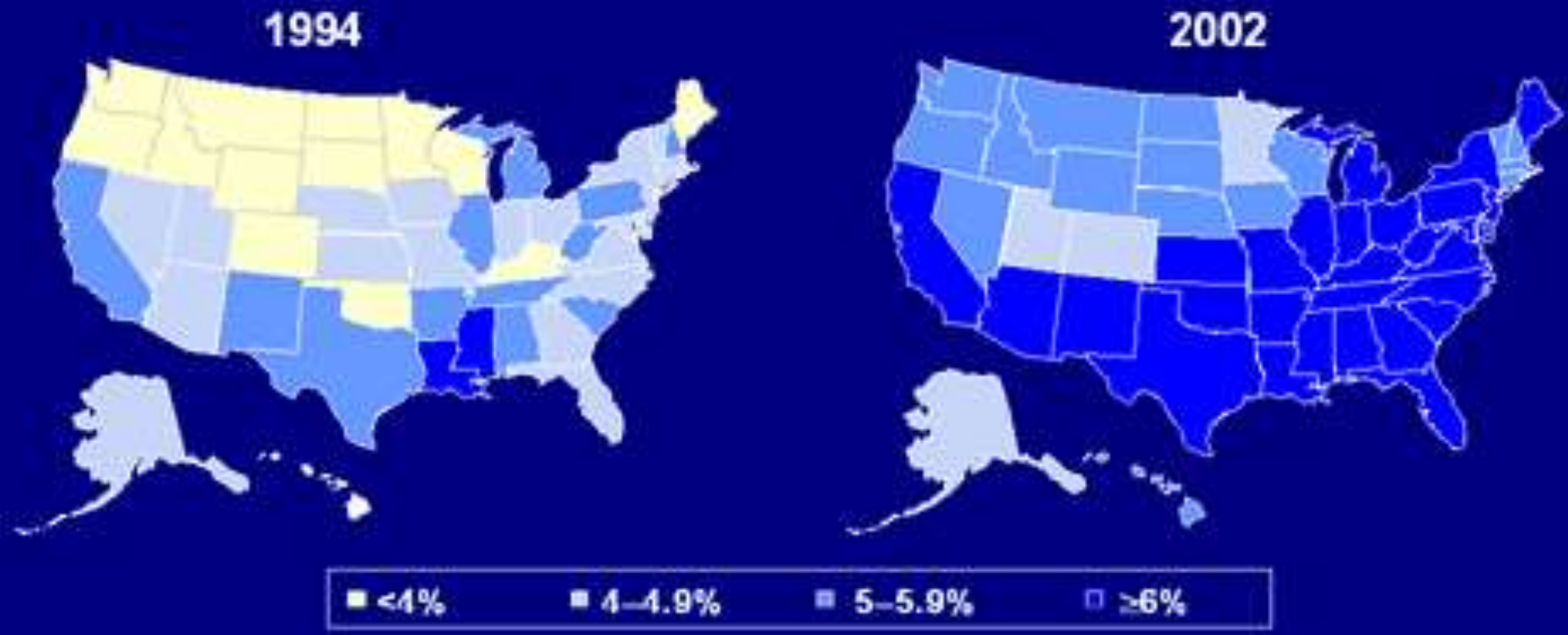
Diabetes Mellitus

Prevalence in Jordan

- 65-83 % of adult females : overweight and obesity
- 63-80 % of adult males : overweight and obesity
- 14-41 % of adults in Jordan have DM and pre-DM (IGT (6-24%)+ DM(8-17%))

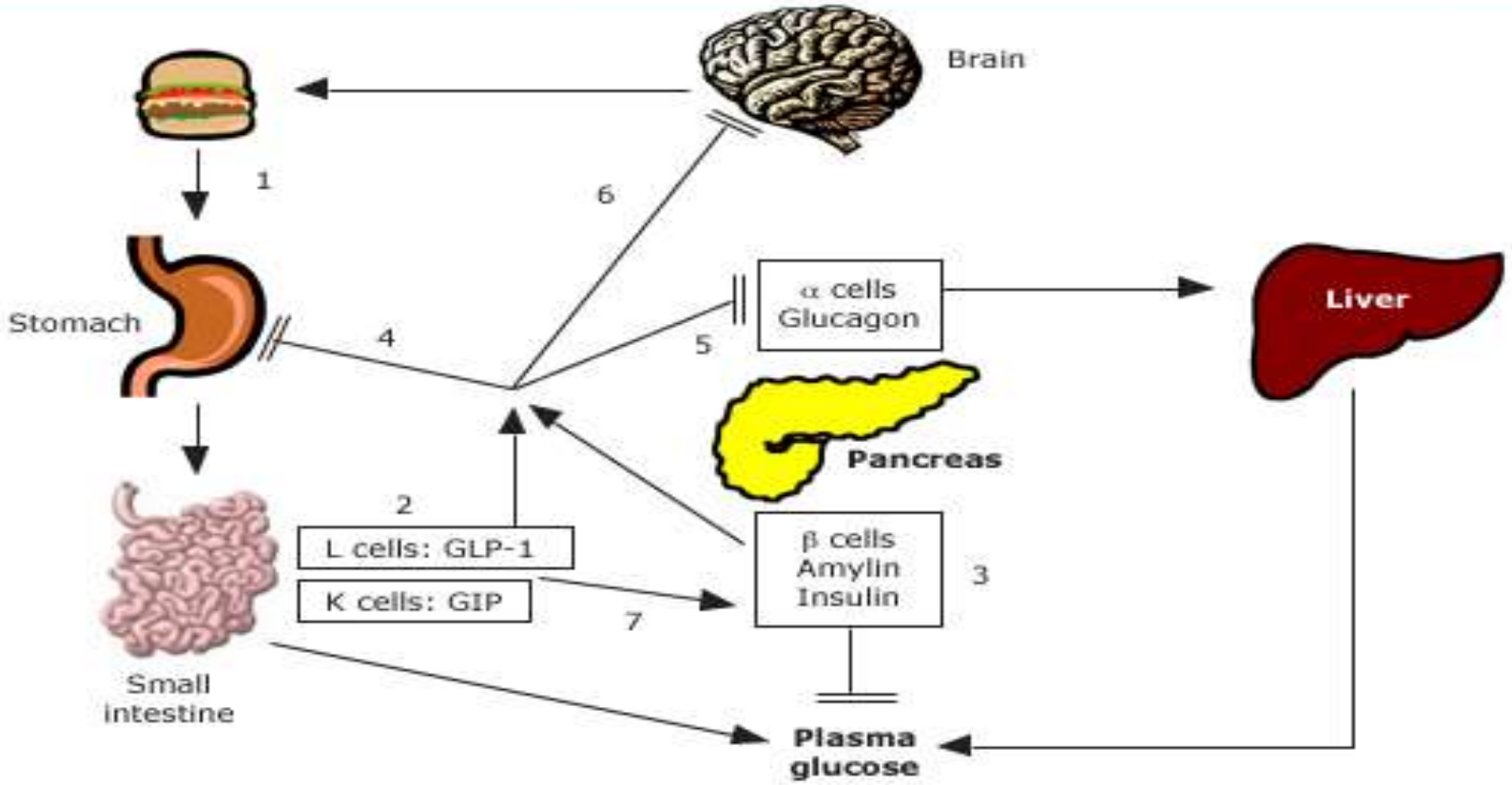
Ajlouni et al 2018
MOH-WHO 2021

Increasing Prevalence of Diagnosed Diabetes in US Adults



Centers for Disease Control and Prevention Web site. Available at: http://www.cdc.gov/diabetes/statistics/prev/state/fig61994and2002.htm. Accessed August 30, 2004.

Plasma glucose multihormonal regulation of glucose



In healthy individuals, (1) ingestion of food results in (2) release of gastrointestinal peptides (GLP-1 and GIP) as well as (3) pancreatic beta cell hormones (insulin and amylin). GLP-1 and amylin, in particular, have inhibitory effects on (4) gastric emptying, (5) glucagon release, and (6) appetite. (7) Following the absorption of food, GLP-1 and GIP promote insulin secretion, otherwise known as the incretin effect. In diabetes, these steps are disrupted.

Classification of Diabetes Mellitus Based Upon the 2004 Expert Committee-I†

Type 1 diabetes
- A. Immune-mediated
- B. Idiopathic

Type 2 diabetes

Other specific types
- A. Genetic defects of beta cell function
  1. Chromosome 12, hepatocyte nuclear fator (HNF)-1-alpha (MODY3)
  2. Chromosome 7, glucokinase (MODY2)
  3. Chromosome 20, HNF-4-alpha (MODY1)
  4. Chromosome 13, insulin promoter factor-1 (IPF-1MODY4)
  5. Chromosome 17, HNF-1-beta (MODY5)
  6. Chromosome 2, NeuroD1 (MODY6)
  7. Mitochondrial DNA
  8. Others
- B. Genetic defects in insulin action
  1. Type A insulin resistance
  2. Leprechaunism
  3. Rabson-Mendenhall syndrome
  4. Lipoatrophic diabetes
  5. Others
- C. Diseases of the exocrine pancreas
  1. Pancreatitis
  2. Trauma/pancreatectomy
  3. Neoplasia
  4. Cystic fibrosis
  5. Hemochromatosis
  6. Fibrocalculous pancreatopathy
  7. Others
- D. Endocrinopathies
  1. Acromegaly
  2. Cushing's syndrome
  3. Glucagonoma
  4. Pheochromocytoma
  5. Hyperthyroidism
  6. Somatostatinoma
  7. Aldosteronoma
  8. Others

Classification of Diabetes Mellitus Based Upon the 2004 Expert Committee-II†

E. Drug- or chemical-linduced
   1. Vacor
   2. Pentamidine
   3. Nicotinic acid
   4. Glucocorticoids
   5. Thyroid hormone
   6. Diazoxide
   7. Beta-adrenergic agonists
   8. Thiazides (minimal effect with low dose therapy)
   9. Phenytoin
   10. Interferon alfa
   11. Others

F. Infections
   1. Congenital rubella
   2. Cytomegalovirus
   3. Others

G. Uncommon forms of immune-mediated diabetes
   1. "Stiff man" syndrome
   2. Anti-insulin receptor antibodies
   3. Others

H. Other genetic syndromes sometimes associated with diabetes
   1. Down syndrome
   2. Klinefelter syndrome
   3. Turner syndrome
   4. Wolfram syndrome — diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD)
   5. Freiderich ataxia
   6. Huntington chorea
   7. Laurence-Moon-Biedl syndrome
   8. Myotonic dystrophy
   9. Porphyria
   10. Prader-Willi syndrome
   11. Others

Gestational diabetes mellitus

Pathophysiology- Type 2 DM

- 1. Progressive beta cell dysfunction:

- 2. Insulin resistance:
  - genetics
  - increases with age and weight.
  - glucotoxicity: reduces insulin gene expression.
  - lipotoxicity

Pathophyisiology-T2DM

- 3. Impaired insulin processing:
  proinsulin 40% of secreted insulin in type 2 DM (NL 10-15 %)

Pathophysiology –Type 1DM

- Autoimmune destruction of B cells (97%)
- Idiopatic (3%)

– bimodal distribution:

a. one peak at 4–6 years of age

b. second in early puberty (10–14 years)

- M=F.

Genetic susceptibility –T1DM

- No family history: 0.4 %
- Affected mother: 2 – 4 %
- Affected father: 5 to 8 %
- Both parents affected: 30 %
- Non-twin sibling of affected patient: 5 %
- Dizygotic twin: 8 %
- Monozygotic twin: 50 % lifetime risk

Genetic susceptibilty- T2DM

- 2-6 x more prevalent in African Americans in USA than in whites
- 39% of pts have at least 1 parent T2DM
- monozygotic twin: 90 % of unaffected twins develop the disease
- The lifetime risk for a first-degree relative of a pt with T2DM is 5-10 x higher than age- & wt-matched subjects w/out f/h of DM

Environmental factors-T1DM

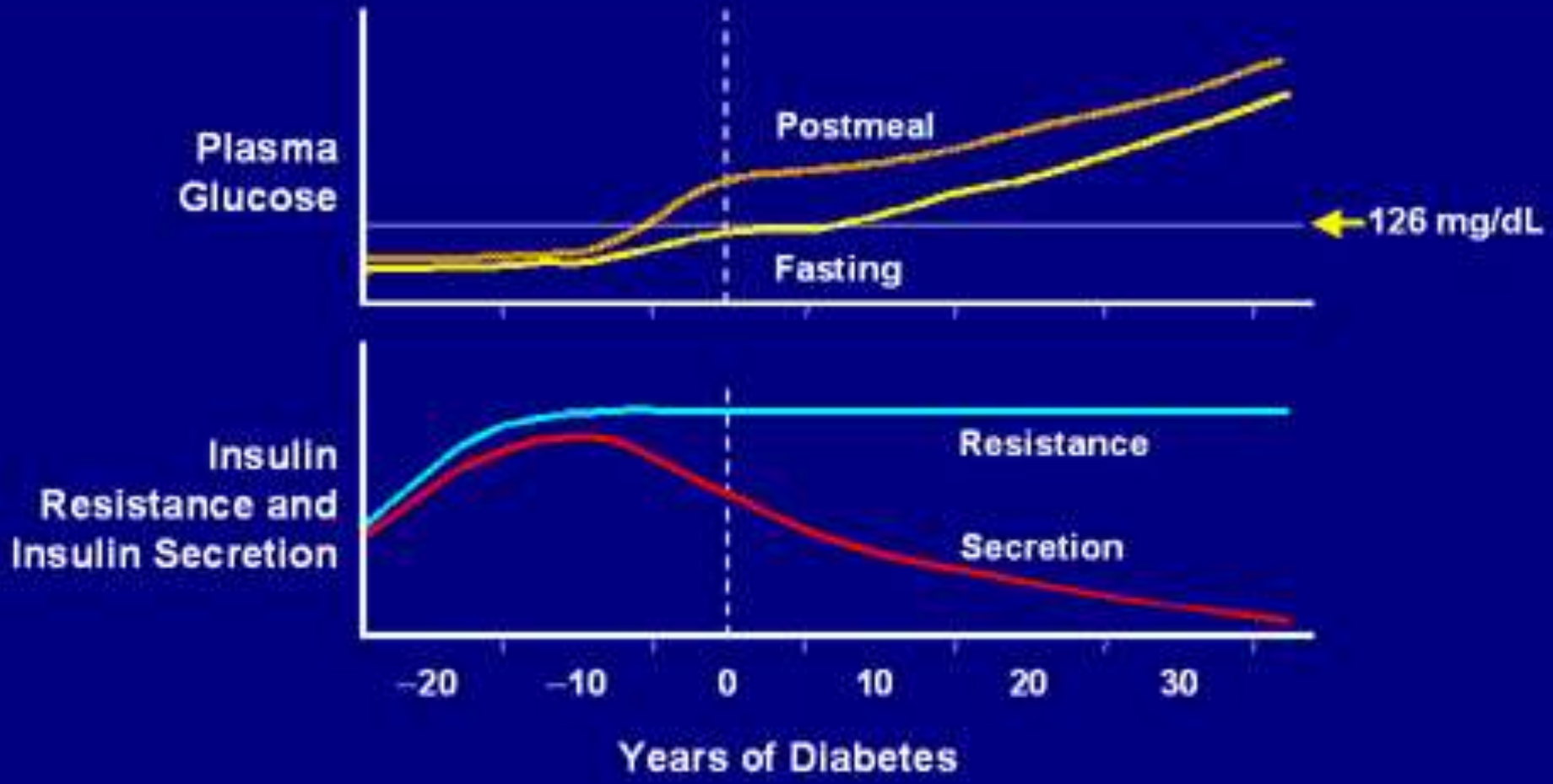
- • Viral infections
- • Immunizations
- • Diet: cow's milk at an early age
- • Vitamin D deficiency
- • Perinatal factors: maternal age, h/o pre-eclampsia, and neonatal jaundice.

- **Low birth weight decreases the risk of developing type 1 diabetes**

Type 1 versus type 2 diabetes

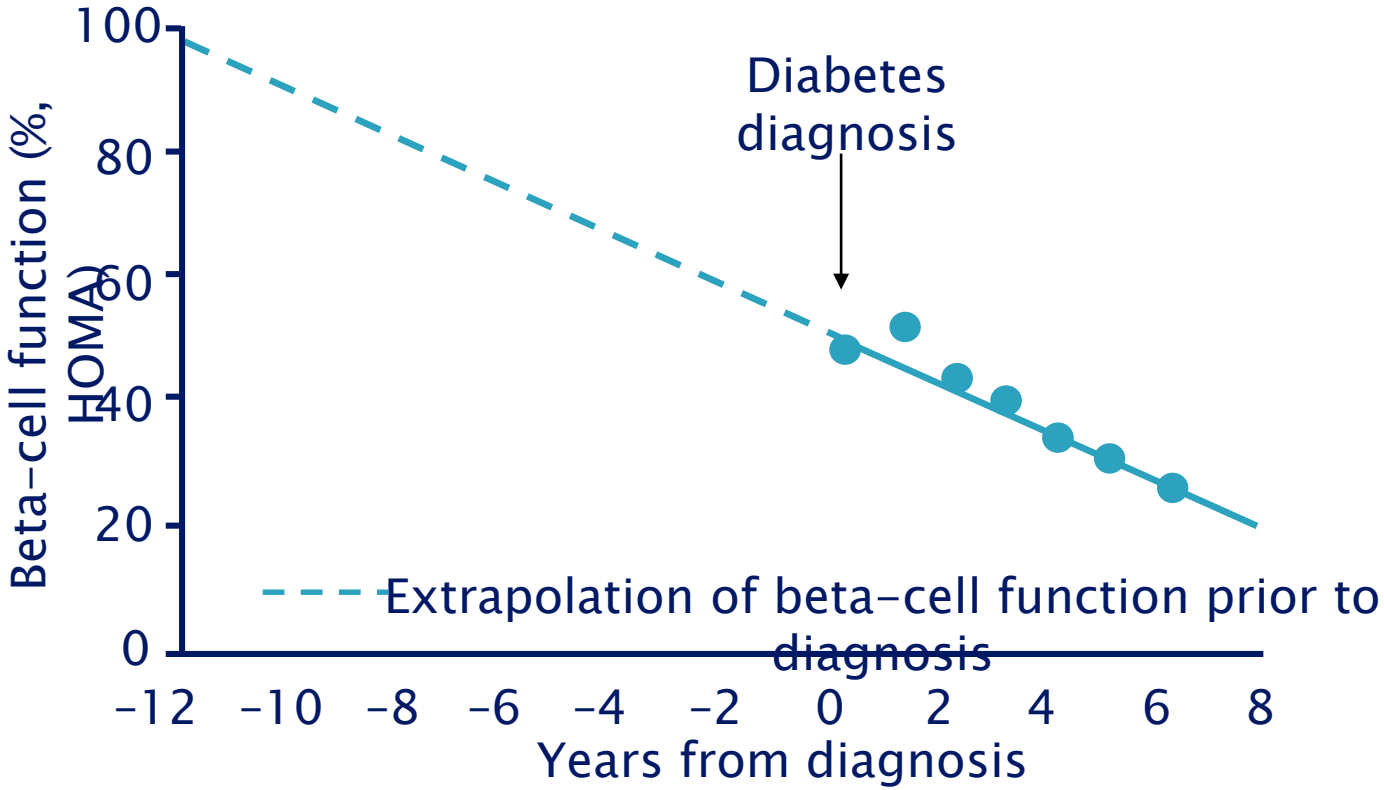
	T1DM	T2DM
1 • Body habitus :	Lean	overweight.
2 • Age :	4-6/10-14	after puberty
3 • insulin resistance		acan. nigricans
5 • Autoimmunity:	Antibody + GAD tyrosine phosphatase (IA2) insulin Zinc transporter Abs	Antibody -

Development of Type 2 Diabetes: A Long-term Process



Adapted from International Diabetes Center (IDC). Minneapolis, Minnesota.

Beta-cell function progressively declines

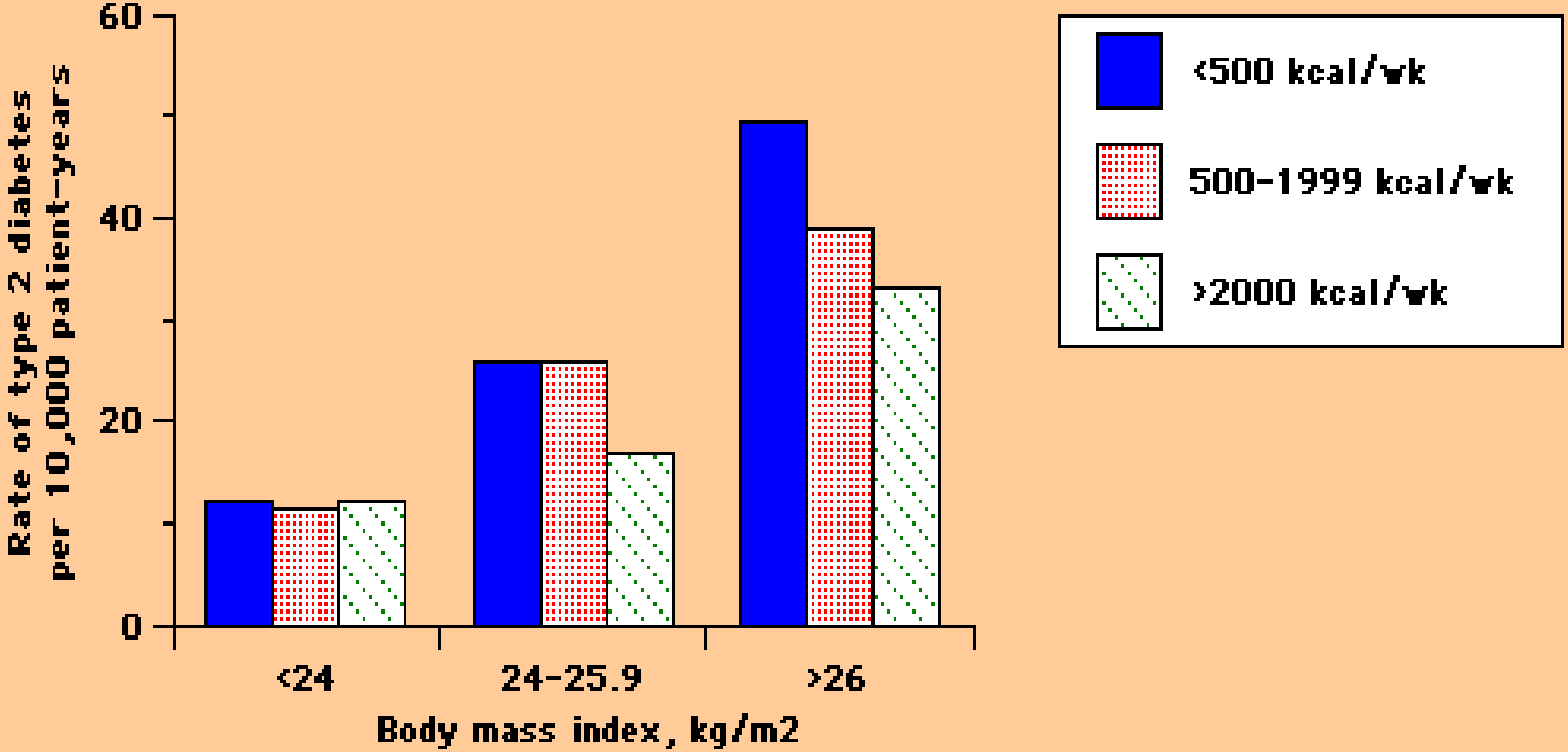


HOMA: homeostasis model assessment

Lebovitz. *Diabetes Reviews* 1999;7:139–53 (data are from the UKPDS population: UKPDS 16. *Diabetes* 1995;44:1249–58)

ROLE OF DIET and OBESITY

- Increasing weight and less exercise
- Obesity epidemic
- Increasing T2DM in children and adolescents



Importance of body weight and exercise on development of type 2 diabetes Adjusted incidence of type 2 diabetes mellitus in 5990 men in relation to body mass index (BMI, in kg/m2) and the level of physical activity (in kcal/wk). The risk of type 2 diabetes was directly related to BMI, while regular exercise was protective except for men with a BMI below 24. Data from Helmrich, SP, Ragland, DR, Leung, RW, Paffenbarger, PS, N Engl J Med 1991; 325:147.

MAJOR RISK FACTORS (Type2DM)

- FH of DM
- Overweight (BMI > 25 kg/m2)
-physical inactivity
-Race/ethnicity (African-Americans)
- h/o IFG or IGT
-H/o GDM or delivery of a baby weighing >4.3 kg
-insulin resistance or conditions associated with insulin resistance :
  *Hypertension (140/90 mmHg in adults)
  *HDL cholesterol 35 mg/dl and/or a triglyceride level 250 mg/dl
  *Polycystic ovary syndrome
  *acanthosis nigricans

Symptoms

- Polyuria, increased frequency of urination, nocturia.
- Increased thirst, and dry mouth
- Weight loss
- Blurred vision
- Numbness in fingers and toes
- Fatigue
- Impotence (in some men)

Signs

- Weight loss: muscle weakness
- Decreases sensation
- Loss of tendon reflexes
- Foot Inter-digital fungal infections
- Retinal changes by fundoscopy

Criteria for the diagnosis of diabetes

1. **A1C ≥6.5 percent.** *
- 2. **FPG ≥126 mg/dL .** No caloric intake for at least 8 h.*
- 3. **Two-hour plasma glucose ≥200 mg/dL** during an OGTT. 75 g anhydrous glucose dissolved in water.*
- 4. In a patient **with classic symptoms** of hyperglycemia or hyperglycemic crisis, **a random plasma glucose ≥200 mg/dL .**

* In the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing.

Diabetes Prevention–DPP trial

3234 obese (BMI 34 kg/m2)
25–85 yrs high risk (Obese+ IFG/IGT) :

- 1. **Intensive lifestyle changes**: reduce wt by 7 % through a low-fat diet and exercise for 150 min / wk
  - reduce DM risk by 58% vs Placebo
- 2. metformin (850 mg BID) **plus information on diet and exercise**
  - reduce DM by 31 %
- 3. **Placebo plus information on diet** and exercise

DPP

- The diet and exercise group lost an average of 6.8 kg (7%) of wt in 1st yr.
- At 3 yrs:

DM incidence (14 % versus 22 and 29 in the lifestyle, metformin and placebo groups, respectively).

- **Lifestyle intervention: effective in men and women, all age groups and ethnic groups.**

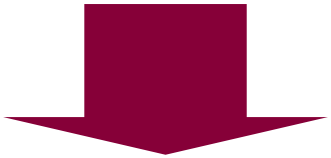
DPP

- 16 % reduction in DM risk for every kg reduction in wt

Management of Type2DM

- 1. Lifestyle modifications:
- – Medical nutrition therapy
- – increased physical activity
- – weight reduction
- 2. Oral Drug Therapy
- 3. Noninsulin injectable therapy
- 4. Insulin therapy

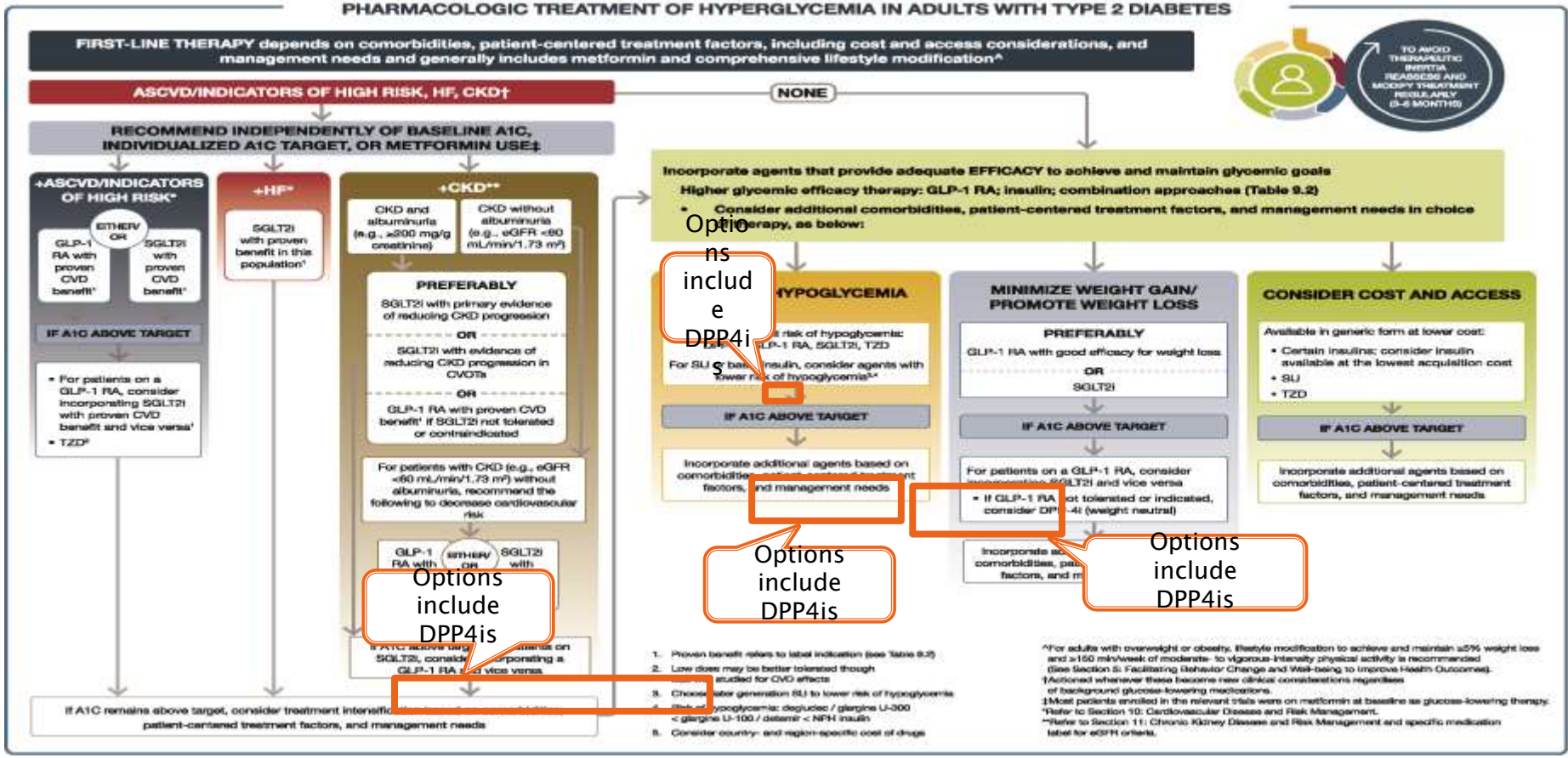
Key challenges of type 2 diabetes: outcome



43% of patients
do not
achieve glycaemic targets
($HbA_{1c} < 7\%$)

Ford *et al* (NHANES). *Diabetes Care* 2008;31:102–4

DPP4 inhibitors are still recommended in international guidelines



Current available Therapy

- **1. Biguanides: Metformin**
- -decrease hepatic glucose output
- -increases glucose utilization in peripheral tissues (such as muscle and liver)
- -antilipolytic effect
- -increases intestinal glucose utilization
- - wt neutral

Efficacy : HbA1c reduction by 1-1.5%

S/E: GI upset, Lactic acidosis (9 cases/ 100,000 person-yrs)

C/I :

renal impairment S.Cr > 1.5 mg/dl males, and S.Cr > 1.4 Females

liver failure

advanced heart failure

sepsis

hypotension

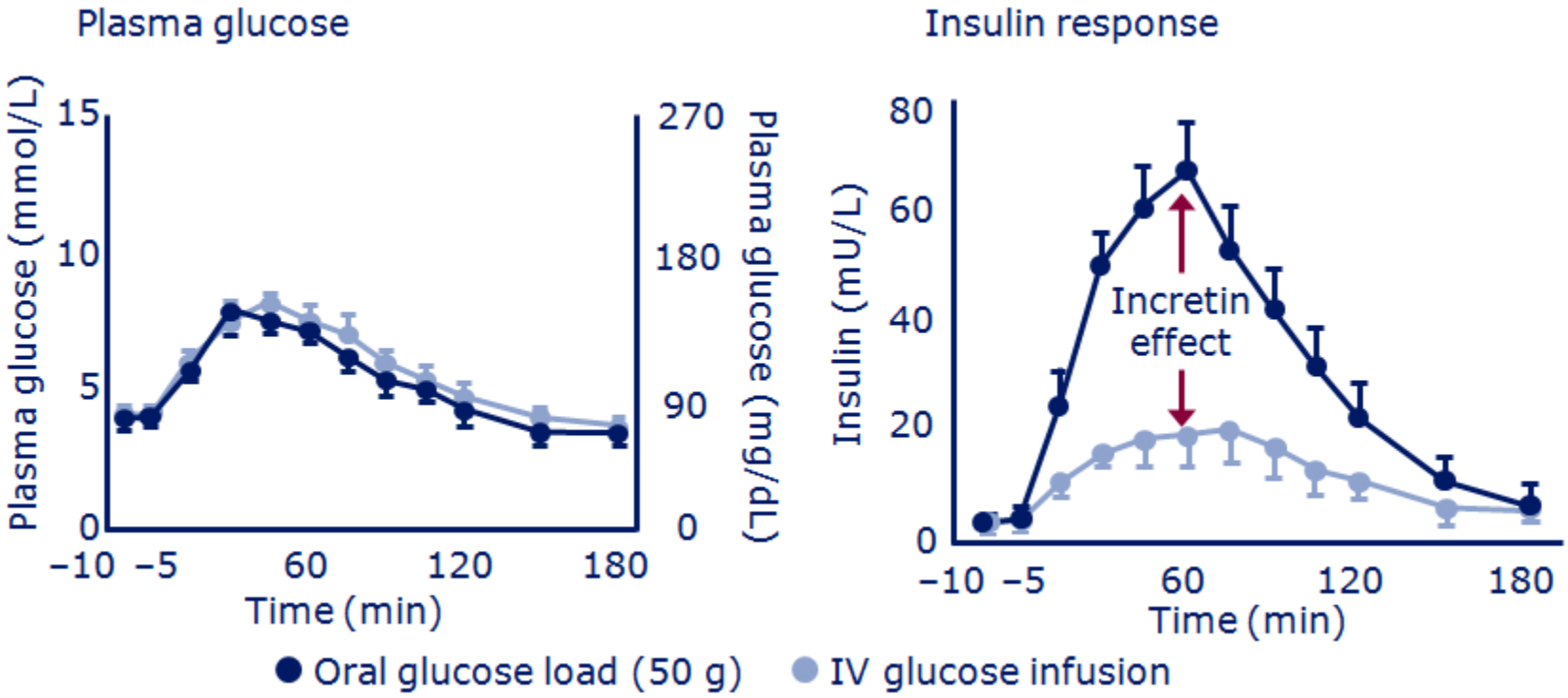
- 2. Sufonylureas and Meglitinides: Glibenclamide, Repagnilide
  - activate SU receptor, insulin relrease
  - Efficacy : HbA1c reduction 1-2 % (SU), <1% Glinides
  - S/E: Hypoglycemia, wt gain
  - C/I: pregnancy

- 3. Alpha- glucosidase inhibitors: Acarbose
  - inhibits GI glucose absorption
  - GI S/E
  - modest HbA1c reductions 0.6%

- 4. Thiazolidinediones: e.g. Pioglitazones
  - PPAR- Gamma agonists
  -insulin sensitizer on adipose tissue, liver, skeletal muscles.
  -S/E: fluid retention-edema,CHF,
    Hepatotoxicity, bone fractures, macular edema, ? IHD

  -Efficacy: HbA1c reduction 1-1.5 %

The incretin hormones play a crucial role in a healthy insulin response



- Insulin response is greater following oral glucose than IV glucose, despite similar plasma glucose concentration

Nauck *et al. Diabetologia* 1986;29:46–52, healthy volunteers (n=8); Wick & Newlin. *J Am Acad Nurse Pract* 2009;21:623–30

- 5. Incretin based therapy:
  a. DPP4 Inhibitors:
  - inhibit enzyme which inactivates native GLP-1
  - oral
  - Efficacy:HbA1c 0.6 -0.9 %
  - S/E: ? Pancreatitis, hepatotoxicity, Skin reactions
  - wt neutral

- **b. GLP1 agonists**:

  Exenetide: synthetic exendin4, 53% homology with natural GLP1.

  - glucose-dependent insulin release
  - slows gastric emptying,
  - suppresses elevated glucagon levels
  - weight loss (increased satiety)
  - HbA1c reduction 1.1%
  - S/E : GI (nausea), acute pancreatitis, acute renal failure

Liraglutide :

GLP-1 analog, binds to serum albumin resulting in slower degradation,

- Once daily injection
- HbA1c reduction of 1.0 -1.5%
- weight reduction
- S/E: GI, pancreatitis, ? Thyroid C-cell hyperplasia/malignancy in animals.

- 6. **Amylin analogues**:

  AMYLIN: peptide stored in beta cells and co-secreted with insulin .

  Amylin is deficient in T1DM and relatively deficient in insulin-requiring T2DM

  - slowed gastric emptying,
  - regulation of postprandial glucagon
  - reduction of food intake

- PRAMLINTIDE : amylin analog
  -approved for T1D and insulin-treated T2D
  - glucose-dependent insulin release. It does not cause hypoglycemia
  - HbA1c reduction < 1%
  - S/E : nausea, increase hypoglycemia risk if insulin dose not reduced.

7. SGLT2 inhibitors:

inhibit sodium and glucose reabsorption in proximal tubules.

CVS protection

S/E: UTI, dizziness, hypotension, dehydration

8. Insulins

1. Ultra-short acting : Aspart-Lispro-Glulisine
- 2. Short acting: Regular
- 3. Intermediate acting : NPH
- 4. intermediate—long : Insulin Detimir
- 5. Long acting : Insulin Glargine

Hypoglycemic disorders

Hypoglycemia in DM pts

- With insulin or insulin secretagogues Rx.
- Higher risk:
  TIDM
  tight/near normal glycemic control

- unawareness with repeated hypoglycemia.
- Severe prolonged can lead to permanent neurological deficit

hypoglycemia

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

hypoglycemia

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

Hypoglycemic disorders

- Whipple's Triad

- Classification:
  - Ill- looking
  - seemingly well-looking

ILL looking patients:

- 1. Drugs
  Insulin or insulin secretagogue
  Alcohol
- 2. Critical illnesses
  Hepatic, renal, or cardiac failure /Sepsis
- 3. Hormone deficiency
  Cortisol
  Glucagon
- 4. Nonislet cell tumor

Seemingly well individual

5. Endogenous hyperinsulinism
   - Insulinoma
   - Functional β-cell disorders (nesidioblastosis)
     - -Post gastric bypass hypoglycemia
   - Insulin autoimmune hypoglycemia
     - - Antibody to insulin / insulin receptor
   - Insulin secretagogue

6. Accidental hypoglycemia

Diagnostic approach

- Renal failure, liver failure, sepsis, medications (oral hypoglycemic agents (OHA), ETHOL)
- RBG, KFT, LFT, cortisol

- In seemingly well subjects:

  diagnostic workup during symptomatic hypoglycemia

72-hour Fasting test

Protocol

- Allow calorie-free and caffeine-free beverages

- The pt is active during waking hours.

- Insulin antibodies
- Sulfonylurea level

Test end points and duration

- plasma glucose ≤45 mg/dL
- symptoms or signs of hypoglycemia,
- 72 hours have elapsed,

or

- plasma glucose < 55 mg/dL if Whipple's triad was documented previously

Ending the fast

- plasma glucose, insulin, C-peptide, proinsulin, B-OH-Butyrate, and OHA

- 1 mg of iv glucagon and the plasma glucose measured 10, 20, and 30 min

- The pt is fed

72 hour fast---Interpretation

S+S	Gluc mg/dl	Insulin miU/L	C-pep ng/ml	βOHB mmol/l	glucagon /BG resp.	OHA	Ab + /insulin	Dx
N	<55	<3	<0.6	>2.7	<25	N	N	Normal
Y	<55	>>3	<0.6	≤2.7	>25	N	N	Exog insu
Y	<55	≥3	≥0.6	≤2.7	>25	N	N	Insulinom
NIPHS, PGBH								
Y	<55	≥3	≥0.6	≤2.7	>25	Y	N	OHA
Y	<55	>>3	>>0.6	≤2.7	>25	N	P	autoim
Y	<55	<3	<0.6	≤2.7	>25	N	N	IGF-me
Y	<55	<3	<0.6	>2.7	<25	N	N	Not insu
(or IGF)-mediated								

LOCALIZING STUDIES

DDx Endogenous hyperinsulinemia:

a - **insulinoma, nesidioblastosis/islet cell hypertrophy,**

b - **OHA-induced hypoglycemi**a,

c - **insulin autoimmune hypoglycemia .**

A localizing study is required if insulin ab and OHA are negative

Radiologic studies

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

- If initial imaging is negative:
  - endoscopic u/s or
  - selective arterial calcium stimulation

Arterial calcium stimulation

- **gastroduodenal**
- **splenic**
- **superior mesenteric arteries**

  with sampling of the hepatic venous effluent for insulin
- **doubling or tripling** of basal insulin concentrations is positive

- In pts with insulinoma, the response is + in one artery
- Islet cell hypertrophy: + responses are usually observed after injection of multiple arteries

Insulinoma

Fasting hypoglycemia: most common feature

Due to reduced hepatic glucose output rather than increased glucose utilization

Mayo Clinic Series

Cases:

1987-2007: 237 pts

- age: 50 yrs (range 17-86),
- 57 % were women

- **Symptoms** :

Neuroglycopenic: confusion, visual change, and unusual behavior.

Sympathoadrenal: palpitations, diaphoresis, and tremulousness

- median duration of symptoms < 1.5 yrs
- 20 % misdiagnosed with a neurologic (? Seizures) or psychiatric disorder.
- Wt gain in 18 % of pts
- Fasting hypoglycemia 73 %
- Fasting and postprandial symptoms 21%
- Only postprandial symptoms 6%

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**

- Thank You

- Insulinomas arise from cells of the ductular/acinar system of the pancreas rather than from neoplastic proliferation of islet cells .
- The mechanism by which insulinomas maintain high levels of insulin secretion in the presence of hypoglycemia is unknown.
- ? Variant of insulin mRNA with increased translation efficiency is present in high amounts in insulinomas when compared to normal islet