AN OVERVIEW OF GLYCEMIC TREATMENT FOR DIABETES

Mayer B. Davidson, MD
Professor of Medicine
Charles R. Drew University &
David Geffen School of Medicine
at UCLA
CONFLICTS OF INTEREST

Advisory Board – Sanofi Pharmaceutical Company

Chief Medical Officer – Insulin Algorithms, Inc
TOPICS

1. PATHOPHYSIOLOGY OF TYPE 2 DIABETES
2. TREATMENT TARGETS
3. MEDICATIONS
4. DESCRIPTION OF PROTOCOLS
5. WHEN AND HOW TO USE INSULIN
6. OUTCOMES OF USING PROTOCOLS
Development and Progression of Type 2 Diabetes (Conceptual Representation)

NGT → Insulin → IGT/IFG → Type 2 Diabetes

Glucose Regulation

Postprandial glucose

Fasting glucose

Metabolic Activity

Insulin level

Beta-cell function

Insulin resistance—hepatic and peripheral

NGT=normal glucose tolerance; IGT=impaired glucose tolerance; IFG=impaired fasting glucose.

Kendall DM, Bergenstal RM. ©2005 International Diabetes Center, Minneapolis, MN. All rights reserved.
Adapted from Ferrannini E. Presentation at 65th ADA in Washington, DC, 2006.
Insulin Resistance With Normal $\beta$ Cells

‘Climbing the Curve’

- Insulin level
- Insulin sensitivity
- Normal curve

- Resistant
- Sensitive

©1998 PPS
Pathogenesis of Type 2 Diabetes

‘Falling Off the Curve’

- Insulin level
  - Resistant
  - Type 2 diabetes
  - Insulin sensitivity
- Normal curve
- Sensitive

Treatment of Type 2 Diabetes

‘Getting Back on the Curve’

- Insulin level
- Normal curve
- Diabetes
- Resistant
- Insulin sensitivity
- Sensitive

©1998 PPS
UKPDS: Progressive Deterioration in β-Cell Function Over Time

β-Cell function (%)

Years from diagnosis

β-cell function, as assessed by homeostasis model assessment (HOMA) for patients in the UKPDS: (a) Subset of patients remaining on their allocated therapy at 6 years, comparing those allocated to diet ($n=376$) and those allocated to sulphonylurea ($n=511$); and (b) Subset of patients allocated to diet ($n=110$) and those allocated to metformin ($n=159$).

DCCT
Relative risk of progression of diabetic complications by mean HbA$_{1c}$

*Based on DCCT data

Figure 1—Personalizing A1C targets for individuals with type 2 diabetes.

- Short life expectancy
- Long disease duration
- Frailty
- Comorbidities
- Advanced diabetes complications

Usual target A1C
<7.0 %
(<53 mmol/mol)

- Personal preferences

- Social and educational issues
- Cognitive dysfunction
- Psychiatric issues
- Drug tolerance issues
- Drug access/cost issues

Amended target A1C
7.5—8.5 %
(58—69 mmol/mol)
## TWELVE CLASSES OF DRUGS TO TREAT TYPE 2 DIABETES

<table>
<thead>
<tr>
<th>Metformin</th>
<th>DPP-4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas*</td>
<td>GLP-1 Agonists</td>
</tr>
<tr>
<td>Glinides</td>
<td>Pramlintide</td>
</tr>
<tr>
<td>α-Glucosidase Inhibitors</td>
<td>Dopaminergic Agent**</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>SGLT***-2 Inhibitors</td>
</tr>
<tr>
<td>Colesvelam (WelChol)</td>
<td>Insulin</td>
</tr>
</tbody>
</table>

*Glucagon-Like Peptide
**Cycloset
***Sodium-Glucose Transporter
## Characteristics of Oral Antidiabetes Agents

<table>
<thead>
<tr>
<th>Metformin</th>
<th>(glucophaghe)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Disadvantages</strong></td>
</tr>
<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, &gt;80 yr</td>
</tr>
<tr>
<td></td>
<td>Potential for lactic acidosis?</td>
</tr>
<tr>
<td></td>
<td>BID/TID dosing</td>
</tr>
</tbody>
</table>
Characteristics of Oral Antidiabetes Agents

Sulfonylureas

**Advantages**
- Rapid onset of action
- Few adverse effects
- Dosing often qd
- Generic formulations available

**Disadvantages**
- Hypoglycemia
- Weight gain
Characteristics of Oral Antidiabetes Agents

Glinides
(repaglinide, nateglinide)

Advantages
- Rapid onset of action
- Short time to peak
- Short half life
- Enhances insulin response to meals

Disadvantages
- Hypoglycemia
- Weight gain
- Frequent admin
α-Glucosidase Inhibitors  
(acarbose, miglitol)

**Advantages**  
No hypoglycemia*  
No weight gain

**Disadvantages**  
Flatulence common  
Very slow dose titration  
Dosing three times a day  
Contraindications (creatinine >2 mg/dl; intestinal disorders)

*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 in milk to glucose)*
<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<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 contraindication</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 (now generic)</td>
</tr>
<tr>
<td></td>
<td>?Increased bladder cancer</td>
</tr>
</tbody>
</table>
Characteristics of Oral Antidiabetes Agents

Colesvelam (WelChol®)*

**Advantages**
Lowers LDL cholesterol
Less GI side effects than other bile acid resins

**Disadvantages**
Raises triglycerides
Some GI side effects

*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

Postprandial Glucagon is Excessive and Not Corrected by Exogenous Insulin

“One wonders if the development of a pharmacological means of suppressing glucagon to appropriate levels would not increase the effectiveness of available insulin, markedly reduce insulin requirements, and perhaps improve control of the diabetic state.”

— R.H. Unger

The Incretin Effect
Beta-Cell Response to Oral vs IV Glucose

Crossover of Healthy Subjects (n = 6)
- Oral Glucose
- Intravenous (IV) Glucose

Plasma Glucose (mg/dL)
- Mean (SE): *P ≤ 0.05
- Data from Nauck MA, et al. J Clin Endocrinol Metab. 1986;63:492-498

C-peptide (nmol/L)
- *Incretin Effect

Time (min)
GLP-1 Effects in Humans
Understanding the Natural Role of Incretins

GLP-1 secreted upon the ingestion of food

Promotes satiety and reduces appetite

Alpha cells:
↓ Postprandial glucagon secretion

Beta cells:
Enhances glucose-dependent insulin secretion

Liver:
↓ Glucagon reduces hepatic glucose output

Stomach:
Helps regulate gastric emptying

Data from Larsson H. et al. Acta Physiol Scand. 1997;160:413-422
Data from Nauck MA. et al. Diabetologia. 1996;39:1546-1553
Data from Drucker DJ. Diabetes. 1998;47:159-169
GLP-1 and GIP Are Degraded by the DPP-4 Enzyme

Meal

Intestinal GIP and GLP-1 release

DPP-4 Enzyme

GIP-(1–42)
GLP-1(7–36)
Intact

Rapid Inactivation

GIP-(3–42)
GLP-1(9–36)
Metabolites

GIP and GLP-1 Actions

Half-life*
GLP-1 ~ 2 minutes
GIP ~ 5 minutes


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

**DPP-4 Inhibitors**  
(Sitagliptin)

<table>
<thead>
<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
EXENATIDE

THE FIRST INCRETIN AGONIST
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

Adapted from Nielsen LL, et al. Regul Pept. 2004;117:77-88
# 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>Hepatic glucose output</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Regulates gastric emptying</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Rate of nutrient absorption</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Food intake</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Plasma glucose acutely to near-normal levels</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Resistant to DPP-IV degradation</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Duration in plasma following a subcutaneous (SC) injection</td>
<td>Short</td>
<td>Long</td>
</tr>
</tbody>
</table>
Characteristics of Injectable Antidiabetes Drugs

Glucagon-Like Peptide (GLP) – 1 Agonists
Exenatide (Byetta), Liraglutide (Victoza) - Daily
Bydureon, Dulaglutide, Albiglutide - Weekly

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss common</td>
<td>Initial nausea</td>
</tr>
<tr>
<td>No hypoglycemia</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td>?Pancreatitis</td>
</tr>
</tbody>
</table>
Characteristics of Another Injectable Antidiabetes Drug

Pramlinitide (Symlin)

### Advantages
- Increases satiety
- Glucagon
- Gastric emptying

### Disadvantages
- Nausea/vomiting
- Injectable
- Insulin dose needs adjusting
SODIUM GLUCOSE TRANSPORTER -2 INHIBITORS
## SODIUM GLUCOSE TRANSPORTER-2 INHIBITORS

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not require insulin secretion</td>
<td>Urinary Frequency/Dehydration</td>
</tr>
<tr>
<td>Weight loss (~2 kg)</td>
<td>UTIs (7.5% vs 5.7%)</td>
</tr>
<tr>
<td>BP lowering (~4/2)</td>
<td>Mycotic infections (6.6% vs 1.7%)</td>
</tr>
<tr>
<td></td>
<td>Vulvovaginitis (females)</td>
</tr>
<tr>
<td></td>
<td>Balanitis (males)</td>
</tr>
<tr>
<td></td>
<td>eGFR affects dose</td>
</tr>
</tbody>
</table>

- UTIs (7.5% vs 5.7%)
- Mycotic infections (6.6% vs 1.7%)
- Vulvovaginitis (females)
- Balanitis (males)
- eGFR affects dose
DAPAGLIFLOXIN (FARXIGA)
CANAGLIFLOXIN (INVOKANNA)
EMPAGLIFLOXIN (JARDIANE)

Free for at least one year (to some)
Can be monotherapy or added to metformin, SUs, DPP-4 inhibitors, TZDs or even insulin
## Characteristics of Another Injectable Antidiabetes Drug

### Insulin

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most effective drug</td>
<td>SMBG required</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td>Consistency of life style required</td>
</tr>
</tbody>
</table>
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
COST OF DIABETES DRUGS

- Cost of drugs for diabetes between 2001 and 2007 almost doubled from approximately $7 billion to $13 billion, largely due to new, more expensive ones (Ann Intern Med 154:131, 2011)

- Each year from 2007 through 2010, diabetes drugs topped the list contributing to overall growth in drug spending (2011 Medco Drug Trend Report)
META-ANALYSIS* OF NON-INSULIN DRUGS VS PLACEBO

Number of randomized clinical trials – 61
Number of type 2 diabetic patients – 26,361
Drugs–TZDs, SUs, glinides, metformin, α-glucosidase inhibitors, DPP-4 inhibitors
Conclusion – all drugs associated with similar HbA1c reductions

*Sherifali et al: Diabetes Care 33:1859, 2010
META-ANALYSIS* OF NON-INSULIN DRUGS ADDED TO METFORMIN

Number of randomized clinical trials – 27
Number of type 2 diabetic patients - 11,198
Drugs–TZDs, SUs, glinides, GLP-1 agonists, α-glucosidase inhibitors, DPP-4 inhibitors
Conclusion – all drugs associated with similar Hb A1c reductions

META-ANALYSIS* OF NON-INSULIN DRUGS ADDED TO METFORMIN PLUS A SULFONYLUREA

Number of randomized clinical trials – 18
Number of type 2 diabetic patients – 4,535
Drugs–TZDs, GLP-1 agonists, α-glucosidase inhibitors, DPP-4 inhibitors
Conclusion – all drugs associated with similar Hb A1c reductions

HEAD TO HEAD COMPARISONS*
OF NON-INSULIN DRUGS

Number of randomized clinical trials – 57
Number of type 2 diabetic patients – 22,443
Drugs—metformin vs SU, TZD & DPP-4 inhibitors;
   SU vs glinides & TZD;
Conclusion – all drugs equally efficacious (except metformin more so than DPP-4 Inhibitors)

TREATMENT ALGORITHM
(Oral Drugs)

**Short Term Goal**
- Start Metformin
  - FPG < 130 mg/dl
  - *After achieving short term goal*

**Long Term Goal**
- A1C < 7.0%
  - 3 months later*

**Fail**
- Add sulfonylurea Agent (SU)
  - FPG < 130 mg/dl
  - *After achieving short term goal*
  - If occurs, reduce dose of SU

**Fail**
- Add TZD (max dose)
  - Avoid hypoglycemia *
  - A1C ≤ 7.5%
  - 4 months later

* After achieving short term goal
* If occurs, reduce dose of SU
Figure 1—FPG values measured on consecutive days. The identity line is also shown.

DIABETES CARE 22: 394, 1999
Variability of fasting blood sugar levels of diabetics determined repeatedly within one-week interval.

Diabetes 15:901, 1966
TREATMENT ALGORITHM (Oral Drugs)

Short Term Goal

Start Metformin
- FPG < 130 mg/dl
- Add sulfonylurea Agent (SU)
- Avoid hypoglycemia +

Fail
- FPG < 130 mg/dl
- Add TZD (max dose)
- A1C ≤ 7.5%

Long Term Goal

- A1C < 7.0%
- 3 months later*
- A1C < 7.0%
- 3 months later*
- A1C ≤ 7.5%
- 4 months later

* After achieving short term goal
+ If occurs, reduce dose of SU
L.A. COUNTY REQUIREMENTS FOR EXENATIDE TREATMENT

Restricted to Endocrinology
Type 2 diabetes
Failure of metformin + SU + Pio
A1C 8.0-9.5%
BMI ≥30
Add exenatide (Byetta)
A1C after 6 months >8.0%, D/C
Using Exenatide

• Start with 5 mcq b.i.d. for one month
• Month 1 - increase to 10 mcg b.i.d.
• Month 3 - measure A1C
  If A1C is >8.0% and has not decreased by at least 0.5%, D/C and start bedtime insulin; otherwise, continue exenatide
• Month 6 – measure A1C
  If A1C <8.0%, continue exenatide
  If A1C >=8.0%, D/C and start bedtime insulin
TREATMENT ALGORITHM
(Insulin)

Short Term Goal

Add bedtime NPH

Long Term Goal

Fail

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

Split/Mixed Regimen (Basal/Bolus Regimen)
D/C SU (and metformin if lean)

A1C<7.5%
3 months later*

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

Ongoing

A1C<7.0%

*After achieving short term goal
Responses to Bedtime Insulin, Daytime Sulfonylurea (BIDS) Therapy

Before BIDS  BIDS Success  BIDS Failure

Blood Glucose (mg/dl)

Breakfast  Lunch  Dinner  Bedtime NPH  Breakfast
Figure 3—24-h plasma glucose level. A: total 24-h plasma glucose values at baseline (week 0) and after 16 weeks of treatment with bedtime NPH insulin (week 16). Significant differences were observed between baseline and treatment values at each time interval (P < 0.001).

DIABETES CARE 18: 843, 1995
Bedtime Insulin

**Starting Dose**

Obese – 16 units (NPH, glargine, detemir)
Lean – 10 units (NPH, glargine, detemir)

**Incremental Doses**

Obese – 4 units or 10% of current dose, whichever is greater
Lean - 2 units or 10% of current dose, whichever is greater
INITIAL SELF TITRATION

Each morning that the FPG (measured at home) is >130 mg/dl (7.2 mmol/L), that evening’s insulin dose is increased by 1 unit in lean patients and 2 units in overweight/obese patients.

If a morning FPG value is <70 mg/dl (3.9 mmol/L), that evening’s insulin dose is decreased by 1 unit in lean patients and 2 units in overweight/obese patients.

If there have been no changes in the insulin dose for one week, self titration ceases and changes are made by the physician on an ongoing pattern basis.
TREATMENT ALGORITHM
(Insulin)

Short Term Goal

Add bedtime NPH

Long Term Goal

Fail

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

A1C<7.5%
3 months later*

Split/Mixed Regimen
(Basal/Bolus Regimen)
D/C SU (and metformin if lean)

A1C<7.0%

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

Ongoing

*After achieving short term goal
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Before Breakfast</th>
<th>Before Lunch</th>
<th>Before Supper</th>
<th>Before Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>NPH/regular or rapid-acting</td>
<td>—</td>
<td>NPH/regular or rapid-acting</td>
<td>—</td>
</tr>
<tr>
<td>B</td>
<td>NPH/regular or rapid-acting</td>
<td>—</td>
<td>Regular or rapid-acting</td>
<td>NPH</td>
</tr>
<tr>
<td>C</td>
<td>Regular or rapid-acting</td>
<td>Regular or rapid-acting</td>
<td>NPH/regular or rapid-acting</td>
<td>NPH</td>
</tr>
<tr>
<td>D</td>
<td>Regular or rapid-acting</td>
<td>Regular or rapid-acting</td>
<td>Regular or rapid-acting</td>
<td>NPH</td>
</tr>
<tr>
<td>E</td>
<td>Regular or rapid-acting</td>
<td>Regular or rapid-acting</td>
<td>Regular or rapid-acting</td>
<td>Glargine or detemir</td>
</tr>
</tbody>
</table>
INTENSIFICATION FROM BEDTIME (BASAL) INSULIN

**Basal/Bolus Insulin Regimen**

- Stop all oral drugs except metformin in overweight/obese patients to mitigate weight gain
- Maintain bedtime (basal) dose
- Add 2-4 units (lean) or 4-6 units (overweight/obese) of short- or rapid-acting insulin before meals
INTENSIFICATION FROM BEDTIME (BASAL) INSULIN

Self-Mixed/Split Insulin Regimen

• Stop all oral drugs except metformin in overweight/obese patients to mitigate weight gain
• Take 80% of bedtime (basal) dose and give 2/3rds before bkft and 1/3rd before supper as NPH insulin
• In about 1 month, add 2-4 units (lean) or 4-6 units (overweight/obese) of short- or rapid-acting insulin before bkft and supper
• Maximum NPH insulin dose is 40 units before bkft and 20 units before supper
<table>
<thead>
<tr>
<th>Insulin</th>
<th>Time Injected</th>
<th>Test Reflecting Insulin Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>Before breakfast</td>
<td>Before supper/After lunch</td>
</tr>
<tr>
<td>NPH</td>
<td>Before supper or bedtime</td>
<td>Before breakfast</td>
</tr>
<tr>
<td>Glargine</td>
<td>Before breakfast or before</td>
<td>Before breakfast</td>
</tr>
<tr>
<td></td>
<td>bedtime</td>
<td></td>
</tr>
<tr>
<td>Detemir</td>
<td>before bedtime or half of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dose at each time</td>
<td></td>
</tr>
</tbody>
</table>
### Relationship Between Insulin Injection and Time of Testing.

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Time Injected</th>
<th>Test Reflecting Insulin Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>Before a meal</td>
<td>Both following meal before which insulin is injected and before next meal or bedtime snack</td>
</tr>
<tr>
<td>Lispro</td>
<td>&quot;</td>
<td>(if insulin taken before supper)</td>
</tr>
<tr>
<td>Aspart</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Glulisine</td>
<td>&quot;</td>
<td></td>
</tr>
</tbody>
</table>
Two or More Injections of Insulin

Adjust each dose component of the insulin regimen until ≥50% of appropriate pre-prandial SMBG values are within target range, 70-130 mg/dl (3.9-7.2 mmol/L).*

*ADA recommended target
Split/Mixed Insulin Regimen

Starting Doses

<table>
<thead>
<tr>
<th>Obese</th>
<th>Before Bkft</th>
<th>Before Supper</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20N/4-6R*</td>
<td>10N/4-6R*</td>
</tr>
<tr>
<td>Lean</td>
<td>10N/2-4R*</td>
<td>6N/2-4R*</td>
</tr>
</tbody>
</table>

Incremental Doses

Obese – 4 units or 10% of current dose, whichever is greater
Lean - 2 units or 10% of current dose, whichever is greater

*Analogue rapid-acting insulins can be used

Most glucose levels before breakfast and supper should be <200 mg/dl (11.1 mmol/L) before increasing short-or rapid-acting insulin doses.
# Basal/Bolus Insulin Regimen

<table>
<thead>
<tr>
<th></th>
<th>Bkft</th>
<th>Lunch</th>
<th>Supper</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese</td>
<td>6-8R*</td>
<td>6-8R*</td>
<td>6-8R*</td>
<td>16**</td>
</tr>
<tr>
<td>Lean</td>
<td>4R*</td>
<td>4R*</td>
<td>4R*</td>
<td>10**</td>
</tr>
</tbody>
</table>

**Incremental Doses**

Obese – 4 units or 10% of current dose whichever is greater

Lean - 2 units or 10% of current dose whichever is greater

*Analogue rapid-acting insulins can be used

**NPH, glargine or detemir insulin
**CORRECTION DOSES OF INSULIN***

<table>
<thead>
<tr>
<th>Glucose (mg/dl)</th>
<th>Lean (units)</th>
<th>Overweight/Obese (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>-1</td>
<td>-2</td>
</tr>
<tr>
<td>70-150</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>151-200</td>
<td>+1</td>
<td>+2</td>
</tr>
<tr>
<td>201-250</td>
<td>+2</td>
<td>+4</td>
</tr>
<tr>
<td>251-300</td>
<td>+3</td>
<td>+6</td>
</tr>
<tr>
<td>&gt;300</td>
<td>+4</td>
<td>+8</td>
</tr>
</tbody>
</table>

*short- or rapid-acting; subsequent goal is 100-150 mg/dl
PRE-MIXED (70/30, 75/25, 50/50) INSULIN

NOT RECOMMENDED because cannot adjust each component separately; therefore, meeting targets more difficult.

Example – common pattern is high before bedtime (snack) glucose levels and target FPG values – increasing evening dose problematic because of potential for overnight hypoglycemia.

Example – another common pattern is high before lunch glucose levels and target before supper values – increasing morning dose problematic because of potential for afternoon hypoglycemia.

Almost all patients can be taught to mix insulin if enough time and effort devoted to it.
Protocol # 8
Treatment of Markedly Symptomatic Type 2 Patients

Therapeutic Consideration

- >90% of these pts can be successfully treated with sulfonylureas*
  - maximal doses in pts <65
  - half-maximal doses in pts ≥65
- Use insulin if necessary

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
TREATMENT OF NEWLY DIAGNOSED, MARKEDLY SYMPTOMATIC TYPE 2 DIABETIC PATIENTS

Start maximal dose* SA

Wait 1 wk

>120% DBW

<120% DBW

Symptoms?

FPG (mg/dL)

<300

≥300

Insulin

<130

130 - 200

>200

Decrease SA

Continue SA

Start metformin

Wait 2 wks

FPG (mg/dL)

Follow Standard Protocols

*Start with half-max dose if pt > 65 y old and increase to max dose at 1 week if no response

SA – Sulfonylurea Agent; DBW – Desirable Body Weight
WHAT’S IMPORTANT IN ACHIEVING ADA’S GLYCEMIC GOALS AND WHAT’S NOT?

Not Important – which drug(s) are being used

Important – Intensifying therapy when the present regimen is ineffective with timely, appropriate treatment decisions
MEETING THE AMERICAN DIABETES ASSOCIATION STANDARDS OF CARE

An Algorithmic Approach to Clinical Care of the Diabetes Patient

Mayer B. Davidson, MD
Hb A1c Outcomes of Nurse Following Treatment Algorithms for One Year in a Minority Population* (~75% Latinos, 25% African-Americans)

Study #1 (N = 367 randomized patients)
Hb A1c levels fell from 8.9% to 7.0%
(25% ended up on insulin – mostly bedtime alone)

Study #2 (N = 178 referred patients)
Hb A1c levels fell from 11.1% to 7.2%
(83% ended up on insulin – mostly ≥2 injections)

### PERCENT ACHIEVING A1C (<7.0%), LDL CHOL (<100 MG/DL) AND BP (<130/80 MM HG) GOALS

<table>
<thead>
<tr>
<th>Year (Ref)</th>
<th>N</th>
<th>Setting</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002 (1)</td>
<td>1,372</td>
<td>Two Urban Medical Centers</td>
<td>3.2</td>
</tr>
<tr>
<td>2004 (2)</td>
<td>1,218</td>
<td>NHANES III</td>
<td>7.3</td>
</tr>
<tr>
<td>2004 (2)</td>
<td>404</td>
<td>NHANES 1999-2000</td>
<td>5.2</td>
</tr>
<tr>
<td>2005 (3)</td>
<td>1,765</td>
<td>Academic Medical Centers</td>
<td>10.0</td>
</tr>
<tr>
<td>2005 (4)</td>
<td>439</td>
<td>Population Survey - Australia</td>
<td>2.0</td>
</tr>
<tr>
<td>2007 (5)</td>
<td>7,120</td>
<td>Academic Hospitals</td>
<td>13.0</td>
</tr>
<tr>
<td>2008 (6)</td>
<td>395</td>
<td>Endocrine Practices</td>
<td>7.3</td>
</tr>
<tr>
<td>2008 (7)</td>
<td>3,131; 3,971*</td>
<td>Primary Care Practices</td>
<td>8.5; 12.6*</td>
</tr>
<tr>
<td>2009 (8)</td>
<td>1,694</td>
<td>NHANES 1999-2006</td>
<td>12.2</td>
</tr>
<tr>
<td>2009 (9)</td>
<td>511</td>
<td>Primary Care Practices</td>
<td>7.5</td>
</tr>
<tr>
<td><strong>2010(10)</strong></td>
<td><strong>178</strong></td>
<td><strong>Community Clinic – Minorities</strong></td>
<td><strong>46.9</strong></td>
</tr>
<tr>
<td>2013 (11)</td>
<td>1,343</td>
<td>NHANES 2007-2010</td>
<td>18.8</td>
</tr>
</tbody>
</table>

DCCT

Relative risk of progression of diabetic complications by mean HbA$_{1c}$

*Based on DCCT data

Superior doctors prevent the disease.
Mediocre doctors treat the disease before evident.
Inferior doctors treat the full-blown disease.

--Huang Dee: Nai-Ching
(2600 BC First Chinese Medical Text)
Link to CDU website for copy of slides
http://www.cdrewu.edu/assets/downloads/Treatment%20of%20Diabetes-Diabetes%20Day.ppt

THANK YOU