Hypoglycemic syndromes

- Diabetes related
- Spontaneous
  - Fasting
  - Postprandial

Relationship between HbA1c; risk of progression of retinopathy; and risk of severe hypoglycemia in T1D

![Graph showing relationship between HbA1c and hypoglycemia](image)

Population based study on hypoglycemia

115 severe episodes per 100 patients years T1D

35 severe episodes per 100 patient years insulin treated T2D

(9 episodes in 4 T1D; 5 episodes in 5 T2D)
Impact of hypoglycemia

- Acute hypoglycemia (BG <54mg/dl)
  - Impairs complex, attention demanding & speed dependent responses
- Recurrent hypoglycemia
  - Increases anxiety, may cause depression
  - Fear of hypoglycemia
- Long term cognitive function unaffected
- Death ~6% - may explain “dead in bed syndrome”

23 year old man with 12 yr history found “dead in bed” at 9am


Hypoglycemia causes prolongation of QTc in adolescents with T1D (n = 16)

* patient’s twin also had DM and was found “dead in bed” age 16; also had another nondiabetic sib found dead in bed at age 3 yrs

Sinus bradycardia (31 beats/min) recorded at 06:10 hrs with a CGM of 56 mg/dl, having been < 40 for the previous 35 mins

Couplet of multifocal ventricular ectopic beats recorded at 01:20 hrs, and preceded by a QTc interval of 560 ms. The CGM level at the time was 61 mg/dl with values in the 52 to 56 range for some time before.

Variable P wave structure, recorded at 04:30 hours with a CGM of 31 mg/dl. The patient continued at or below this level for a further 90 min

Gill et al. Diabetologia 52: 42 (2009)

Hypoglycemia-induced electrocardiographic changes

Baseline                                   Fingerstix BG 56     6 hours later


| ↓ Insulin          | Glycogenolysis; hepatic & renal gluconeogenesis; ketogenesis; limit glucose use by skeletal & cardiac muscles |
|                   | Glycogenolysis, facilitate activity of hepatic gluconeogenesis enzymes |
| ↑ Glucagon        | ↑FFA, hepatic glycogenolysis, renal gluconeogenesis. ↑ cardiac output. Regional blood flow changes. Arousal |
| Norepinephrine &  | Facilitate lipolysis. Promote protein catabolism & amino acid release for gluconeogenesis |
| epinephrine at    | |
| sympathetic nerve  | |
| endings            | |
| Cortisol           | |
| Growth hormone     | Antagonize insulin action at muscle. Promote lipolysis |
| Acetylcholine      | Induced sensation of hunger (parasympathetic) and sweating |
Glucagon response to hypoglycemia declines with longer duration of DM


Preventing a fall in intra-islet insulin in normal subjects during hypoglycemia prevents the rise in glucagon

DCCT – within intensively treated group, those who were C-peptide positive had lower rates of severe hypoglycemia

<table>
<thead>
<tr>
<th>Stimulated C-peptide levels</th>
<th>0.2 - 0.5</th>
<th>&lt; 0.2</th>
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<tbody>
<tr>
<td>Severe hypoglycemia / 100 pat. yrs</td>
<td>6.6</td>
<td>17.3</td>
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Antecedent hypoglycemia attenuates sympathoadrenal response to subsequent hypoglycemia in T1D

Epinephrine responses to controlled induced hypoglycemia before and after intensification of diabetes control in T1D
Hypoglycemic symptoms

**Autonomic symptoms**
- Sweating
- Shaking
- Anxiety
- Palpitations

**Cerebral glucose deficiency**
- Drowsy
- Confused
- Slurred speech
- Blurred vision
- Irritability

Hypoglycemic unawareness alters the threshold for autonomic symptoms – affects 20 to 25% of patients with T1D

82 – insulin suppressed
86 – ↑ glucagon; ↑epinephrine
54 – autonomic
49 – neurogenic
18 – coma

Changes in BG uptake in brain on lowering plasma BG from 105 mg/dl to 54 mg/dl in type 1 patients stratified by HbA1c values & in normals

Boyle et al. NEJM 1995; 333:1726
Treatment of hypoglycemia

• If conscious – give glucose containing foods
• Fructose containing sweeteners are not transported across blood brain barrier
• 20-50 mls of 50% dextrose iv
• 1 mg glucagon im or iv (do not use in sulfon furylurea induced hypoglycemia)
Hypoglycemic unawareness is reversible with meticulous glycemic control in T1D


Correlation of mild hypoglycemia frequency and HbA1c Values


Long term use of CGM on severe hypoglycemia and HbA1c

JDRF CGM group Diabetes Care 32: 2047 (2009)
Summary slides

- On average, aiming for a mean plasma glucose of 155 in insulin treated DM can be projected to precipitate severe hypoglycemia every 1.6 yrs
- About 6% of mortality in DM is attributed to hypoglycemia
- DM is associated with impairment in counter regulatory systems – in particular glucagon and sympathoadrenal systems
- Meticulous glucose control can restore awareness of hypoglycemia

Realistic glucose targets – higher in the elderly and those with CAD or history of severe hypoglycemia
- Blood glucose awareness training
- Multidose physiological insulin regimens
- Frequent BG monitoring; use of CGM
- Islet or pancreas transplant
- Closed loop systems in the near future

Spontaneous hypoglycemia
Fasting hypoglycemia

- Endocrine disorders – hypopituitarism, Addison’s, isolated GH deficiency
- Liver malfunction – alcoholism or liver failure, inborn errors of metabolism
- Mutations of the sulfonlurea receptor complex; activating glucokinase mutation
- Renal failure – malnutrition, decreased hepatic glucose production
- Immunological – antibodies activating insulin receptor
- Tumors – beta cell, nonpancreatic

An islet adenoma separated from the pancreas by a thin collagenous capsule. A few normal islets are seen in the pancreas on the right.
Epidemiology of insulinomas

- 1 – 2 per million
- Birth to old age – 80 % 20 to 60 yrs
- Majority single benign
- 10-15 % malignant (metastatic)
- 10 % part of MEN 1
- 99 % located within the pancreas

Whipple’s triad

- hypoglycemic symptoms
- associated fasting blood glucose of 40 or less
- immediate recovery upon administration of glucose
Symptoms

- Frequently in the morning or after a missed meal; with exercise
- Neuroglycopenic symptoms
  - blurred vision, diplopia, headache, slurred speech, weakness
  - Personality & mental changes
  - Convulsions or coma

Diagnosis at first ER visit of 38 patients with hypoglycemia due to insulinoma

- 20 (53%) hypoglycemia - 8 admitted to hospital to rule out hyperinsulinism
- 8 (21%) BG not measured & hypoglycemia not diagnosed
- 10 (26%) BG not measured & neurologic or psychiatric diagnoses
  - seizures
  - stroke or TIA
  - conversion hysteria

Patient with history consistent with hypoglycemia

- Home BG monitoring at time of symptoms
- If patient has symptoms with exercise or short period of fasting: then supervised observation in the office. If symptoms occur or fingerstick BG < 50; then draw labs for plasma glucose, insulin, C-peptide, sulfonylurea screen, β hydroxybutyrate level, antibodies to insulin
Supervised fast (up to 72 hrs)

- Baseline glucose, insulin, C-peptide, proinsulin
- Calorie free & caffeine free fluids; stay active.
- Check finger sticks every 4hrs until < 60 then check each hour.
- Send glucose, insulin, C-peptide, proinsulin when finger stick < 49.
- Stop fast if symptoms of hypoglycemia or if lab glucose < 45. Send glucose, insulin, C-peptide, proinsulin, β-hydroxybutyrate & sulfonylurea levels

Sex difference
- Women normally can fall to 36mg/dl by 72 hrs
- Men can fall to ~ 55mg/dl by 72 hrs
- At 72 hrs, rise with exercise (> 55)
- Insulinoma patients – 43 % symptomatic by 12 hrs; 67 % by 24 hrs; 93 to 95 % by 48 hrs

Diagnostic criteria

- Plasma glucose < 45 mg/dl
- Plasma insulin (RIA) ≥ 6 µU/ml
- Plasma insulin (ICMA) ≥ 3 µU/ml
- Plasma C-peptide ≥ 200 pmol/L
- Plasma proinsulin ≥ 5 pmol/L
- β-hydroxybutyrate ≤ 2.7 mmol/L
- Sulfonylurea screen Negative
  (include repaglinide & nateglinide)

Conversion factors: insulin uU/ml x 7.175 = pmol/L; Cpeptide ng/ml x 0.33 = pmol/L
Biochemical confirmation of insulinoma

Pancreatic dual phase thin section CT scan (82-94%) or MRI scan with gadolinium (85%)

Obvious tumor

Negative or equivocal

Endoscopic US with FNA

Negative or equivocal

Positive neuroendocrine tumor

Calcium stimulated angiography

Positive localization

Negative

Surgery with confirmatory intraoperative US

Review diagnosis
Clinical case

- 43 year old woman with ~ 1.5 year history of sleepiness, tremulousness, nervousness if missed meal or exercise.
- Symptoms improved 15 minutes after consuming rapid acting CHO
- Clothes went from size 4 to size 10
Had not eaten for 6 hours when seen in clinic

Had patient walk with supervision for 30 minutes

Labs at time of symptoms:

Glucose 34 mg/dl
Insulin 8.9 uU/ml (+ ve ≥ 6 µU/ml)
C peptide 825 pmol/L (+ ve ≥ 200 pmol/L)
Proinsulin 27.4 pmol/L (+ ve ≥ 5 pmol/L)
Sulfonylurea screen negative

Calcium stimulated angiography

Inject calcium gluconate 0.0125 mmol/kg diluted in 5mls saline into GDA (head); splenic (tail & body); SMA (uncinate)

Collect insulin samples at 0, 30, 60, 90, 120 & 180 seconds.

Positive test – 2 fold elevation at 30 or 60 secs

After overnight fast; D/C diazoxide for 48 to 72 h; dextrose infusion during procedure
Treatment

- Surgery
- Diazoxide 300-600 mg / day in divided doses
  - 50mg/ml liquid preparation
  - Side effects - hirsuitism, salt retention, edema, gastric irritation.
  - Add hydrochlorothiazide 25 to 50 mg per day

Non-islet cell tumor hypoglycemia (NICTH)

- Retroperitoneal fibrosarcomas, hepatomas, GI tumors, mesothelioma, adrenal cortical carcinomas, renal cell tumors, lymphomas, leukemias
- Low glucose levels; low insulin and C-peptide levels

In NICTH, release of “big” IgF-II

Diagram showing levels of pre-pro-IGF-II, Pro-IGF-II, and IgF-II.
Identification of Pro-IgF-II by size exclusion chromatography or SDS PAGE

Treatment of NICTH

- Surgery
- Growth hormone – increases IGFBP-3 levels & ALS promotes ternary complexes
- Glucocorticoids – suppresses big IGF-2 levels; stimulates gluconeogenesis
Postprandial (reactive) hypoglycemia

- GI surgery
- Noninsulinoma pancreatogenous syndrome (NIPHS)
- Autoimmune hypoglycemia
- Occult diabetes

Clinical case

42 year old Caucasian man underwent Roux-en-Y surgery (282 lbs, BMI 44)

After losing 30 pounds, symptoms of light headedness, visual symptoms of black and white spots, shaking, not thinking clearly - about 1 ½ hr after meal. Fingerstick BG as low as 35. No symptoms with low CHO meals

Late dumping syndrome is a complication of gastric surgery

- Gastrectomy, vagotomy, pyloroplasty, gastrojejunostomy, Nissan fundoplication, Billroth II, Roux-en-Y gastric bypass
- Rapid delivery of CHO into the bowel resulting in rapid rise in glucose and insulin
- Hyperinsulinemia leads to subsequent hypoglycemia
- GLP1 and GIP may play a role in insulin stimulation

Typically hypoglycemic symptoms occur 90 to 120 minutes after consuming large amounts of readily absorbable carbohydrates

Usually occurs a few months after Roux-en-Y surgery following some weight loss
12 patients with history of postprandial hypoglycemia following Roux-en-Y surgery

Postgastric bypass hypoglycemia

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Fasting glucose (mg/dL)</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>Peak glucose (mg/dL)</th>
<th>Basal insulin (μIU/mL)</th>
<th>Basal glucagon (pg/mL)</th>
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<td>1.0-6.7</td>
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</table>

*HOMA-IR = Homeostasis Model Assessment; % = percentage of change from baseline; %Δ = change from baseline to change from baseline 1 hour after oral glucose load. Percentile comparison was made using Wilcoxon signed rank test. *p<0.05 compared with control group, **p<0.01 compared with control group, ***p<0.001 compared with control group.

Treatment

- Smaller, more frequent meals; low glycemic index foods
- Alpha glucosidase inhibitors
- Octreotide 50mcg subcutaneously 2 or 3 times a day 30 minutes before each meal
- Surgery – to delay gastric emptying
- Partial pancreatectomy?
Noninsulinoma Pancreatogenous Hypoglycemia syndrome

- Postprandial hypoglycemia (never fasting)
- Negative 72 hr fast
- Positive arterial calcium stimulation test
- Pathology shows islet hyperplasia
- No mutation in Kir 6.2 and SUR1 genes

Treatment with diazoxide; if ineffective then gradient directed pancreatectomy


Insulin autoimmune syndrome

- Spontaneous hypoglycemia in the presence of insulin binding antibodies
- Association with Graves’, SLE, RA
- Total insulin in plasma is elevated
- Hypoglycemia is mild & self limiting
Mechanism by which anti-insulin antibodies cause hypoglycemia

Glucose or meal causing insulin release

Postprandial – insulin dissociation from antibodies