Hypoglycemia in Diabetes:
The Dark Side of Glycemic Control

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Hypoglycemia in Diabetes

- Definition
- Physiologic response
  - Antecedent hypoglycemia and impaired counter-regulatory hormone response
  - Hypoglycemic unawareness
- Clinical impact
- Iatrogenic hypoglycemia
**Hypoglycemia - Definitions**

- Biochemical Definition = Glucose $\leq 70$ mg/dl
- Minor hypoglycemia = Patient can self-treat
- Severe hypoglycemia: Patient requires assistance
  - With or without coma and/or seizure


**Hypoglycemia - Frequency**

Proportion Experiencing at Least 1 Episode of Severe Hypoglycemia Over 9 to 12 Months

**Hypoglycemia - Frequency**

Population-based estimates of the incidence of hypoglycemia in type 1 DM and type 2 DM

<table>
<thead>
<tr>
<th></th>
<th>Any</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 DM</td>
<td>4300</td>
<td>115</td>
</tr>
<tr>
<td>Type 2 DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin-treated</td>
<td>1600 (37%)</td>
<td>35 (30%)</td>
</tr>
</tbody>
</table>


**Hypoglycemia - Frequency**

Similar Risks of Severe Hypoglycemia in Type 1 and Type 2 Diabetes Matched for Duration of Insulin Treatment

Age 63 vs 38 Years, HbA1c 10.5% vs 10.3%

Hypoglycemia - Frequency

✓ Severe hypoglycemia requiring emergency medical services:
  - 7.1% annual rate DM 1
  - 7.3% annual rate DM 2 on insulin


Hypoglycemia - Physiologic Response

- ↓ βeta-cell insulin secretion
- Glucagon – most important counterregulatory hormone with respect to effect on normalization of blood glucose level
- Epinephrine (norepinephrine) – decreases insulin production and decreases glucose uptake in peripheral tissues. Also stimulates hepatic glucose production

![Diagram]

Gerich, JE. *Diabetes* 1988;37:1608
Symptoms of Hypoglycemia

Range of frequencies (%) of individual symptoms of hypoglycemia reported in eight population studies

<table>
<thead>
<tr>
<th>Autonomic:</th>
<th>Neuroglycopenic:</th>
<th>Nonspecific:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Sweating (47-84%)</td>
<td>✓ Incoordination (31-75%)</td>
<td>✓ Weakness (28-71%)</td>
</tr>
<tr>
<td>✓ Shaking (32-78%)</td>
<td>✓ Confusion (13-53%)</td>
<td>✓ Headache (24-36%)</td>
</tr>
<tr>
<td>✓ Palpitations (8-62%)</td>
<td>✓ Drowsiness (16-33%)</td>
<td>✓ Anxiety (10-44%)</td>
</tr>
<tr>
<td>✓ Hunger (39-49%)</td>
<td>✓ Speech difficulty (7-41%)</td>
<td>✓ Nausea (5-20%)</td>
</tr>
<tr>
<td></td>
<td>✓ Tingling around mouth (10-39%)</td>
<td></td>
</tr>
</tbody>
</table>


Hypoglycemia - Loss of Physiologic Response

- All of these defenses are typically compromised in DM 1 and advanced DM 2:
  
  Decreased adrenal epinephrine response
  
  Decreased autonomic neurosympathetic activation
  
  Seems to stem from progressive insulin deficiency, improved glycemic control, and antecedent hypoglycemia
  
  Increases risk for iatrogenic hypoglycemia

Physiologic Effects of Insulin Deficiency on Hypoglycemia Risk

- Loss of β-cell signal (intra-islet insulin)
- Loss of α-cell glucagon response
- Loss of adrenomedullary epinephrine secretion (CNS driven?)

Progressive Defective Endocrine Counterregulation With Increasing Duration of Type 1 Diabetes

Peak Hormone Responses to Insulin-Induced Hypoglycemia (45 mg/dL)

- Epinephrine
- Glucagon

Patients With Type 1 Diabetes

- Nondiabetic
- 1 Month
- 1-5 Years
- 14-31 Years

The Glucagon Response to Hypoglycemia is Reduced in More Advanced Type 2 Diabetes

Glucagon Response at Plasma Glucose 45 mg/dL


Effects of Duration of Insulin Treatment on Risk of Severe Hypoglycemia

Effects of Insulin Deficiency on Hypoglycemia Risk

- **Adapted from Steffes MW, et al. Diabetes Care. 2003;26:832-836**

- **Stimulated C-Peptide at Baseline**
  - Undetectable:
    - Conventional: 37%
    - Intensive: 66%
  - Minimal:
    - Conventional: 30%
    - Intensive: 59%
  - Baseline only:
    - Conventional: 18%
    - Intensive: 60%
  - Sustained:
    - Conventional: 26%
    - Intensive: 35%

- **Effects of Antecedent Hypoglycemia**

- Insulin-deficient diabetes (no decrease in insulin, no decrease in glucagon, imperfect insulin replacement)
  - Hypoglycemia
  - Reduced sympathoadrenal responses to hypoglycemia
    - Decreased sympathetic nervous system response
    - Hypoglycemia unawareness
      - Recurrent hypoglycemia
  - Exercise
    - Decreased epinephrine response
    - Defective glucose counterregulation

### Effects of Antecedent Hypoglycemia

**Effect of 2 Episodes of Antecedent Hypoglycemia in Type 2 Diabetes**

Responses measured 1 day apart

<table>
<thead>
<tr>
<th>Epinephrine (pg/mL) at 60 mg/dL</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1000</strong></td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td><strong>2000</strong></td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td><strong>3000</strong></td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td><strong>4000</strong></td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td><strong>5000</strong></td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Symptom score at 60 mg/dL

<table>
<thead>
<tr>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

2x2 hours at ≈60 mg/dL


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### Effects of Antecedent Hypoglycemia Before and After 6 Months of Improved Glycemic Control

Responses measured 1 day apart

<table>
<thead>
<tr>
<th>Epinephrine (pg/mL) at 60 mg/dL</th>
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</tr>
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<td>10</td>
<td>15</td>
</tr>
<tr>
<td><strong>5000</strong></td>
<td>5</td>
<td>10</td>
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</tbody>
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Symptom score at 60 mg/dL

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<tr>
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</table>

2x2 hours at ≈60 mg/dL

Hypoglycemic Unawareness

“I am scared to death to go to bed with a good blood sugar because I don’t wake up when I am low. I can’t do it…I honestly think I’ll die during the night.”

“I don’t feel my lows. I hate it. Doctor, I would rather go blind than be low and not feel it.”

“I would rather be 400 than 40, because I don’t feel it when I am low.”

Prevalence:
Type 1 diabetes: 25%
Type 2 diabetes: 7-8% (and possibly higher)

Cryer, P. Insulin 2007;2:127-133
Hypoglycemic Unawareness

Consequences:
Increases risk of severe hypoglycemia by 6-fold


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Hypoglycemic Unawareness

Risk factors:
- Lower HbA₁c
- Antecedent hypoglycemia
- Older age
- Post-exercise (up to 16 hours)
- Sleep

Cryer, P. *Insulin* 2007;2:127-133
In a Hypoglycemic Clamp Study of Healthy Men, Symptom Recognition of Hypoglycemia Was Lower Among Older People

Sleep-Related, Hypoglycemia-Associated Autonomic Failure

Mean Sleep Efficiency during Hypoglycemia in Eight Non-diabetic Persons and Four Patients with Type 1 Diabetes

Banar S, Cryer PE. Diabetes 2003;348:1195-1203
Exercise-Related, Hypoglycemia-Associated Autonomic Failure

Reduced response to epinephrine and sympathetic nerve activity in muscle to hypoglycemia day following exercise

Symptoms of hypoglycemia not reduced


Hypoglycemia – Clinical Impact

Acute morbidity and mortality

Acute ischemia in high-risk patients

Acute inflammatory response & myocardial blood flow

QT prolongation – “dead in bed syndrome”

Quality of life
**Hypoglycemia – Clinical Impact**

Diabetes drug-induced hypoglycemic coma in 102 diabetic patients (92 type 2 DM, 10 type 1 DM)

- Mortality ≈ 5%
- Acute MI ≈ 2%
- Stroke ≈ 1%


**Hypoglycemia – Clinical Impact**

72-hours of continuous glucose monitoring (CGM) and holter-monitoring

(21 patients with type 2 diabetes, existing CAD, and on insulin)

- 54 episodes of < 70 mg/dl:
  - 18% of time = angina
  - 8% of time ECG changes

**Hypoglycemia – Clinical Impact**

**Hypoglycemia and acute inflammatory response**

Effect of experimental hypoglycemia on vascular parameters (14 healthy subjects: 2-hour hypoglycemic clamps on consecutive days at 53 mg/dl)

- Significant increase in plasminogen activator inhibitor-1 (PAI-1)
- Significant increase in ICAM-1
- Significant increase in endothelial adhesion molecule P-selectin
- Significant impairment in flow-mediated dilation of the brachial artery using D Doppler ultrasound


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**Hypoglycemia – Clinical Impact**

**Hypoglycemia and acute inflammatory response**

Effect of experimental hypoglycemia on myocardial blood flow (19 healthy subjects: dipyridamole scan after 1-hour euglycemic clamp and after 1-hour hypoglycemic clamp at 51-52 mg/dl)

- Myocardial blood flow **increased** by 24% during stress and euglycemia
- Myocardial blood flow **decreased** by 7% during stress and hypoglycemia

Hypoglycemia – Clinical Impact

“Dead in Bed Syndrome”

50 sudden deaths in young people (< 50 years of age) in the UK during 1990

Tattersal RB, Gill GV. *Diabet Med* 1991;8:49-58

Effect of experimental hypoglycemia on QT interval (15 patients with DM 1 or DM 2: 2 hours hypoglycemia at 54mg/dl)

Hypoglycemia – Clinical Impact

“Dead in Bed Syndrome”

Changes in QT interval in 8 individuals with type 1 diabetes during experimental hypoglycemia (40 mg/dl) lasting 120 minutes


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Hypoglycemia – Clinical Impact

“Dead in bed syndrome” and increased cardiovascular risk – potential mechanisms

Hypoglycemia-induced QT prolongation

Hypoglycemia-induced hypokalemia

Direct effect of hypoglycemia on ventricular myocardium and myocardial blood flow

Acute inflammatory effects on vascular endothelium

Rises in circulating epinephrine concentrations

Hypoglycemia-induced seizure activity
Hypoglycemia – Clinical Impact

Survey of 15,549 patients with diabetes:
96% type 2 DM and 4% type 1 DM

✓ 54% of respondents anxious about hypoglycemia all or most of the time


Iatrogenic Hypoglycemia:
Sabotaging our efforts to reduce cardiovascular disease in diabetes with aggressive glycemic control?
### Glycemic Control & CV Outcomes: UKPDS

**BMJ. 12 August, 2000**

![Graph showing glycemic control over time](image)

### Glycemic Control & CV Outcomes: ACCORD vs. ADVANCE vs. VADT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome (intensive vs. standard)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median HbA1c at end (%)</td>
<td>6.4 vs. 7.5</td>
<td>6.3 vs. 7.0</td>
<td>6.9 vs. 8.5</td>
</tr>
<tr>
<td>On TZD at study end (%)</td>
<td>91 vs. 58</td>
<td>17 vs. 11</td>
<td>53 vs. 42</td>
</tr>
<tr>
<td>On insulin at study end (%)</td>
<td>77 vs. 55</td>
<td>40 vs. 24</td>
<td>89 vs. 74</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR for mortality</td>
<td>1.22*</td>
<td>0.93</td>
<td>1.07</td>
</tr>
<tr>
<td>Major/severe hypoglycemia (%)</td>
<td>16.2 vs. 5.1</td>
<td>2.7 vs. 1.5</td>
<td>21.2 vs. 9.9</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>3.5 vs. 0.4</td>
<td>0.0 vs. -1.0</td>
<td>8.2 vs. 3.4</td>
</tr>
<tr>
<td>Weight gain &gt; 10 kg (%)</td>
<td>28 vs. 14</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>BMI change</td>
<td>2.5 vs. 1.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Glycemic Control & CV Outcomes: ACCORD vs. ADVANCE vs. VADT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
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</thead>
<tbody>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration (yr)</td>
<td>3.4</td>
<td>5.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Medical treatment at completion (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>77 vs. 55</td>
<td>41 vs. 24</td>
<td>89 vs. 74</td>
</tr>
<tr>
<td>Metformin</td>
<td>95 vs. 87</td>
<td>74 vs. 67</td>
<td></td>
</tr>
<tr>
<td>Secretagogue</td>
<td>87 vs. 74</td>
<td>94 vs. 62</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>92 vs. 58</td>
<td>17 vs. 11</td>
<td>53 vs. 42</td>
</tr>
<tr>
<td>Incretin</td>
<td>18 vs. 5</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>88 vs. 88</td>
<td>46 vs. 48</td>
<td>86 vs. 83</td>
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<tr>
<td>Any antihypertensive drug</td>
<td>91 vs. 92</td>
<td>89 vs. 88</td>
<td></td>
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<tr>
<td>ACE-inhibitor</td>
<td>70 vs. 72</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>76 vs. 76</td>
<td>57 vs. 55</td>
<td>88 vs. 86</td>
</tr>
</tbody>
</table>

## Therapies for Type 2 DM in 2010

( Pathophysiologic Effects of Drugs for the Treatment of Type 2 DM)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Insulin Deficiency</th>
<th>Insulin Resistance</th>
<th>Excessive Hepatic Glucose Production</th>
<th>Inappropriate Elevated Glucagon Secretion</th>
<th>Gastric Emptying Dysregulation</th>
<th>Body Weight Dysregulation</th>
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<tbody>
<tr>
<td>Biguanides</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Neutral</td>
</tr>
<tr>
<td>TZDs</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Increase</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Neutral</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Beneficial</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Increase</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Beneficial</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Neutral</td>
</tr>
<tr>
<td>Insulin</td>
<td>Beneficial</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Increase</td>
</tr>
<tr>
<td>Amylinomimetics</td>
<td>None</td>
<td>None</td>
<td>Beneficial</td>
<td>Beneficial</td>
<td>None</td>
<td>Increase</td>
</tr>
<tr>
<td>Incretin mimetics</td>
<td>Beneficial</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Beneficial</td>
<td>Decrease</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>Beneficial</td>
<td>None</td>
<td>None</td>
<td>Beneficial</td>
<td>Unknown</td>
<td>Neutral</td>
</tr>
</tbody>
</table>
The ‘Octuplet’ of Defects in Type 2 Diabetes

At diagnosis: Lifestyle + Metformin

STEP 1
- Lifestyle + metformin + Basal insulin
- Lifestyle + metformin + Sulfonylurea

STEP 2
- Lifestyle + metformin + Intensive insulin
- Lifestyle + metformin + Basal insulin

STEP 3
- Lifestyle + metformin + Pioglitazone
- Lifestyle + metformin + GLP-1 agonist

Tier 1: Well-validated core therapies

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/vomitting
A1C 6.5 – 7.5% **

** Monotherapy

- MET
- GLP-1
- TZD
- AGI

2 - 3 Mos.***

A1C 7.6 – 9.0%

** Dual Therapy

- MET + GLP-1 or DPP4
- TZD
- SU or Glinide

A1C 9.0%

Drug Nexus

- Under Treatment

- No Symptoms

Triple Therapy

- MET + GLP-1 or DPP4 + TZD
- SU

AACE/ACE Algorithm for Glycemic Control Committee

Chairpersons:
- Helena W. Rodbard, MD, FACP, MACE
- Paul S. Jellinger, MD, MACE
Zachary T. Bloomgarden, MD, FACE
Jaime A. Davidson, MD, FACP, MACE
Daniel Einhorn, MD, FACP, FACE
Alan J. Garber, MD, PhD, FACE
James R. Gavin III, MD, PhD
George Grunberger, MD, FACP, FACE
Yehuda Handelsman, MD, FACP, FACE
Edward S. Horton, MD, FACE
Harold Lebovitz, MD, FACE
Philip Levy, MD, MACE
Etie S. Moghissi, MD, FACP, FACE
Stanley S. Schwartz, MD, FACE

May not be appropriate for all patients

*For patients with diabetes and A1C < 6.5%, pharmacologic Rx may be considered

**A1C goal not achieved with any monotherapy

† Preferred initial agent

‡ DPP4 if HbA1c < 7.2% or GLP-1 if HbA1c > 7.2%

§ TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)

¶ AGI if HbA1c < 7.2%

5 Glinide if HbA1c > 7.2% or SU if FPG

6 Low-dose secretagogue recommended

a) Discontinue insulin secretagogue with multidose insulin

b) Can use pramlintide with prandial insulin

2 - 3 Mos.**

A1C 8.5 – 9.0%

Triple Therapy

- MET + GLP-1 or DPP4 + TZD
- SU or Glinide

A1C > 9.0%

- INSULIN + Other Agent(s)

Double Nexus

- Symptom
- No Symptom

Triple Nexus

- Under Treatment
- No Symptoms
- Symptom

2 - 3 Mos.***

HbA1c Over Time

Rosiglitazone vs Metformin: -0.13 (-0.22 to -0.05), P=0.002
Rosiglitazone vs Glyburide: -0.42 (-0.52 to -0.33), P<0.001
### Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>Glyburide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain (kg)</td>
<td>4.8</td>
<td>-2.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Hypoglycemia (%)</td>
<td>10</td>
<td>12</td>
<td>39</td>
</tr>
<tr>
<td>Edema (%)</td>
<td>14</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>

### Hypoglycemia with Commonly-Used Treatment Regimens for Type 2 DM

**Monotherapy Regimen** | **Rate of Hypoglycemia**  
--- | ---  
DPP-IV inhibitors | 1-4% (24 weeks)  
GLP-1 analogs | 4% (24 weeks)  
Thiazolidinediones | 10% (5 years)  
Metformin | 12% (5 years)  
Sulfonylurea | 39% (5 years)
Hypoglycemia: Glyburide vs. Other SUs

Glyburide vs Other 2nd and 3rd generation SUs:

44-83% more hypoglycemia with glyburide

- Trend (NS) to more frequent severe hypoglycemia
- Mechanism uncertain:
  - ↑ biologic T 1/2 ?
  - Tighter SU receptor binding?

No ↑ in CV events, mortality, or weight gain

Diabetes Care 2007;30:389
At diagnosis:

**Lifestyle + Metformin**

**Tier 1: Well-validated core therapies**

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

**STEP 2**
- **Lifestyle + metformin**
- Pioglitazone
- No hypoglycemia
- Edema/CHF
- Bone loss

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

**STEP 3**
- **Lifestyle + metformin**
- Intensive insulin
- Pioglitazone

**Tier 2: Less well validated therapies**

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

**STEP 2**
- **Lifestyle + metformin**
- Sulfonylurea

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

**A1C**

- **6.5 – 7.5%**
  - Monotherapy
  - **MET** + GLP-1 or DPP4
  - TZD
  - AGI

- **7.6 – 9.0%**
  - Dual Therapy
  - **MET** + GLP-1 or DPP4
  - TZD
  - SU or Gluclide

- **9.0%**
  - Triple Therapy
  - **INSULIN** ± Other Agent(s)

**Drug Naive**

- Under Treatment

**Symptoms**

- No Symptoms

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Hypoglycemia with Commonly-Used Treatment Regimens for Type 2 DM

<table>
<thead>
<tr>
<th>Dual-Combination Regimens</th>
<th>Rate of Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-IV inhibitor/TZD</td>
<td>3-4% (24 weeks)</td>
</tr>
<tr>
<td>GLP-1 analog/metformin</td>
<td>5% (30 weeks)</td>
</tr>
<tr>
<td>DPP-IV inhibitor/metformin</td>
<td>5-8% (24-52 weeks)</td>
</tr>
<tr>
<td>TZD/metformin</td>
<td>8% (30 weeks)</td>
</tr>
<tr>
<td>TZD/GLP-1 analog</td>
<td>11% (16 weeks)</td>
</tr>
<tr>
<td>Sulfonylurea/DPP-IV inhibitor</td>
<td>13-15% (24 weeks)</td>
</tr>
<tr>
<td>Sulfonylurea/metformin</td>
<td>18-32% (24 weeks-2 years)</td>
</tr>
<tr>
<td>Sulfonylurea/GLP-1 analog</td>
<td>30-35% (30-32 weeks)</td>
</tr>
</tbody>
</table>

Tier 1: Well-validated core therapies

At diagnosis:
Lifestyle + Metformin

STEP 1
Lifestyle + metformin + Basal insulin

STEP 2
Lifestyle + metformin + Sulfonylurea

三级
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

STEP 2
Lifestyle + metformin + Pioglitazone + Sulfonylurea

STEP 3
Lifestyle + metformin + Basal insulin
Hypoglycemia with Commonly-Used Treatment Regimens for Type 2 DM

### Triple-Combination Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Rate of Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin/DPP-IV/TZD</td>
<td>4% (54 weeks)</td>
</tr>
<tr>
<td>Sulfonylurea/metformin/DPP-IV</td>
<td>12% (24 weeks)</td>
</tr>
<tr>
<td>Sulfonylurea/metformin/GLP-1</td>
<td>19-28% (30 weeks)</td>
</tr>
<tr>
<td>Sulfonylurea/metformin/TZD</td>
<td>51-53% (24-30 weeks)</td>
</tr>
</tbody>
</table>

Roberts L, et al. *Clinical Therapeutics* 2005;27:1535-1547
### Hypoglycemia with Commonly-Used Insulin Regimens

**New to insulin therapy (< 2 years)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hypoglycemic events/pt/y</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT (4-T Study Group)</td>
<td></td>
</tr>
<tr>
<td>Basal insulin Detemir</td>
<td>2.3</td>
</tr>
<tr>
<td>Biphasic Aspart 70/30 bid</td>
<td>5.7</td>
</tr>
<tr>
<td>Prandial insulin Aspart tid</td>
<td>12.3</td>
</tr>
<tr>
<td><strong>Prosective Observational Study</strong></td>
<td></td>
</tr>
<tr>
<td>Oral secretagogues</td>
<td>1.9</td>
</tr>
<tr>
<td>All insulin therapies &lt; 2 yrs</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*N Engl J Med 2007;357:1716  
Diabetologia 2007;50:1140*

### Severe Hypoglycemia with Commonly-Used Insulin Regimens

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Patients with Severe Hypoglycemia over 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT (4-T Study Group)</td>
<td></td>
</tr>
<tr>
<td>Basal insulin Detemir</td>
<td>1.7%</td>
</tr>
<tr>
<td>Biphasic Aspart 70/30 bid</td>
<td>4.7%</td>
</tr>
<tr>
<td>Prandial insulin Aspart tid</td>
<td>6.7%</td>
</tr>
<tr>
<td><strong>Prosective Observational Study</strong></td>
<td></td>
</tr>
<tr>
<td>Oral secretagogues</td>
<td>7.0%</td>
</tr>
<tr>
<td>Type 2 DM on insulin &lt; 2 yrs</td>
<td>7.0%</td>
</tr>
<tr>
<td>Type 2 DM on insulin &gt; 5 yrs</td>
<td>25%</td>
</tr>
<tr>
<td>Type 1 DM on insulin &gt; 15 yrs</td>
<td>46%</td>
</tr>
</tbody>
</table>

*N Engl J Med 2007;357:1716  
Diabetologia 2007;50:1140*
APPROACH TO HYPOGLYCEMIA IN CLINIC

Step 1: Detect episodes

• **Quiz pt + family members q visit**
  – Done in only 30% of 1° care visits

• **Review SMBG log for biochemical hypoglycemia**
  – ↓ sensitivity (<25%) of forearm vs fingertip SMBG

• **Screen for nocturnal hypoglycemia**
  – Nightsweats, AM headache or Δ mentation, nightmares
  – Periodic SMBG

• **CGM studies?**

  Diabetes Care 2005; 28:708
  Diab Educator 2004; 30:126

APPROACH TO HYPOGLYCEMIA IN CLINIC

Step 2: Characterize episodes

• **Mild vs Severe**
  – Severe episodes red flag for:
    • Antecedent hypoglycemia, recognized/unrecognized
    • Hypoglycemic unawareness
    • High risk of future severe episodes

• **Symptom patterns (or absent symptoms)**
  – Teach patients to recognize own unique symptoms
  – Detect hypoglycemia unawareness

  Diabet Med 2001; 18:690
APPROACH TO HYPOGLYCEMIA IN CLINIC

REVIEW OF SYSTEMS

Date: _______________________

PLEASE CHECK ANY NEW SYMPTOMS THAT YOU HAVE DEVELOPED IN EACH CATEGORY SINCE YOUR LAST VISIT

CHECK NO IF THEY DON’T APPLY TO YOU

☐ No ☐ Yes ☐ Weight Loss/ or Gain ☐ Fatigue

☐ No ☐ Yes ☐ Frequent Low Blood Sugar Reactions
☐ Any Episodes of Severe Low Blood Sugar Reactions Requiring Help from Another Person
☐ Excessive thirst or urination

☐ No ☐ Yes ☐ Blurry Vision/Double Vision/ or Change in Vision
☐ Painful Eyes ☐ Floaters

☐ No ☐ Yes ☐ Chest Pain/ Pressure/ or Discomfort ☐ Shortness of Breath
☐ Headaches ☐ Concern about Blood Pressure
☐ Swelling of Legs/ Ankles/ or Feet

☐ No ☐ Yes ☐ Feeling Down/ Sadi/ or Depressed
☐ Lack of Interest or Pleasure in Activities
☐ Feelings of Anxiety or Panic
☐ Feeling that Diabetes Overwhelms Your Life

McAulay, V., Deary, I. J. & Frier, B. M.

Symptoms of hypoglycaemia in people with diabetes.
Diabetic Medicine 18 (9), 690-705.
doi: 10.1046/j.1464-5491.2001.00620.x

Table 5a Hypoglycaemia Symptoms Score Questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warmness</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty speaking</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pounding heart</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inability to concentrate</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shivering</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Double vision</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hunger</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiredness</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tingling lips</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trembling</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Instructions: Please score each of the above symptoms as you feel at this moment, e.g. if you are not hungry then please circle 1 for hunger; or if you are the most hungry you have ever felt then circle 7.
McAulay, V., Deary, I. J. & Frier, B. M.
Symptoms of hypoglycaemia in people with diabetes.
*Diabetic Medicine* **18** (9), 690-705.
doi: 10.1046/j.1464-5491.2001.00620.x

Table 5b: Hypoglycaemia Symptoms Awareness Questionnaire

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Always 1 2 3 4 5 6 7 Never</td>
<td></td>
</tr>
</tbody>
</table>

**APPROACH TO HYPOGLYCEMIA IN CLINIC**

**Step 3: Determine etiology of episode**

- **Absolute/relative ↑ insulin:**
  - Wrong dose
  - Ill-timed dose (esp. NPH/reg, biphasic)
  - Suboptimal insulin type for pt

- **Too little exogenous glucose:**
  - Missed meal/snack
  - Delayed meal
  - Smaller prior meal
APPROACH TO HYPOGLYCEMIA IN CLINIC

Step 3: Determine etiology of episode

- **↑ glucose utilization:**
  - During exercise

- **↑ insulin sensitivity:**
  - Post-strenuous exercise for 16-24h
  - New insulin-sensitizing medications

- **↓ endogenous glucose production:**
  - Alcohol intake (? Only in T1DM?)

APPROACH TO HYPOGLYCEMIA IN CLINIC

Step 4: Prevention – patient ☼ clinician education

- **Patient education materials:**
  - “When glucose levels are too low: a major barrier to taking control of your diabetes.” S Edelman MD
  - www.insulinjournal.com (Click on “Patient Handouts”)

- **Regiment meal-snack times/amounts**
  - Especially with NPH/reg or biphasic regimens
    - Snacks if meals delayed

- **Regiment insulin administration times**
Step 4: Prevention – patient + clinician education

• Frequent SMBG with insulin Rx
  – Routine
  – Periodic HS testing
  – Before, during, after strenuous exercise
    • Snack before
  – With illness
  – Before/during driving, heavy machinery use

• Carry glucose tabs/gels/liquids at all times

• Medical identification

Step 4: Prevention – patient + clinician education

• Insulin adjustments:
  Pre-breakfast hypo ← basal long-acting insulin
  Daytime hypo ← short/rapid-acting insulin
  Nocturnal hypo ← either type insulin

• Insulin types:
  Glargine, determir: 32% less hypoglycemia than NPH
  Rapid-acting analogues: less hypoglycemia than regular

Diabetes 2007; 56(Suppl 1):603
Step 4: Prevention – patient θ clinician education

• **Hypoglycemic unawareness:**
  – Reset higher glycemic goals (± temporary)
  – Frequent SMBG; no fasts > 4h
  – Educate family/friends re symptoms/signs
  – Glucagon kit and instructions
  – Avoid hypoglycemia x 4 wks → restore symptoms

• **Severe hypoglycemia:**
  – Adjust insulin(s) if no apparent cause

Step 5: Appropriate Rx

• **Access to rapidly absorbed CHO at all times**
  – Home, office, care, purse, pocket

• **“Rule of 15”:**
  – 15 g CHO raises glucose 50 mg% in 15 min

• **Commercial glucose products preferred**
  – Portable
  – ↓ calories
  – Less temptation
  – No fat to slow glucose absorption