UPDATE ON MANAGEMENT OF TYPE 2 DIABETES – NEW AND OLD TREATMENT OPTIONS

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- Professor of Medicine
- Charles Drew University & David Geffen School of Medicine at UCLA

CURRENT AMERICAN DIABETES ASSOCIATION GUIDELINES

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hb A1c</td>
<td>every 6 months if goal attained; every 3 months if greater</td>
</tr>
<tr>
<td>2. LDL Cholesterol</td>
<td>yearly or more often as necessary</td>
</tr>
<tr>
<td>3. Triglycerides</td>
<td>yearly or more often as necessary</td>
</tr>
</tbody>
</table>

*Once LDL cholesterol at goal, the NCEP suggests considering treatment for triglyceride concentrations >200 mg/dl if the non-HDL cholesterol is >130 mg/dl.
### Characteristics of Oral Antidiabetes Agents

#### Metformin (glucophage)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hypoglycemia</td>
<td>Adverse GI effects</td>
</tr>
<tr>
<td>No weight gain</td>
<td>Slow dose titration</td>
</tr>
<tr>
<td>Favorable lipid effects</td>
<td>CI: renal/hepatic dysfxn</td>
</tr>
<tr>
<td>Generic available</td>
<td>alcoholism, CHF, &gt;80yo</td>
</tr>
<tr>
<td></td>
<td>Potential for lactic acidosis?</td>
</tr>
<tr>
<td>BID/TID dosing</td>
<td></td>
</tr>
</tbody>
</table>

#### Characteristics of Oral Antidiabetes Agents

#### Sulfonylureas

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset of action</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Few adverse effects</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Dosing often qd</td>
<td></td>
</tr>
<tr>
<td>Generic formulations avail</td>
<td></td>
</tr>
</tbody>
</table>

### Identification of Type 2 Diabetes

All three components must be present:
- Minority status
- Obesity
- At least one first degree relative, i.e., parent, sibling or child, must have type 2 diabetes*
  *Very important criterion
PATIENTS
Total Enrolled (n): 55
Lost to F/U at 4 Mths: 6
Sex (Female/Male): 13/42
Age (Years): 48.7 ± 19 (Range 14-77)
Race: Hispanic - 6; Black - 25; Asian - 8; Caucasian - 16
New Onset (n): 44
Baseline DM (kg/m²): 30.8 ± 0.9 (Range 18.2-91.7)
Initial Therapy: Glyburide-33; Chlorpropamide-1; Gilipride-1

GLYCATED HEMOGLOBIN LEVELS
% ± SE
Baseline
Four Months
*p < 0.001 vs. Baseline
Upper Limit of Normal

WEIGHT CHANGE
Pounds ± SE
Baseline n = 55
4 Months n = 44
p < 0.01

PLASMA GLUCOSE CONCENTRATIONS
Random Values
Fasting Values
mg/dl ± SE
Baseline n = 55
1 Week n = 53
4 Months n = 47

DM THERAPY AT 4 MONTHS
Lost to F/U: 6
Diet Therapy: 11
Submax OHA: 29
Max Dose OHA: 6
Insulin: 3

BASELINE SERUM BICARBONATE AND URINE KETONE LEVELS
U Ketones Negative: U Ketones Positive
mEq/L ± SE
Normal Range
X = Insulin Rx at 4 Months

X = Insulin Rx at 4 Months

Prospective
Retrospective
Characteristics of Oral Antidiabetes Agents

**Glinides**
(repaglinide, nateglinide)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset of action</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Short time to peak</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Short half life</td>
<td>Freq admin</td>
</tr>
<tr>
<td>Enhances insulin response to meals</td>
<td></td>
</tr>
</tbody>
</table>

**α-Glucosidase Inhibitors**
(acarbose, miglitol)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hypoglycemia*</td>
<td>Flatulence common</td>
</tr>
<tr>
<td>No weight gain</td>
<td>Very slow dose titration</td>
</tr>
<tr>
<td>Dosing three times a day</td>
<td>Contraindications (creatinine &gt; 2 mg/dl; intestinal disorders)</td>
</tr>
</tbody>
</table>

*If hypoglycemia occurs due to SU’s, glinides or insulin, it must be treated with glucose tablets or milk (drugs do not block enzyme that breaks down lactose to glucose)*

**Thiazolidinediones (TZD’s) (Glitazones)**
(Rosiglitazone, Pioglitazone)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>No hypoglycemia</td>
<td>Slow onset of action</td>
</tr>
<tr>
<td>Dosing once daily</td>
<td>Weight gain (increased fat)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Edema (fluid retention)</td>
</tr>
<tr>
<td>not a contra-indication</td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Decreased bone mineral density</td>
</tr>
<tr>
<td></td>
<td>Increased fractures</td>
</tr>
<tr>
<td></td>
<td>Expensive</td>
</tr>
</tbody>
</table>

**Colesvelam (WelChol®)**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowers LDL cholesterol</td>
<td>Raises triglycerides</td>
</tr>
<tr>
<td>Less GI side effects than other bile acid resins</td>
<td>Some GI side effects</td>
</tr>
</tbody>
</table>

*Other bile acid resins do not claim to lower glycemia*
**THE INCRETIN AXIS**

**Deficient Insulin: Hypersecreted Glucagon**

**TYPE 2 DIABETES**

- Defects in diabetes:
  - Deficient insulin release
  - Glucagon not suppressed (postprandially)
  - Hyperglycemia

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**Postprandial Glucagon is Excessive and Not Corrected by Exogenous Insulin**

**IMBALANCED GLUCOSE APPEARANCE AND DISAPPEARANCE**


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**GLP-1 and GIP Are Degraded by the DPP-4 Enzyme**


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**DIPEPTIDYL PEPTIDASE (DPP)-4 INHIBITORS**
### Characteristics of Oral Antidiabetes Agents

**DPP-4 Inhibitors**
(Sitagliptin)

<table>
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<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hypoglycemia</td>
<td>Weight neutral*</td>
</tr>
<tr>
<td>Oral administration*</td>
<td>Expensive</td>
</tr>
</tbody>
</table>

*Compared to injectable GLP-1 agonist

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### Characteristics of Injectable Antidiabetes Drugs

**Glucagon-Like Peptide (GLP) – 1 Agonists**

- **Exenatide (Byetta)**

  **Advantages**
  - Weight loss
  - No hypoglycemia

  **Disadvantages**
  - Initial nausea common
  - Expensive

**Liraglutide**

**THE SECOND INCRETIN AGONIST**

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**EXENATIDE**

THE FIRST INCRETIN AGONIST

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### LEAD 6:
Change in A1C at 26 Weeks
Amylin Is Co-Secreted With Insulin

**Data from Kruger D, et al. Diabetes Care 1999; 22:166-172.**

**EXENATIDE ONCE WEEKLY**

_Lancet 372:1240, 2008_

**SYMLIN (PRAMLIINTIDE)**

**EXENATIDE ONCE WEEKLY**

_Lancet 372:1240, 2008_

**Pramlintide Reduces Postprandial Glucagon**

**Data from Fineman M, et al. Metabolism 2002; 51:636-641**

**Type 2 Diabetes, Late Stage**

**Type 1 Diabetes**

**Data from Fineman M, et al. Horm Metab Res 2002; 34:504-508**

**Healthy male adults (n = 12)**

**Data from Kruger D, et al. Diabetes Care 1999; 22:166-172.**
Pramlintide Improves Postprandial Glucose

**TYPE 1 DIABETES**

<table>
<thead>
<tr>
<th>Time Relative to Meal and Pramlintide (min)</th>
<th>Mean (SE) Plasma Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100 (±10)</td>
</tr>
<tr>
<td>60</td>
<td>110 (±5)</td>
</tr>
<tr>
<td>120</td>
<td>120 (±10)</td>
</tr>
<tr>
<td>180</td>
<td>130 (±15)</td>
</tr>
<tr>
<td>240</td>
<td>140 (±20)</td>
</tr>
</tbody>
</table>

Lispro Insulin

Pramlintide 60 μg + Lispro Insulin

Regular Insulin

Pramlintide 60 μg + Regular Insulin

Evaluable population: Mean (SE)

Pramlintide + Lispro insulin (n = 20)

Pramlintide + Regular insulin (n = 18)

**Pramlintide Acetate Prescribing Information**, 2005

Data from Weyer C, et al. *Diabetes Care* 2003; 26:3074-3079

**Diabetes Care 32:1656, 2009**

**PRAMLINTIDE VS. PRE-PRANDIAL INSULIN IN PATIENTS ON BASAL INSULIN + OAD’S**

**Diabetes Care 32:1577, 2009**

**Diabetes Care 32:1577, 2009**

**Diabetes Care 32:1656, 2009**
**Characteristics of Another Injectable Antidiabetes Drug**

**Insulin**

**Advantages**
- Most effective drug

**Disadvantages**
- SMBG required
- Hypoglycemia
- Weight gain
- Consistency of life style required

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**American Diabetes Association’s Recommended Treatment**

**Tier 1: Well validated core therapies**

1. **Lifestyle + Metformin**
   - No hypoglycaemia, oedema/CHF, bone loss

2. **Lifestyle + Metformin + Pioglitazone**
   - No hypoglycaemia, weight loss, nausea/vomiting

3. **Lifestyle + Metformin + Basal insulin**

**Tier 2: Less well validated therapies**

1. **Lifestyle + Metformin + Exenatide**
   - (Discontinue DPP-4 Inhibitor if taking ID)

2. **Bedtime Insulin**
   - (Discontinue Exenatide and TZD)

3. **Mixed-Split or Basal-Bolus Insulin Regimen**

**CRITERIA FOR SELECTING A CLASS OF DRUGS OR ONE DRUG WITHIN A CLASS OF DRUGS**

(In decreasing order of importance)

1. Effectiveness
2. Adverse effects
3. Ease of adherence
4. Cost

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**Rx of Type 2 Diabetes**

**How Our Current Medical Care System Fails People With Diabetes**

Davidson MB: Diabetes Care 32:370, 2009

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**TREATMENT ALGORITHM (Oral Drugs)**

**Short Term Goal**
- Start Metformin
- FPG < 130 mg/dL

**Long Term Goal**
- A1C < 7.5%
- Adjust as necessary

*After achieving short term goal
* If occurs reduce dose of SU
**TREATMENT ALGORITHM (Oral Drugs)**

**Short Term Goal**
- Add bedtime NPH*

**FPG 70 - 130 mg/dl**
- At least 50% of time

**A1C < 7.5%**
- 3 months later*

**Long Term Goal**
- Fail

**Split/Mixed Regimen**
- Add sulfonylurea or metformin if needed

**Add bedtime NPH**
- A1C < 7.5%
- 3 months later*

**Preprandial PG 70 - 130 mg/dl**
- At least 50% of time

**A1C < 7.0%**
- 3 months later*

**TREATMENT ALGORITHM (Insulin)**

**Short Term Goal**
- Add bedtime NPH

**FPG 70 - 130 mg/dl**
- At least 50% of time

**A1C < 7.5%**
- 3 months later*

**Preprandial PG 70 - 130 mg/dl**
- At least 50% of time

**A1C < 7.0%**
- 3 months later*

**Long Term Goal**
- Fail

**Split/Mixed Regimen**
- Basal/Bolus Regimen

**Add bedtime NPH**
- A1C < 7.5%
- 3 months later*

**Preprandial PG 70 - 130 mg/dl**
- At least 50% of time

**A1C < 7.0%**
- 3 months later*

**Study #1** (N = 367 randomized patients)
Hb A1c levels fell from 8.8% to 7.0%

**Study #2** (N = 178 referred patients)
Hb A1c levels fell from 11.1% to 7.2%
AN INCONVENIENT TRUTH

• Treatment of diabetes is straightforward.

• Treating the diabetic patient is challenging.

THANK YOU