HYPOGLYCEMIA

- Hypoglycemia is a major issue in managing type 1 and type 2 diabetes mellitus
- Two conditions contribute to this problem:
  - defective glucose counterregulation
  - hypoglycemia unawareness

Clinical Hypoglycemia: Definition

Clinical Hypoglycemia (low blood sugar) in a treated person with diabetes is a glucose value less than 70 mg/dL.

DCCT DEFINITION OF SEVERE HYPOGLYCEMIA

Requires:
1. Symptoms of hypoglycemia
2. Assistance of another
3. Blood glucose <50 mg/dL or prompt recovery after glucose or glucagon

Symptoms of Hypoglycemia

Autonomic system symptoms:
- Shakiness
- Palpitations
- Sweating
- Anxiety
- Nausea

Neuroglycopenia symptoms: (effects on the brain)
- Confusion
- Unusual behavior
- Loss of consciousness
- Dizziness
- Headache
- Seizure
Question

1. What glucose was used in the DCCT to diagnose severe hypoglycemia?
   a) Blood glucose of <70 mg/dl
   b) Blood glucose of <50 mg/dl
   c) Blood glucose of <30 mg/dl

The Body’s Response To Hypoglycemia

- Decrease insulin secretion
- Increase epinephrine (adrenaline) secretion
- Increase glucagon secretion
- Increase cortisol secretion
- Increase growth hormone secretion

The Body’s Response To Hypoglycemia

- Epinephrine and glucagon work within minutes to elevate glucose levels.
- Cortisol and growth hormone work several hours later to elevate glucose levels.

Why Diabetics May Get Hypoglycemia

If a person with diabetes is being treated with a sulfonylurea or insulin, insulin levels are increased, and insulin secretion cannot be completely shut off despite low glucose.
Symptoms of Hypoglycemia

The body’s strategy
- Autonomic symptoms warn the body to prevent more serious hypoglycemic effects (neuroglycopenia).
- They are coupled to metabolic systems which are designed to inhibit endogenous insulin secretion, release glucose from the liver, and impair peripheral tissue glucose uptake.

CLASSIC SITES OF INSULIN ACTION

1. MUSCLE- UPTAKE AND OXIDATION OF GLUCOSE
2. ADIPOSE TISSUE- UPTAKE OF GLUCOSE AND SYNTHESIS AND STORAGE OF FAT
3. LIVER- INHIBITION OF GLUCOSE PRODUCTION

Question

What hormones are changed within minutes to counter-regulate hypoglycemia?

a) insulin  
b) epinephrine  
c) glucagon  
d) cortisol  
e) all of above  
f) a, b, c above  
g) just b, c above

INSULIN ACTION IN THE BRAIN

- 1. REDUCE HEPATIC GLUCOSE PRODUCTION
- 2. SUPRESS APPETITE
- 3. REDUCE BODY FAT AND WEIGHT
- 4. INCREASE ENERGY EXPENDITURE

FOOD INTAKE SUPPRESSION DURING CHRONIC INTRA-CEREBROVENTRICULAR INSULIN INFUSION IN BABOONS

Why is there weight gain with Intensive Insulin Therapy?

- 98 one month old male rats treated weekly with insulin to lower glucose to 30-40 mg/kg for three hours.
- 60 minute IV GTT was given 3-4 days before and after the test.
- Wt., Fat pad content, food intake, and motor activity were assessed at 4, 8, and 12 months.
CONCLUSION

IN THIS STUDY:
IATROGENIC HYPOGLYCEMIA LEADS TO WEIGHT GAIN THAT IS ASSOCIATED WITH A INCREASED METABOLISM RATHER THAN AN INCREASE IN CALORIES


WHAT IS THE CLINICAL HYPOGLYCEMIA EXPERIENCE WITH TYPE 1 DIABETES?

PERCENT OF TYPE 1 DIABETIC PATIENTS WITH DEFECTIVE HORMONAL RESPONSES

<table>
<thead>
<tr>
<th>Duration of diabetes</th>
<th>Glucagon (%)</th>
<th>Epinephrine (%)</th>
<th>Cortisol (%)</th>
<th>GH (%)</th>
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<tbody>
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<td>&lt; 1 year</td>
<td>27</td>
<td>9</td>
<td>0</td>
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<td>1-5 years</td>
<td>73</td>
<td>25</td>
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<td>5-10 years</td>
<td>100</td>
<td>44</td>
<td>11</td>
<td>11</td>
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<tr>
<td>&gt; 10 years</td>
<td>92</td>
<td>66</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>


Hypoglycemic Unawareness

Patients do not get the autonomic warning symptoms.

The first signs of hypoglycemia are the neuroglycopenic symptoms.

This occurs in patients who have had frequent hypoglycemia or in some type 1 diabetic patients after having diabetes for many years.

HYPOGLYCEMIA ASSOCIATED AUTONOMIC FAILURE

Hypoglycemia-Associated Autonomic Failure in Type 1 Diabetes Mellitus

“Hypoglycemia Begets Hypoglycemia”

Absence of glucagon

Imperfect Insulin Replacement

Defective Glucose Counterregulation

Reduced Autonomic Symptoms

Reduced Epinephrine Response
**Severe Hypoglycemia During the DCCT**

![Graph showing severe hypoglycemia during the DCCT trial with data points for HbA1c = 7.0% and HbA1c = 9.1% between intensive and conventional treatments.]

**DCCT RISK OF SEVERE HYPOGLYCEMIA**

![Graph showing the risk of severe hypoglycemia with data points for conventional and intensive treatments.]

**Rate of Severe Hypoglycemia in 1683 Western Australian Youth**

![Graph showing the rate of severe hypoglycemia in Western Australian youth with a downward trend from 2000 to 2008.]

**Changes in Diabetes Treatment of Type 1 Diabetes in Western Australian Youth**

![Graph showing changes in diabetes treatment with data points for continuous subcutaneous insulin infusion, twice daily injections, and multiple daily injections.]

**Adult Type 1 Diabetes Registry—Mean HbA1c/year vs % Severe Hypoglycemia and % ketoacidosis/year**

![Graph showing the relationship between mean HbA1c/year and severe hypoglycemia and ketoacidosis.]

**Question**

Which are the factors that increase hypoglycemia risk for patients with Type 1 Diabetes?

- a) Insulin treatment
- b) Recent hypoglycemia
- c) Exercise
- d) SGLT-2 inhibitor treatment
- e) All of the above
- f) a, b, c
HYPOGLYCEMIA IN TYPE 2 DIABETES

FREQUENCY OF SEVERE HYPOGLYCEMIA IN A YEAR

SUMMARY OF HYPOGLYCEMIA IN THREE RECENT INSULIN TREATMENT TRIALS- ACCORD, ADVANCE AND VADT

- NO BENEFIT FOR INTENSIVE VS STANDARD TREATMENT FOR PREVENTION OF MACROVASCULAR OUTCOME
- HIGHER INCIDENCE OF SEVERE HYPOGLYCEMIA

Oral Diabetic Medications That Do Not Cause Hypoglycemia

- Metformin
- Thiazolidinedione (Actos, Pioglitizone)
- DPP4 Inhibitors (Sitagliptin, J anuvia), (Saxagliptin, Onglyza), (Linagliptin, Tradjenta ) (Alogliptin, Nesina)
- GLP-1 Agonists (Exenatide, Byetta), (Liraglutide, Victoza).
- Alpha-glucosidase inhibitors (Acarbose, Precose), (Miglitotol, Glyset)
- SGLT-2 inhibitor (Canagliflozin, Invokana)
- But cause hypoglycemia with SU or Insulin
What to do if you think you have hypoglycemia

Check your blood sugar

Symptoms may be caused by something else

What to do if you have hypoglycemia

If you have confirmed hypoglycemia (glucose < 70 mg/dl), ingest 15 grams of carbohydrate.

Liquids work quickest: 4 oz of juice or soda; or 3 glucose tablets (5 gm each)

What to do if you have hypoglycemia

Recheck your glucose in 15-20 minutes.
(Re-treat if glucose is still < 70 mg/dl)

What to do if you have severe hypoglycemia

• Glucagon injection
• Glucose gel (or cake frosting) inside the cheek
• Call 911 if patient is unconscious

How to Minimize Hypoglycemia

• Test home glucose frequently
• Do not miss meals
• Know which medications are associated with hypoglycemia
• If you are having hypoglycemic reactions, be sure to discuss this with your doctor!

QUESTION

WHAT IS THE FIRST THING TO DO FOR AN UNCONSCIOUS PATIENT SUSPECTED OF HAVING SEVERE HYPOGLYCEMIA?

a) check blood glucose
b) give glucagon
c) give oral glucose
d) give IV glucose
SUMMARY

1. CLINICAL DEFINITION OF HYPOGLYCEMIA AND SEVERE HYPOGLYCEMIA
2. NEUROENDOCRINE SYSTEMS FOR GLUCOSE COUNTERREGULATION
3. SITES OF INSULIN ACTION
4. CLINICAL EXPERIENCE WITH HYPOGLYCEMIA IN TYPE 1 AND TYPE 2 DIABETES
5. PREVENTION AND TREATMENT OF HYPOGLYCEMIA