Hypoglycemia And LADA

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Goals of Optimal Glucose Control

- Maintain euglycemia
- Minimize hyperglycemia
- Avoid hypoglycemia
- Prevent complications
- Normalize lifestyle / flexibility

Classification of hypoglycemia in diabetes:

- Severe hypoglycemia:
  - Event requiring assistance of another person to actively administer carbs, glucagon, or take other corrective actions. Glucose levels may not be available during an event, but neurological recovery following, the return of the glucose to normal is considered sufficient evidence that event was induced by low glucose.

- Documented symptomatic hypoglycemia:
  - Event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose level <70 mg/dL.

- Pseudo-hypoglycemia:
  - Event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured plasma glucose >70 mg/dL but approaching that level.
99,628 ED visits - adverse drug events in adults >65 y/o yearly from 2007 - 2009

Hypoglycemia and “Tight” Control

DCCT-Type 1

UKPDS-Type 2

ACCORD, ADVANCE, and VADT

- Episode of severe hypoglycemia associated increased risk of subsequent mortality.
- In ACCORD, those who had one or more severe hypoglycemic episodes had higher rates of death than those without such episodes across both study arms (hazard ratio 1.41 [95% CI 1.03–1.93])
- In VADT, a recent severe hypoglycemic event was the strongest independent predictor of death at 90 days
- In ADVANCE, where rates of hypoglycemia were low, hypoglycemia was a predictor of death
Physiology of Hypoglycemia

Symptoms of Hypoglycemia

<table>
<thead>
<tr>
<th>AUTONOMIC (Neurogenic)</th>
<th>NEUROGLYOPENIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaky/tremulous</td>
<td>Confused</td>
</tr>
<tr>
<td>Heart pounding</td>
<td>Tired/drowsy</td>
</tr>
<tr>
<td>Nervous/anxious</td>
<td>Weak</td>
</tr>
<tr>
<td>Sweaty</td>
<td>Difficulty speaking</td>
</tr>
<tr>
<td>Hungry</td>
<td>Difficulty with coordination</td>
</tr>
</tbody>
</table>

Nocturnal Hypoglycemia

- Often asymptomatic but roughly counts 50% of hypoglycemia.
- Often unrecognized by the patient.
- Leads to more severe hypoglycemic episodes.
- Reduces energy level the next day.

Contributing Factors to Hypoglycemia

- Medications
  - Insulin
  - Sulfonylureas
- Delayed gastric emptying-gastroparesis
- Exercise
- Sleep
- Alcohol
- Age
- Duration of diabetes
- Hypoglycemia unawareness
- Previous hypoglycemia
Sequence of Responses to Falling Arterial Plasma Glucose

<table>
<thead>
<tr>
<th>Plasma Glucose (mg/dl)</th>
<th>Countercalulatory hormone release</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>Glucagon and Epinephrine</td>
</tr>
<tr>
<td>80</td>
<td>Adrenergic symptoms</td>
</tr>
<tr>
<td>70</td>
<td>Neuroglycopenic symptoms</td>
</tr>
<tr>
<td>60</td>
<td>Decreased cognition, aberrant behavior, Lethargy</td>
</tr>
<tr>
<td>50</td>
<td>Coma and/or Convulsions</td>
</tr>
<tr>
<td>40</td>
<td>Neuronal death (brain death)</td>
</tr>
</tbody>
</table>

Type 1 Diabetes and Advanced Type 2: Hypoglycemia Unawareness

- Glucose ↓
- Insulin ↓
- Glucagon ↑
- Attenuated Epinephrine ↑
- Growth Hormone and Cortisol ↑
- Other Hormones and Neurotransmitters

Hypoglycemia Begets Hypoglycemia: Hypoglycemia Associated Autonomic Failure (HAAF)

- Relative insulin deficiency and insulin resistance
- Type 2 Diabetes
- Pharmacotherapy and absolute insulin excess
- Sleep
  - Reduced sympathetic neural responses
  - Reduced hypothalamic suppression
- Autonomic Hypoglycemia
  - Reduced sympathetic neural responses
  - Reduced epinephrine response
  - Effective glucose counterregulation
- Hypoglycemia Unawareness
- Recurrent hypoglycemia
Complications of Hypoglycemia

- Seizures/unconsciousness
- Behavior changes and diminished cognitive function
- Reduce quality of life
  - Weight gain
  - Decreased treatment satisfaction
- Negative effect on adherence to treatment and glycemic control

Vercruy P et al. Diab Obes and Metab. 2008;10 (suppl 1):S5-S24

Complications of Severe Hypoglycemia

Plasma glucose level

Increased Risk of Cardiac Arrhythmia
- Abnormal prolonged corrected QTc interval
- ST and QT dispersion
- Sudden death

Progressive Neuroglycopenia
- Cognitive impairment
- Unusual behavior
- Seizure
- Coma
- Brain death

2. Shi Y et al. Diabetes Metab. 2005;31:520-525

Nocturnal Hypoglycemia

- Episodes Can Be Fatal
  - Cardiac Arrhythmia thought to be cause
- Effects during subsequent day
  - Impaired mood
  - Increased physical fatigue
  - Increased morning food intake

Severe Hypoglycemia and Dementia

<table>
<thead>
<tr>
<th>Number of Hypoglycemic Episodes</th>
<th>Number of Dementia Cases</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Episode</td>
<td>130</td>
<td>1.26 (1.10 - 1.49)</td>
</tr>
<tr>
<td>2 Episodes</td>
<td>57</td>
<td>1.00 (0.97 - 1.03)</td>
</tr>
<tr>
<td>3 or More Episodes</td>
<td>43</td>
<td>1.04 (1.02 - 1.06)</td>
</tr>
</tbody>
</table>

Hypoglycemia: Short Term Disability and Health Care Costs

<table>
<thead>
<tr>
<th></th>
<th>Patients With Hypoglycemia* (n=424)</th>
<th>Patients Without Hypoglycemia (n=2232)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or More Episodes of Short-term Disability</td>
<td>47%</td>
<td>32%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Days of Short-term Disability Per Person-Years</td>
<td>19.5</td>
<td>11.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Annualized Health Care Expenditure</td>
<td>$1169</td>
<td>$1012</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Strategies to Prevent Hypoglycemia

1) Discuss hypoglycemia risk factors and treatment routinely with patients receiving treatment with insulin or sulfonylurea/glinide drugs
   a. Especially those with a history of recurrent hypoglycemia or impaired awareness of hypoglycemia.
2) Patients must understand how their medications work so they can minimize the risk of hypoglycemia.
3) When evaluating report of hypoglycemia, adopt approaches that guide the patient to a correct identification of the precipitating factors of the episodes of hypoglycemia.
   a. Skipper or mealskipped, unusual exertion, alcohol ingestion, insulin dosage mishaps, etc.
   b. To increase patient's appreciation of the behavioral factors that predispose to hypoglycemia.
Strategies to Prevent Hypoglycemia

- Dietary intervention
- Exercise management
- Medication adjustment
- Glucose monitoring
  - Continuous glucose monitoring

Restoring Hypoglycemia Awareness

- Hypoglycemia unawareness partly caused by frequent and recurrent hypoglycemia.
  - To avoid such frequent hypoglycemia, adjustments in the treatment regimen that avoid hypoglycemia are necessary
  - Restoration of autonomic symptoms of hypoglycemia can occur within 2 weeks, and complete reversal of hypoglycemia unawareness by 3 months.
  - In some but not all reports, the recovery of symptoms is accompanied by the improvement in epinephrine secretion
  - Return of hypoglycemic symptom awareness was associated with a modest increase (0.5%) of A1c

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)
4. OTHER CONSIDERATIONS

- Age: Older adults
  - Reduced life expectancy
  - Higher CVD burden
  - Reduced GFR
  - At risk for adverse events from polypharmacy
  - More likely to be compromised from hypoglycemia
  - Less ambitious targets
  - HbA1c <7.5–8.0% if tighter targets not easily achieved
  - Focus on drug safety

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Recommendations: When Goal is to Avoid Hypoglycemia

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

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AADO (patients with new-onset diabetes)^

<table>
<thead>
<tr>
<th>Drug</th>
<th>Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TZD (Rosiglitazone)</td>
<td>9.8</td>
</tr>
<tr>
<td>Metformin</td>
<td>11.6</td>
</tr>
<tr>
<td>Sulfonlurea (Glyburide)</td>
<td>38.7*</td>
</tr>
</tbody>
</table>
4. OTHER CONSIDERATIONS

- Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

- Metformin: CVD benefit (UKPDS)
- Avoid hypoglycemia
- SU & ischemic preconditioning
- Pioglitazone & ↓ CVD events
- Effects of incretin-based therapies

- Increased risk of hypoglycemia
- Metformin & lactic acidosis
- US: stop if SQ ≥ 1.5 (L.4 women)
- UK: half dose if GFR 45 & stop if GFR < 30
- Caution with SUs (esp. glyburide)
- DPP-4 IS – dose adjust for most
- Avoid exenatide if GFR > 30
4. OTHER CONSIDERATIONS

- Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

Emerging concern regarding association with increased morbidity/mortality
Proper drug selection is key in the hypoglycemia prone

Diabetes Care 2012;35:S64–S70
Diabetologia 2012;55:1577–1596

AGS 2012 BEERS CRITERIA FOR POTENTIALLY INAPPROPRIATE MEDICATION USE IN OLDER ADULTS

<table>
<thead>
<tr>
<th>Drugs to Avoid</th>
<th>Rationale</th>
<th>Recommend</th>
<th>Quality of Evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin, sliding scale</td>
<td>Hypoglycemia risk</td>
<td>Avoid</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>Chlorpropamide Glyburide</td>
<td>Hypoglycemia risk</td>
<td>Avoid</td>
<td>High</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Diabetes and Driving

- Special care should be taken to prevent hypoglycemia while operating a vehicle in drivers with type 1 diabetes and in at risk patients with type 2 diabetes
  - Instruct to always check blood glucose before getting behind the wheel and at regular intervals while driving for periods of 1 hour or greater.
  - Consider factors that may precipitate a fall in blood glucose: time of insulin dose, timing of the last food ingestion, and exercise type, duration, intensity, and timing.
  - Low glucose should be treated immediately and appropriately: the driver should not drive until glucose is in a safely acceptable range, usually after 30–60 min because of delayed recovery of cognitive function.
  - Always carry a glucose meter and snacks, including a quick-acting source of sugar (such as juice, nondiet soda, hard candy, or dextrose tablets) as well as snacks with complex carbohydrates, fat, and protein (e.g., cheese crackers) in vehicle.
  - Never begin an extended drive with low normal blood glucose (e.g., 70–90 mg/dL) without prophylactic carbohydrate consumption to avoid a fall in blood glucose during the drive.
Hypoglycemia: Patient Barriers

- Fear of severe hypoglycemia can inhibit use of medications and impair ability to control diabetes
- Hypoglycemia leads to less satisfaction with medications
  - Lower adherence
  - Powerlessness, anxiety, and decreased quality of life
- Fear hypoglycemia as much as complications of diabetes
- Fear of hypoglycemia itself
- Nocturnal hypoglycemia can lead to "hangover" the next day and loss of energy

Treating Hypoglycemia

- Treatment should be administered by the "Rule of 15s".
  - 15 grams of oral glucose followed by SMBG in 15 minutes
  - Examples:
    - 1-4 glucose tablets
    - 1-2 pieces of hard candy
    - 6 oz of regular soda
    - 4 oz of fruit juice
    - 1/2 cup milk
    - Glucose gel
- Following correction of acute event, intake of long-acting carbohydrates is advised

Treating options include:
- Glucagon:
  - 0.5-1.0 mg SQ or IM via glucagon injection kit
  - 0.5-1.0 mg IV
- Intravenous Dextrose:
  - 25 grams of 5% dextrose

LADA
**What Is LADA?**

1. The missing word in the phrase “Gotta ____ Love”
2. Latent Autoimmune Diabetes of Adults
3. Russian car company

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**Patient Case, Frances: LADA?**

- 36-year-old female with diabetes for 9 months
- Failing maximum doses of glyburide and metformin, and low-carb diet
  - BMI of 24
  - Fasting plasma glucose: 210 mg/dL
  - HbA1c: 9.2%

**Question: What are the possible alternatives for management?** + anti-GAD and anti-ICA

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**LADA: Definition**

1. Adult age of onset of diabetes
2. Presence of circulating islet antibodies
3. Lack of requirement for insulin for at least 6 months after diagnosis
4. Oral agents fail earlier

LADA: Definition of Autoimmunity Terms

- GADA = glutamic acid decarboxylase antibody (GAD antibody, GAD 65 ab)
- ICA = islet cell antibody
- IA-2 = islet antigen-2

Latent Autoimmune Diabetes of Adults (LADA):
Previous and Suggested Terminology

- Type 1.5 diabetes
- Slowly progressive autoimmune diabetes
- Type 1 diabetes and "change"
- Slowly progressive insulin-dependant diabetes
- Autoimmune diabetes in adults with slowly progressive beta cell failure (ADASP)
- ADA classification –still under Type 1 autoimmune diabetes

Features of LADA

- Patients usually aged ≥ 25 years
- Clinical presentation “masquerading” as non-obese type 2 diabetes
- Initial control achieved with diet alone or diet and oral hypoglycaemic agents
- Insulin dependency occurs within months but can take 10 years or more
- Other features of type 1 diabetes
  - Low fasting and post-glucagon stimulated C-peptide
  - HL.A susceptibility alleles
  - ICA+ GADA+
### 10% – 15% Type 2 Are LADA

<table>
<thead>
<tr>
<th></th>
<th>Type 2</th>
<th>LADA (Type 1.5)</th>
<th>Type 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (yrs)</td>
<td>30–90</td>
<td>35–70</td>
<td>0–35</td>
</tr>
<tr>
<td>Range</td>
<td>&gt;40</td>
<td>35–70</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Predominance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of diabetic patients</td>
<td>70%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Presence of GADA, ICA, IA2</td>
<td>No</td>
<td>Yes (35%)</td>
<td>Yes (64%)</td>
</tr>
<tr>
<td>Increased risk for endocrine autoimmunity</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Yrs to progress to insulin requirement</td>
<td>8 (6–10)</td>
<td>4 (2–6)</td>
<td>Insulin dependent from diagnosis</td>
</tr>
<tr>
<td>Prevalence of macrovascular complications</td>
<td>Very high</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>


### Further Breakdown of Prevalence of LADA

- 10% of patients with type 2 diabetes
- ~25% of patients diagnosed with type 2 diabetes under the age of 35

### Beta Cell Function Over Time in Patients With and Without Islet Antibodies

Stenström et al. Diabetes 54 (Supplement 2): S68
Islet Cell Autoimmunity in a Triethnic Adult Population of the NHANES III

- The prevalence of GAD65 autoantibody was higher in diabetic participants compared with nondiabetic participants in...
  - Non-Hispanic whites (n=920; 6.3% vs 2.0%; P=0.001) and...
  - Non-Hispanic blacks (n=534; 3.7% vs 1.3%; P=0.08)
  - But not in Mexican-Americans (n=646; 1.2% vs 2.6%; P=0.18)


UKPDS 25 . . .

- 3672 Caucasian patients between the ages of 25 and 65 (12% had + ab)
- 94% of patients who were GADA + or ICA + required insulin within 6 years as opposed to only 14% of those without antibodies
  - Proportion with ICA and GADA decreased with increasing age at diagnosis
  - ICA +
    - 21% ages 25-34
    - 4% ages 55-65
  - GADA +
    - 34% ages 25-34
    - 7% ages 55-65


Is Identifying LADA Clinically Useful?

- Early diagnosis of LADA may aid in determining therapy
- Early and intensive therapy with insulin may have benefits
  - Intensive therapy using insulin in LADA patients may help preserve ß-cell function
  - Preserving ß-cell function may lead to fewer complications and less hypoglycemia
Patient Case, Frances: LADA?

- 36-year-old female with diabetes
- Failing maximum doses of glyburide and metformin, and low-carb diet for 9 months
  - BMI of 24
  - Fasting plasma glucose: 210 mg/dL
  - HbA1c: 9.2%
- **Question: How should you intervene with this LADA patient?**

LADA-Review

- Autoimmune type of diabetes
- Initially identified as Type 2 diabetes
- Progression to needing insulin is more rapid
- Clinical features:
  - Tend to be young at onset (<45 y/o)
  - Lower BMI
  - Caucasian or African American
- Laboratory findings:
  - Positive GADA and/or ICA

LADA: Conclusion

- Next time a new “Type 2” patient with characteristics of LADA presents, consider antibody testing
- If the patient has LADA, consider starting insulin and intensify therapy
Hypoglycemia Patient Questionnaire

1. To what extent can you tell by your symptoms that your blood glucose is LOW?
   Never ____ Rarely ____ Sometimes ____ Often ____ Always ____

2. In a typical week, how many times will your blood glucose go below 70 mg/dL? ______ a week

3. When your blood glucose goes below 70 mg/dL, what is the usual reason for this?

4. How many times have you had a severe hypoglycemic episode (where you needed someone's help and were unable to treat yourself)?
   Since the last visit ____ times. In the last year ______ times

5. How many times have you had a moderate hypoglycemic episode (where you could not think clearly, properly control your body, had to stop what you were doing, but you were still able to treat yourself)?
   Since the last visit ____ times. In the last year ______ times

6. How often do you carry a snack or glucose tablets (or gel) with you to treat low blood glucose?
   Check one of the following: Never ___ Rarely ___ Sometimes ____ Often ____ Almost always___

7. How LOW does your blood glucose need to go before you think you should treat it?
   Less than ____ mg/dL

8. What and how much food or drink do you usually treat low blood glucose with?

9. Do you check your blood glucose before driving? Check one of the following:
   Yes, always ___ Yes, sometimes ___ No ___

10. How LOW does your blood glucose need to go before you think you should not drive? ______ mg/dL

11. How many times have you had your blood glucose below 70 mg/dL while driving?
   Since the last visit ____ times. In the last year ______ times

12. If you take insulin, do you have a glucagon emergency kit? Yes ___ No ___

13. Does a spouse, relative, or other person close to you know how to administer glucagon? Yes ___ No ___

Which of the following is NOT a potential contributor to hypoglycemia in people with diabetes?

A. Insulin and sulfonylureas
B. Sleep
C. Alcohol intake
D. Previous hypoglycemia
E. Caffeine intake
Which of the following is NOT a feature of LADA?

A. Patients are usually >25 years old  
B. The patient will probably never need insulin  
C. May have + ICA and GADA antibodies  
D. Patients “masquerade” as having non obese type 2 diabetes  
E. Initially may be controlled with diet and/or oral hypoglycemics.

Which of the following are complications of hypoglycemia?

A. Behavior changes and diminished cognitive function  
B. Reduce quality of life with weight gain and decreased treatment satisfaction  
C. Negative effect on adherence to treatment and glycemic control  
D. Improved mood as hypoglycemia helps treat depression  
E. A, B, and C

Which of the following is true concerning LADA?

A. 10-15% of patients classified as having type 2 diabetes may have LADA  
B. Patients tend to be more overweight than other people with diabetes  
C. Patients with LADA are more often Caucasian or African American  
D. Patients with LADA are not at increased risk for other endocrine autoimmunity  
E. A and C