victoza® approved by FDA January 2010
- Concern regarding medullary thyroid CA in rodents
Incretin Therapy and Pancreatitis

- Reports of acute pancreatitis in pts treated with Byetta, Januvia, and Victoza have resulted in FDA advisories
- Type 2 diabetes is associated with a 2.5 fold increased risk for acute pancreatitis\(^1\)
- A claims-based drug safety system found no evidence of a greater risk of pancreatitis with exenatide or sitagliptin compared to metformin or glyburide\(^2\)

Role of Incretins in Glucose Homeostasis

Ingestion of food

GI tract

Release of gut hormones — Incretins

Active GLP-1 & GIP

Pancreas

Glucose-dependent

↑ Insulin from beta cells (GLP-1 and GIP)

β cells

α cells

Blood glucose

↓ Glucose production by liver

DPP-4 enzyme

Glucose dependent

↓ Glucagon from alpha cells (GLP-1)

↓ Glucose uptake by muscles

GI tract

Active GLP-1 & GIP

DPP-4 enzyme

Inactive GLP-1

Inactive GIP

GLP-1

GIP

DPP-4 = dipeptidyl-peptidase 4
DPP IV Inhibitors: Sitagliptin (Januvia™) and Saxagliptin (Onglyza™)

- Amplify incretin activity by inhibition of DPP 4 enzyme responsible for degradation of GLP1 and GIP
- Januvia approved by FDA October 1, 2006, Onglyza approved July 2009
- Indicated in Type 2 diabetes as monotherapy or in combination with metformin or TZD’s
- Hypoglycemic risk same as placebo
- Weight neutral
- A1c reductions of .6-1.4%
Amylin Is Co-Secreted With Insulin

Healthy male adults (n = 6)

Pramlintide (Symlin™) Mimics Three Important Actions of Amylin

<table>
<thead>
<tr>
<th>Action</th>
<th>Amylin*</th>
<th>Pramlintide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibits inappropriately high postprandial glucagon secretion</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Slows gastric emptying</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Promotes satiety and reduces caloric intake</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Pramlintide Acetate Prescribing Information, 2005
Pramlintide Indications

Given at mealtimes and is indicated for:

• **Type 2 diabetes**, as an adjunct treatment in patients who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.

• **Type 1 diabetes**, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.
New Diabetes Drugs

- Byetta LAR (Bydureon): once weekly Byetta NDA pending

- Cycloset: rapid release bromocriptine recently approved by FDA for diabetes

- Glucokinase activators: βcell glucose sensor

- SGLT-2 inhibitors: increase urinary glucose excretion
Weight and Glucose with Caloric Restriction

Benefits of Weight Loss

- **Diabetes**: improved glycemic control, decreased need for antihyperglycemic therapies
- **Blood pressure**: reduced systolic and diastolic BP, decreased need for antihypertensive meds
- **Lipids**: ↓ LDL, ↓ TG, ↑ HDL
- **Pre-diabetes (Insulin resistance syndrome)**: ↓ insulin levels, reduced risk of developing diabetes (56% reduction in DPP)
NWCR: Long Term Maintenance of Weight Loss

- Subjects in the National Weight Control Registry have lost at least 30lbs and kept it off for at least 1 yr (avg=5.7 yrs)
- All eat a low calorie low fat (25%) diet
- All engage in high levels of physical activity: > 2800 kcal/week
- Most (80%) report eating breakfast daily

Wyatt.2002.ObesRes.10:78
Prevention of Weight Gain during Intensification of Diabetes Therapy

- MD/Team emphasize importance of weight maintenance
- Patient should monitor weight regularly similar to blood glucose monitoring
- Use metformin whenever possible
- Use exenatide and pramlintide when possible
- Encourage activity and avoidance of restaurants and processed high fat foods
Encourage Daily Activity!