Diabetic complications /Hypoglycemic Disorders (Insulinomas)

complications

- **Acute:**
- 1. Diabetic Ketoacidosis

- 2. Hyperglycemic Hyperosmolar state

- 3. Hypoglycemia: (patients under treatment)

- Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

EPIDEMIOLOGY

- DKA: Type1 DM
- T2DM: serious infection, trauma, CV events
- DKA is more common in younger (<65 years) diabetic patients and F>M

- Poor prognostic signs:
  - extremes of age
  - coma
  - hypotension

- **HHS** :
  - older than 65 yrs with type 2 DM .
  - Mortality is higher: 5 -20 %

PATHOGENESIS

- **Insulin** deficiency and/or resistance.
- **Glucagon** excess: lack of insulin suppression

- -increased **catecholamines and cortisol contribute**

Insulin actions

1. diminish hepatic glucose production
2. increase glucose uptake by skeletal muscle and adipose tissue.
3. Inhibition of glucagon secretion
4. Inhibits lipolysis

Precipitating factors

- Infections (pneumonia, gastroenteritis, and UTI 40 - 50 %)
- pancreatitis, AMI, stroke, trauma, and alcohol and drug abuse
- The omission of insulin in the setting of an acute illness.

hyperglycemia

- HHS usu > 1000 mg/dL
- DKA usu < 800 mg/dL

  - DKA often present early with symptoms
  - DKA pts tend to be young with better GFR

Hyperglycemia

- Impaired glucose uptake in peripheral tissues and skeletal muscles

-Increased gluconeogenesis

-Increased glycogenolysis

Ketoacidosis

-Insulin deficiency and increased cca
- enhance lipolysis, and liver FFA delivery
- normally it will convert FFA into TG

Acetoacetic acid is formed then reduced to **B-OH-butyric acid** or decarboxylated to **acetone**.

- KA synthesis requires Free Fatty acyl CoA entry to mitochondria which is regulated by carnitine palmitoyl transferase I (CPT I)

- Glucagon increases CPT I activity and ketogenesis

Absence of Ketosis in HHS

- Insulin required to suppress lipolysis is 10% of that required to suppress hyperglycemia

- Sufficient insulin in HHS to block lipolysis (and ketogenesis) but not enough to promote glucose utilization

CLINICAL PRESENTATION

- DKA usually evolves rapidly / 24 hr
- HHS presents over several days
- ? lethargy, focal signs, and obtundation, and coma
- Neurological symptoms are most common in HHS
- Hyperventilation and abdominal pain are **limited** to DKA.

Neurologic symptoms and plasma osmolality

- Neurologic deterioration occurs if effective p. osmolality > 320 - 330 mosmol/kg .
- Mental obtundation and coma are more frequent in HHS
- HHS may have focal neurologic signs (hemiparesis or hemianopsia) and/or seizures .

- Effective Posm = [2 x Na (meq/L)] + [glucose (mg/dL) ÷ 18]
- Effective Posm = Measured Posm - [BUN (mg/dL) ÷ 28]

Abdominal pain in DKA

- abdominal pain more common in children
- Abdominal pain is unusual in HHS
- 46 % of patients with DKA have abdominal pain

Abd pain

- associated with metabolic acidosis:

  - 86 % ($HCO_3 < 5$)

  - 13 % ($HCO_3 > 15$)
- does not correlate with the severity of hyperglycemia
- Due to delayed gastric emptying and ileus (**metabolic acidosis** and **electrolyte imbalance)**

Physical examination

- Signs of volume depletion
- Neurologic findings (HHS)
- fruity odor
- compensatory hyperventilation (Kaussmaul respirations).
- Fever is rare

Diagnostic criteria for (DKA) and (HHS)

	DKA			HHS
	Mild	Moderate	Severe	
• Plasma glucose (mg/dL)	>250	>250	>250	>600
• Arterial pH	7.25-7.30	7.00-7.24	<7.00	>7.30
• Serum bicarbonate (mEq/L)	15-18	10 - <15	<10	>18
• Urine ketones*	Positive	Positive	Positive	
Small				
• Serum ketones*	Positive	Positive	Positive	
Small				
• Effective s. osm. (mOsm/kg)•	Variable	Variable	Variable	>320
• Anion gapΔ	>10	>12	>12	Variable
• Mental status	Alert	Alert/drowsy	Stupor/coma	

- • Calculation: 2[measured Na (mEq/L)] + glucose (mg/dL)/18.
- Δ Calculation: (Na+) - (Cl- + HCO3-) (mEq/L).

Management -DKA

- 1. Underlying cause
- 2. IV Fluids
- 3. Insulin Therapy
- 4. Electrolyte management
- 5. ? Bicarbonate Therapy

IVF

- 1-2 L Normal Saline Solution initial bolus
- Initially NSS @10-15 ml/Kg for 4-6 hours
- Then ½ NSS @ 4-10 ml Kg
- Switch to D5 ½ NSS when BG is <200 mg/dl (DKA) or < 250-300 mg/dl (HHS)

Insulin

- 0.1 IU/Kg regular insulin iv bolus
- 0.1 IU/Kg/hr iv insulin infusion
- Continue iv insulin until DKA/HHS has resolved
- Start sc insulin once pt start oral feeding

Electrolytes --- K

- If initial K:

  a. < 5.3 mmol/L add KCL once urine ootput > 50 ml/hr

  b. >5.3 mmol/L wait on K supplement

  c. < 3.3 mmol/L add KCL and hold IV insulin

PO4

indicated in:

1.cardiac dysfunction

2. hemolytic anemia

3. respiratory depression

4. S. phosphate < 1.0 mg/dL (0.32 mmol/L)

20 - 30 meq/L of KPO4 can be added to IVF

Bicarbonate Therapy

-**selected patients only :**

1. Arterial pH less <7.00 with decreased cardiac contractility
2. severe hyperkalemia
3. Arterial pH < 6.90

100 meq of $NaHCO_3$ in 400 mL sterile water with 20 meq of KCL if the s K < 5.3 meq/L **over 2 hours**.

- Repeat until the pH rises > 7.00

DKA/HHS resolution

The HHS is resolved when :

1. **mentally alert and able to eat**
2. **p effective osm is < 315 mosmol/kg.**
3. **S glucose 250-300 mg/dl**

The ADA guidelines for (DKA) resolution:

1. **S glucose below 200 mg/dL**
2. **S anion gap <12 meq/L**
3. **S HCO3 ≥18 meq/L**
4. **PH >7.30**

DKA/Complication

- Cerebral edema: **a disease of children** and almost all affected < age 20 yrs
- Symptoms begin within 12-24 hrs of the initiation of treatment

Cerebral edema

- HA followed by lethargy.
- Neurologic deterioration may be rapid, with seizures, incontinence, pupillary changes, bradycardia, and respiratory arrest.
- These symptoms progress if brainstem herniation occurs.
- mortality rate of 20 - 40 % .

Cerebral edema

- Recommendations for treatment:
- - ? benefit from prompt administration of mannitol (0.25 - 1.0 g/kg) and from hypertonic (3 %) saline (5 - 10 mL/kg / 30 min) .

Chronic Complications

- Chronic:

  1.microvascular:

  retinopathy

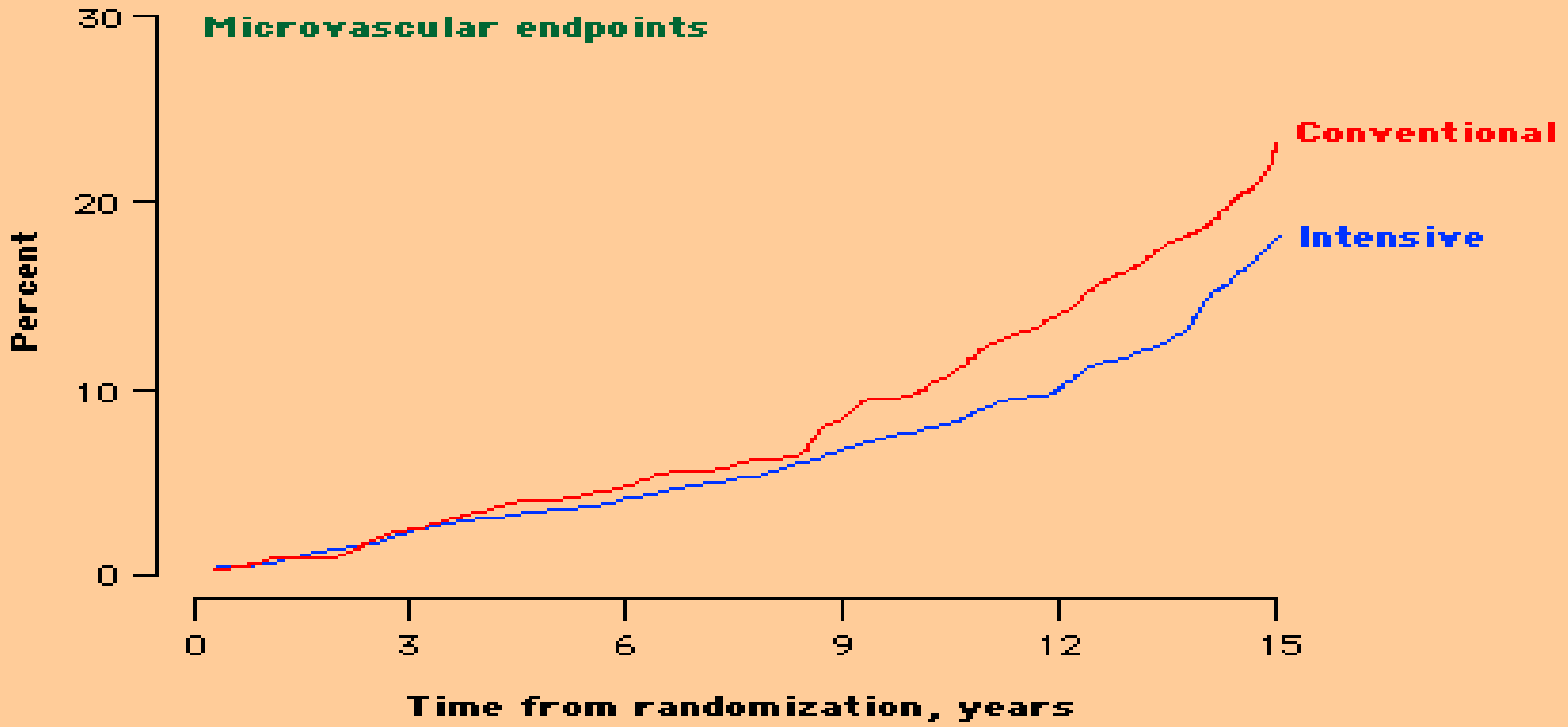
  nephropathy

  neuropathy

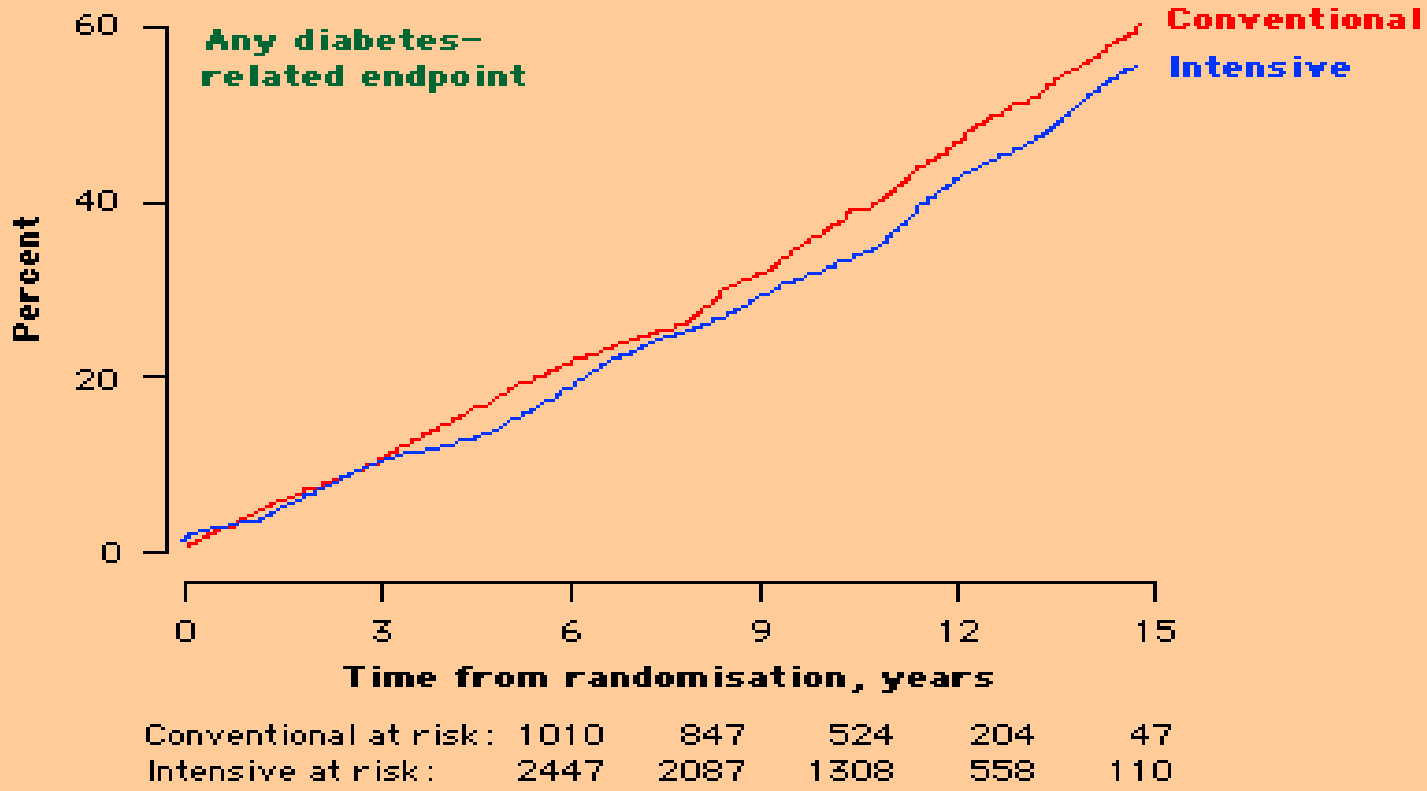
  2. macrovascular:

  coronary ischemia / Stroke

  PVD



Intensive glycemic control prevents microvascular disease in patients with type 2 diabetes Kaplan-Meier plots of aggregate endpoints of microvascular disease in patients with type 2 diabetes mellitus in the United Kingdom Prospective Diabetes Study who were randomly assigned to receive either intensive therapy with a sulfonylurea or insulin or to conventional treatment with diet; drugs were added if the patients had hyperglycemic symptoms or fasting blood glucose concentrations greater than 270 mg/dL (15 mmol/L). Intensive therapy was associated with a 25 percent reduction (P = 0.01) in the development of microvascular disease, which was defined as renal failure, death from renal failure, retinal photocoagulation, or vitreous hemorrhage. (Data from UK Prospective Diabetes Study, Lancet 1998; 352:837.)



Efficacy of intensive glycemic control in type 2 diabetes Kaplan-Meier plots of any diabetes-related endpoint in patients with type 2 diabetes mellitus in the United Kingdom Prospective Diabetes Study who were randomly assigned to either intensive therapy with a sulfonylurea or insulin or to conventional treatment with diet; drugs were added if there were hyperglycemic symptoms or if the fasting blood glucose concentration was greater than 270 mg/dL (15 mmol/L). Intensive therapy was associated with a 12 percent reduction in the development of any diabetes-related endpoint (P = 0.03); it was estimated that 19.6 patients would have to be treated to prevent any single endpoint in one patient at 10 years. (Data from UK Prospective Diabetes Study (UKPDS) Group, Lancet 1998; 352:837.)

Nephropathy

- Urinary albumin excretion
- Normal: < 30 mg /24hrs
- Microalbuminuria 30-300 mg/24 hrs
- Macroalbuminuria >300 mg/24 hrs

classification of chronic kidney disease by stage as determined by (NHANES) performed in 1999 to 2004 :

- Stage 1 disease : normal GFR (**> 90 mL/min** per 1.73 m2) and **persistent albuminuria**

- Stage 2 disease : **GFR between 60 - 89 mL/min per 1.73 m2 and persistent albuminuria**

- Stage 3 disease : **GFR between 30 - 59 mL/min** per 1.73 m2

- Stage 4 disease : **GFR between 15 - 29 mL/min** per 1.73 m2

- Stage 5 disease : **GFR of less than 15 mL/min per 1.73** m2 or **end-stage renal disease**

Nephropathy T1DM

Type 1 diabetes :

- microalbuminuria:

  20 - 30 % after a mean duration of 15 yrs

- ESRD : 4-17 % at 20 yrs

  16 % at 30 yrs

Type 2DM- nephropathy

UKPDS :

10 yrs after diagnosis:

- microalbuminuria 25%
- macroalbuminuria 5%
- elevated Cr (> 2.0 mg/dL) / ESRD: 0.8 %

- Annual **rate of progression**
  - Dx to microalbuminuria: 2.0%
  - microalbum to macroalbuminuria:2.8%
  - macroalbum to high Cr or ESRD: 2.3 %.

- If elevated plasma creatinine (≥2.0 mg/dL): renal replacement Rx was required after a median period of only 2.5 yrs

DM-nephropathy management

T1DM :

screened yearly (after 5 yrs)

Urine alb/Cr ratio (ACR) is recommended.

Measurement of the s. creatinine and eGFR

Elevated ACR should be confirmed 2- 3 samples / several months

- strict glycemic, BP, and lipid control.

- Angiotensin converting enzyme (ACE) inhibitor if BP > 140/80 mmHg
- If BP < 140/80 wait on ACE inhibitor
- Alb/Cr ratio: Q 6-12 months
- ACE -I if clear increase in ACR and/or BP
- clinically evident renal disease : ACEI or ARB (angiotensin receptor blocker) even if BP < 140/80 mmHg

Type 2 diabetes

- microalbuminuria : increased risk of CVD

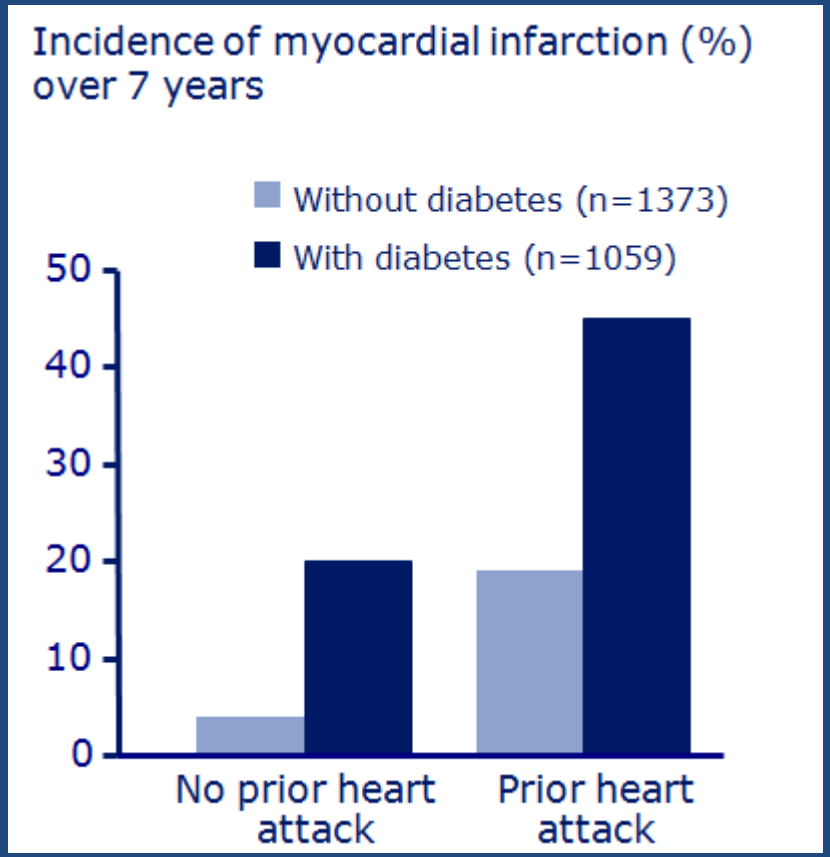
- without aggressive intervention:

  overt proteinuria to ESRD in either form of diabetes averages 6-7 yrs

- The optimal initial Rx of nephropathy in T2DM is (ACE-I or ARB)
- Combined ACE I+ ARBs: **increased mortality**
- **SGLT2 Inhibitors**

Patients with type 2 diabetes are at increased risk of cardiovascular disease

- In this study, the risk of cardiovascular disease was greater in patients with diabetes than in those without ($p<0.001$)[1]
- Up to 80% of people with diabetes will die from cardiovascular disease[2]
- Cardiovascular deaths are potentially preventable if action is taken to address the known risk factors



1. Haffner *et al. N Engl J Med* 1998;339:229–34. 2. IDF. *Diabetes Atlas*, 2003

Macrovascular risk

Near-normal glycemic control (A1C 6.4- 6.9%) does not reduce cardiovascular events in patients **with longstanding diabetes**

Macrovascular complications prevention

- glycemic control
- stop smoking
- BP control
- treatment of dyslipidemia
- secondary prevention: daily aspirin

Diabetic Neuropathy

- symm sensory affecting distal lower limbs
- 10- 18 % at dx
- "stocking-glove" sensory loss
- Motor involvement only later and in more severe cases.

Symptoms and signs

- Loss of vibration sense and proprioception reflect large-fiber loss
- Impairment of pain, light touch and temperature reflects loss of small fibers.

Decreased or absent ankle reflexes occur early in the disease

Symptoms

- pre-DM may present with intensely painful feet.
- Patients with frank diabetic neuropathy may present with pain, paresthesias

Neuropathy

Foot ulcers

- **acute** (dermal abrasion from poorly fitting shoes)

- **chronic** plantar ulcers occurring over weight-bearing areas.

(diabetic neuropathy, autonomic dysfunction and vascular insufficiency)

Treatment of diabetic neuropathy

- The most important method for the **prevention** is optimal glucose control.

- **reduced by 60 % over a 10-yr period with blood glucose control in pts with T1DM**

PAIN CONTROL

Consensus guidelines in 2006:

- First-tier agents: tricyclics as a class, duloxetine, pregabalin, and controlled-release oxycodone
- Second tier agents: carbamazepine, gabapentin, tramadol, and extended-release venlafaxine
- Topical therapies: capsaicin and lidocaine

Hypoglycemia

- With insulin or insulin secretagogues Rx.
- Higher risk:
  - type I compared to type II.
  - tight/near normal glycemic control
  - hypoglycemia unawareness
- Severe prolonged hypoglycemia can lead to permanent neurological deficit

hypoglycemia

- Management
- -Mild-moderate: self, oral glucose (15-20 gm)
- -Severe : needs help by others, IV glucose, glucagon injection

Hypoglycemic disorders

- Whipple's Triad

- ILL- looking patients or seemingly well-looking patients.

Causes of hypoglycemia in adults

Ill or medicated individual

- 1. Drugs
  Insulin or insulin secretagogue
  Alcohol
- 2. Critical illnesses
  Hepatic, renal, or cardiac failure
  Sepsis (including malaria)
  Inanition
- 3. Hormone deficiency
  Cortisol
  Glucagon and epinephrine (in insulin-deficient diabetes mellitus)
- 4. Nonislet cell tumor

Seemingly well individual

5. Endogenous hyperinsulinism
   Insulinoma
   Functional β-cell disorders (nesidioblastosis)
      -Noninsulinoma pancreatogenous hypoglycemia
      -Post gastric bypass hypoglycemia
   Insulin autoimmune hypoglycemia
   Antibody to insulin
   Antibody to insulin receptor
   Insulin secretagogue
6. Accidental, surreptitious, or malicious hypoglycemia

72-hour Fasting test

Protocol

- Discontinue all nonessential medications.
- may drink calorie-free drinks
- patient is active during waking hours.

-Insulin abs and sulfonylurea level done irrespective of BG

Test end points and duration

- plasma glucose ≤45 mg/dL
- symptoms or signs of hypoglycemia
-72 hours have elapsed
-when the plasma glucose < 55 mg/dL if Whipple's triad was documented previously

72 hour fast---Interpretation

S+S	Gluc mg/dl	Insulin miU/L	C-pep ng/ml	OHA /insulin/	Ab +	Dx
N	<55	<3	<0.6	N	N	Normal
Y	<55	>>3	<0.6	N	N	Exog insulin
Y	<55	≥3	≥0.6	N	N	Insulinoma, NIPHS, PGBH
Y	<55	≥3	≥0.6	Y	N	OHA
Y	<55	>>3	>>0.6	N	P	Insulin autoim.
Y	<55	<3	<0.6	N	N	IGF•-mediated
Y	<55	<3	<0.6	N	N	Not insulin / IGF -mediated

LOCALIZING STUDIES

If **endogenous insulin-mediated** hypoglycemia, the differential includes

- insulinoma,

- nesidioblastosis/islet cell hypertrophy,

- **OHA - induced hypoglycemi**a

- **insulin autoimmune hypoglycemia**

Negative circulating OHA and insulin ab's effectively rule out the last two.

A localizing study in all pts with insulin-mediated hypoglycemia, except if + insulin abs or OHA

Radiologic studies

CT, MRI, and transabdominal u/s can detect most insulinomas

- If an insulinoma is not visible with initial imaging:

  endoscopic u/s or **selective arterial calcium stimulation**, are required

Arterial calcium stimulation

Only if negative radiologic localization studies.

- selective injection of Ca gluconate into the **gastroduodenal, splenic, and SMA** with sampling of the hepatic venous effluent for insulin
- A positive result is a **doubling or tripling** of basal insulin concentrations.

- **insulinoma**: **positive in one artery**
- **islet cell hypertrophy**: positive in **multiple arteries**

Insulinoma

CLINICAL FEATURES :

- fasting hypoglycemia is the most common feature

- postprandial hypoglycemia is seen due to reduced hepatic glucose output

Insulinomas arise from the ductular/acinar system rather than from islet cells .

? Variant of insulin mRNA with increased translation efficiency is present in high amounts in insulinomas when compared to normal islet

Mayo Clinic Series

Distribution of cases by age and sex :

Observed from 1987 – 2007

- 237 patients,
- median age was 50 years (range 17 to 86),
- 57 % : women .

Symptoms

- **Neuroglycopenic** : confusion, visual change
- **Sympathoadrenal :** palpitations, diaphoresis, and tremors
- Median duration of symptoms < 1.5 years
- 20 % misdiagnosed with a neurologic or psychiatric disorder.
- Seizure disorder is a common misdiagnosis

- Weight gain in 18 % of patients .
- Fasting hypoglycemia 73 %,
- both fasting and postprandial symptoms 21%
- **only postprandial symptoms 6%** .

MEN1 Prevalence

- MEN1 : Among the 237 pts (Mayo Clinic):
- 14 (**6 %**) had MEN-1, (71 % were men)
- 13 of 14 (93 %) had benign insulinomas.
- 12 of 14 (86 %) had multiple tumors compared with 3 % in the rest of the cohort.

Tumor distribution

- 194 (87 %) had single benign tumors
- 16 (7 %) had multiple benign tumors
- 13 (6 %) had malignant insulinomas, defined as the presence of metastases
- One had islet hyperplasia

management

- Surgery : primary therapy
- Medical :

  1.Diazoxide: first line, S/E: edema, hirsutism

  2.Octreotide : Somatostatin analogues, also inhibits also GH ,TSH

  3.Verapamil (CCB): limited success

  4. Phenytoin: limited success

  5. Everolimus: refractory cases, experimental

- XRT/Chemotherapy: limited use (only for malignant insulinoma).

- THANK YOU

Michigan neuropathy screening score

- Do the feet show **dry skin, callus, fissure, infection or deformities?** The presence of any, is scored as 1 point and an additional point is added if an ulcer is present.
- What is the vibration sense on the dorsum of the great toes? — reduced (0.5 points); or absent (1 point).
- What is the Achilles tendon reflex? — absent (1 point)

A score greater than 2 indicated neuropathy with both a high specificity (95 %) and sensitivity (80 %) .

DIABETIC RETINOPATHY

Classification of diabetic retinopathy

1. Nonproliferative Diabetic Retinopathy (NPDR)

a-Mild NPDR:

At least one microaneurysm

b-Moderate NPDR:

-Hemorrhage/microaneurysm .

-Soft exudates

c. Severe NPDR:

- Hemorrhage/microaneurysm ≥ standard in all 4 quadrants
- Venous beading in at least two quadrants

d. Very severe NPDR:

Any two or more of criteria for severe NPDR

- 2. Proliferative Diabetic Retinopathy (PDR)
  - A. Early PDR:
  - B. High-risk PDR:
    - Neovascularization of the disk
    - Neovascularization of the disk and vitreous or preretinal hemorrhage
  - C. Severe PDR:
    - Center of macula detached
    - Clinically Significant Macular Edema (CSME)
    - Hard exudates and adjacent retinal thickening ≤500µm from macular center