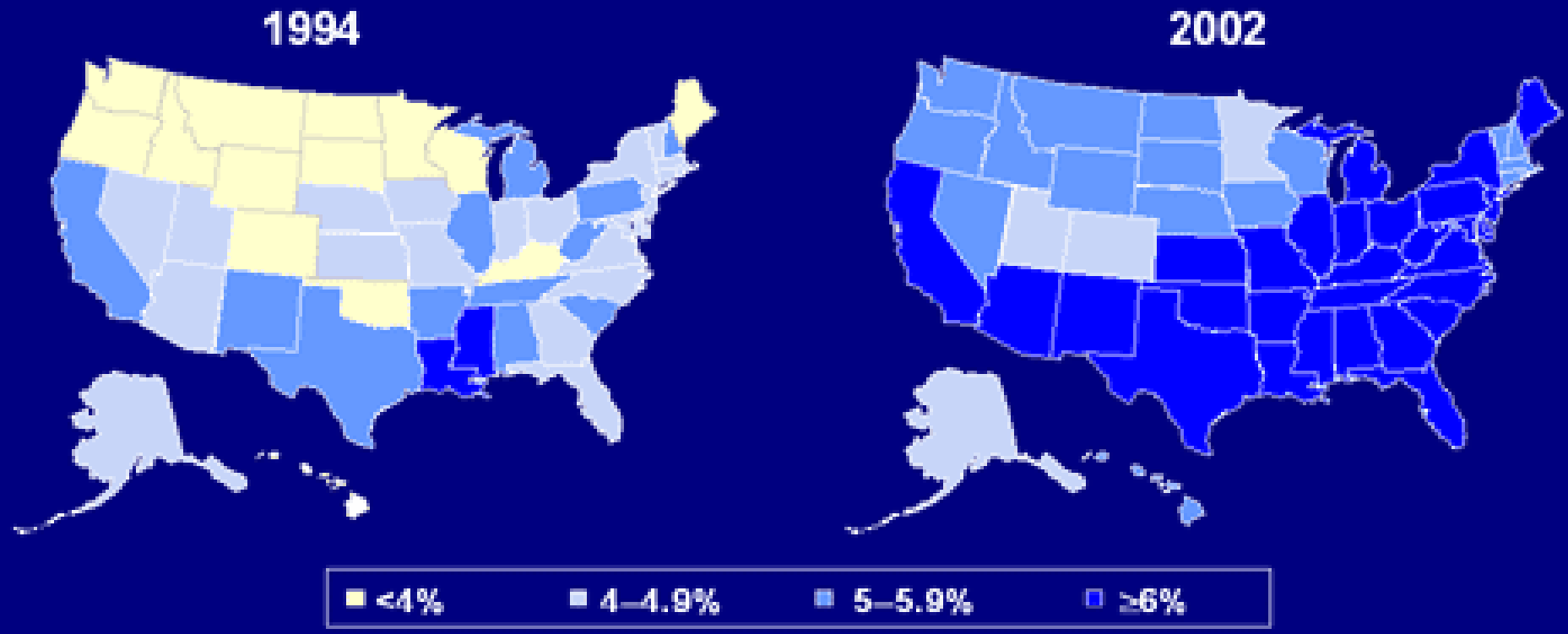
Diabetes Mellitus

Increasing Prevalence of Diagnosed Diabetes in US Adults



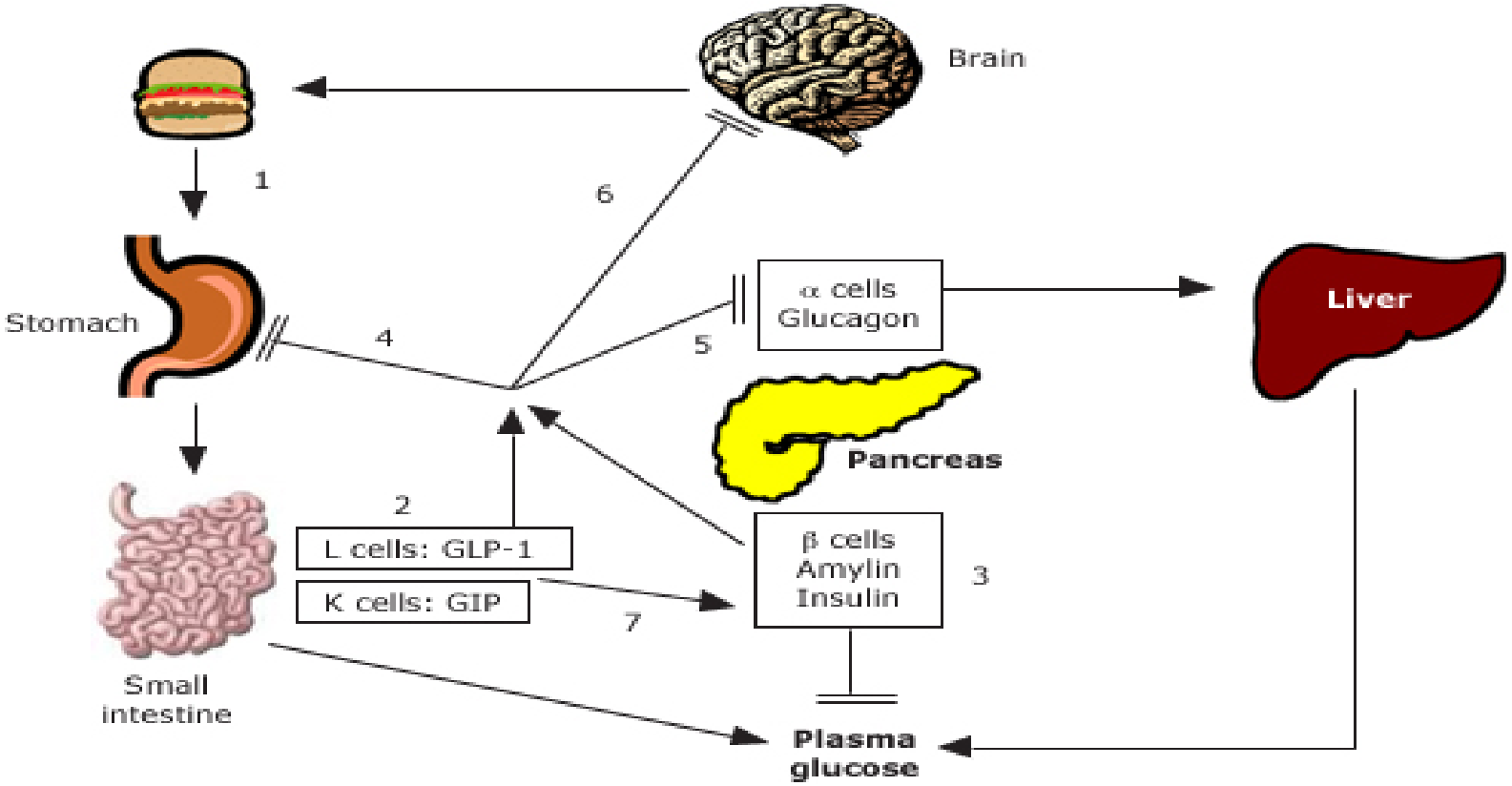
Centers for Disease Control and Prevention Web site. Available at: http://www.cdc.gov/diabetes/statistics/prev/state/fig61994and2002.htm. Accessed August 30, 2004.

Prevalence in Jordan

- 83 % of adult females : overweight and obesity
- 80 % of adult males : overweight and obesity
- 25 % of adults in Jordan have DM and preDM (IGT (7.8%)+ DM(17.1%))

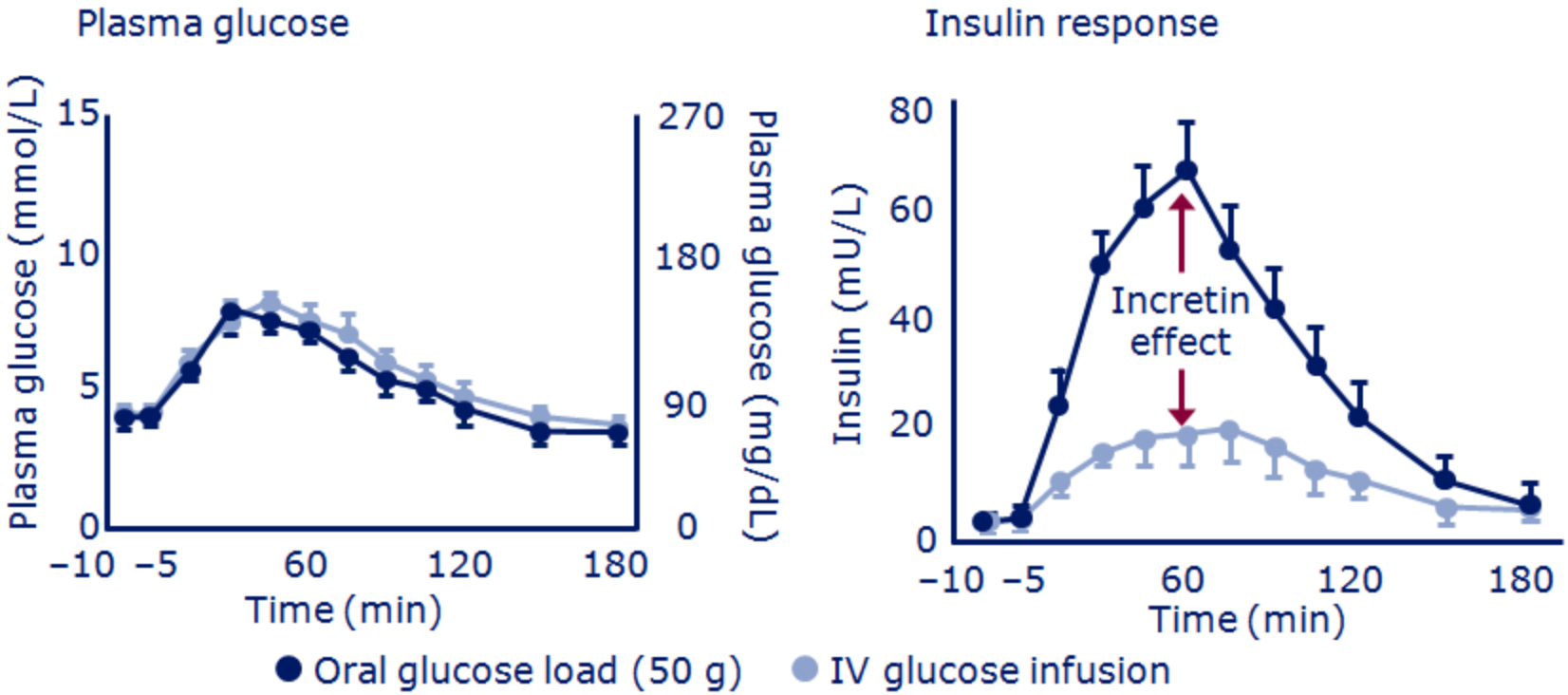
Ajlouni et al

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.

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

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: genetically determined
  -increases with age and weight.
  - glucotoxicity also reduces insulin gene expression.
  - lipotoxicity :cytokine effect

Pathophyisiology-T2DM

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

Pathophysiology –Type 1DM

- **Epidemiology**:
  - 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

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**

TABLE 30-2 Type 1 and Type 2 Diabetes Mellitus

	TYPE 1	TYPE 2
Etiology	Autoimmune destruction of pancreatic β-cells	Insulin resistance, with inadequate β-cell function to compensate
Insulin levels	Absent or negligible	Typically higher than normal
Insulin action	Absent or negligible	Decreased
Insulin resistance	Not part of syndrome but may be present (e.g., in obese patients)	Yes
Age of onset	Typically <30 years	Typically >40 years
Acute complications	Ketoacidosis Wasting	Hyperglycemia (can lead to hyperosmotic seizures and coma)
Chronic complications	Neuropathy Retinopathy Nephropathy Peripheral vascular disease Coronary artery disease	Same as type 1
Pharmacologic interventions	Insulin	A number of drug classes are available, including insulin if other therapies fail

Type 1 and type 2 diabetes mellitus are both associated with increased blood glucose levels, but the two diseases result from distinct pathophysiologic pathways. In type 1 diabetes mellitus, there is an absolute lack of insulin secondary to autoimmune destruction of pancreatic β-cells. The etiology of type 2 diabetes is less well understood but seems to involve impaired insulin sensitivity and an inadequate level of compensatory insulin production by pancreatic β-cells. Although type 1 and type 2 diabetes have different acute complications (*see text*), they share similar chronic complications. Insulin is the primary pharmacologic intervention for type 1 diabetes, while type 2 diabetes can be treated with a number of different agents.

Type 1 versus type 2 diabetes

1 • Body habitus :T2DM: overweight.
T1DM:lean

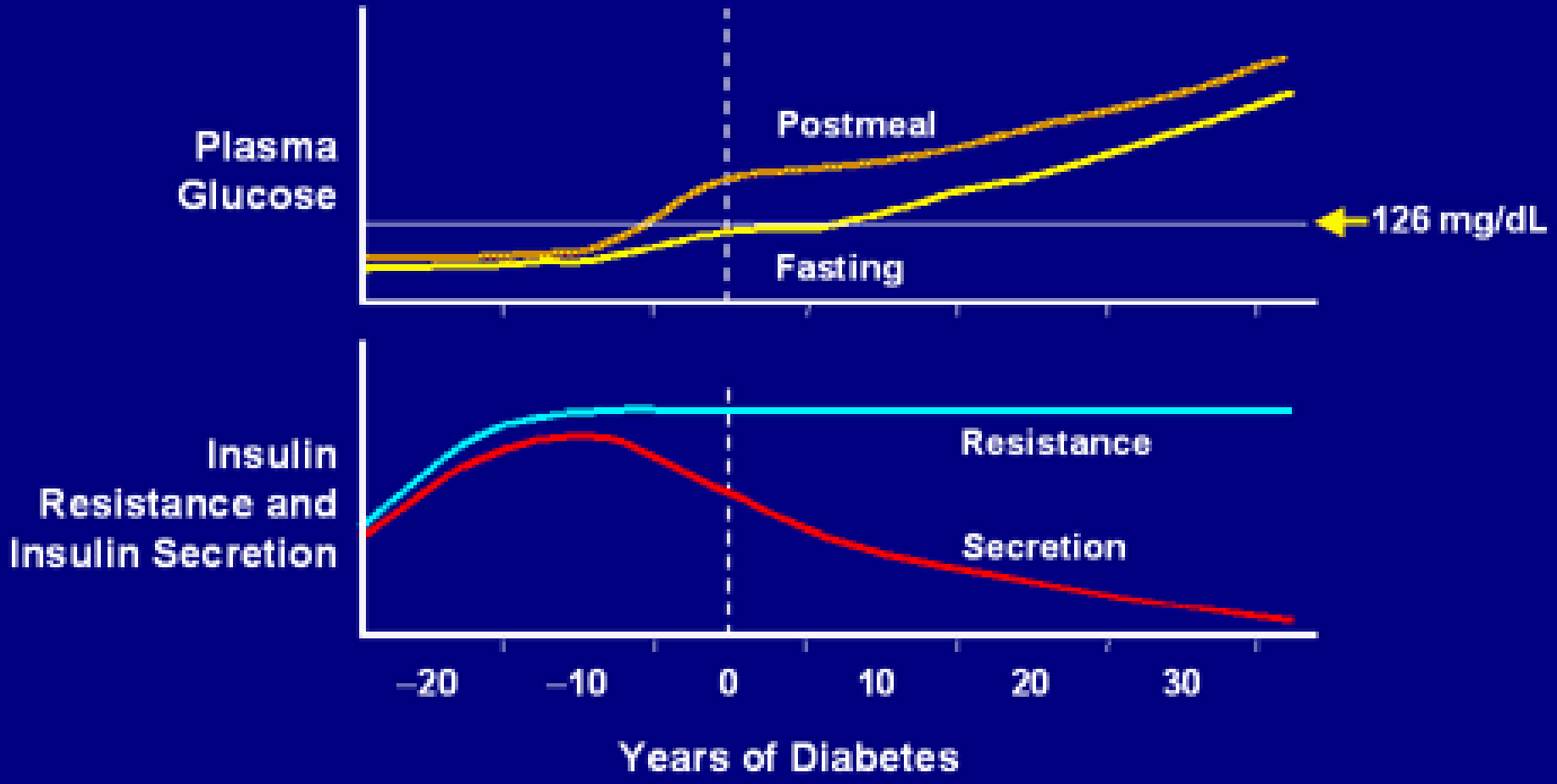
2 • Age :T2DM :after puberty.
T1DM: 4 -6 yrs and 10 -14 yrs

3• Insulin resistance :T2DM: acanthosis nigricans,HTN, dyslipidemia, and PCOS

4• FH: (+) in both type 2 > type 1

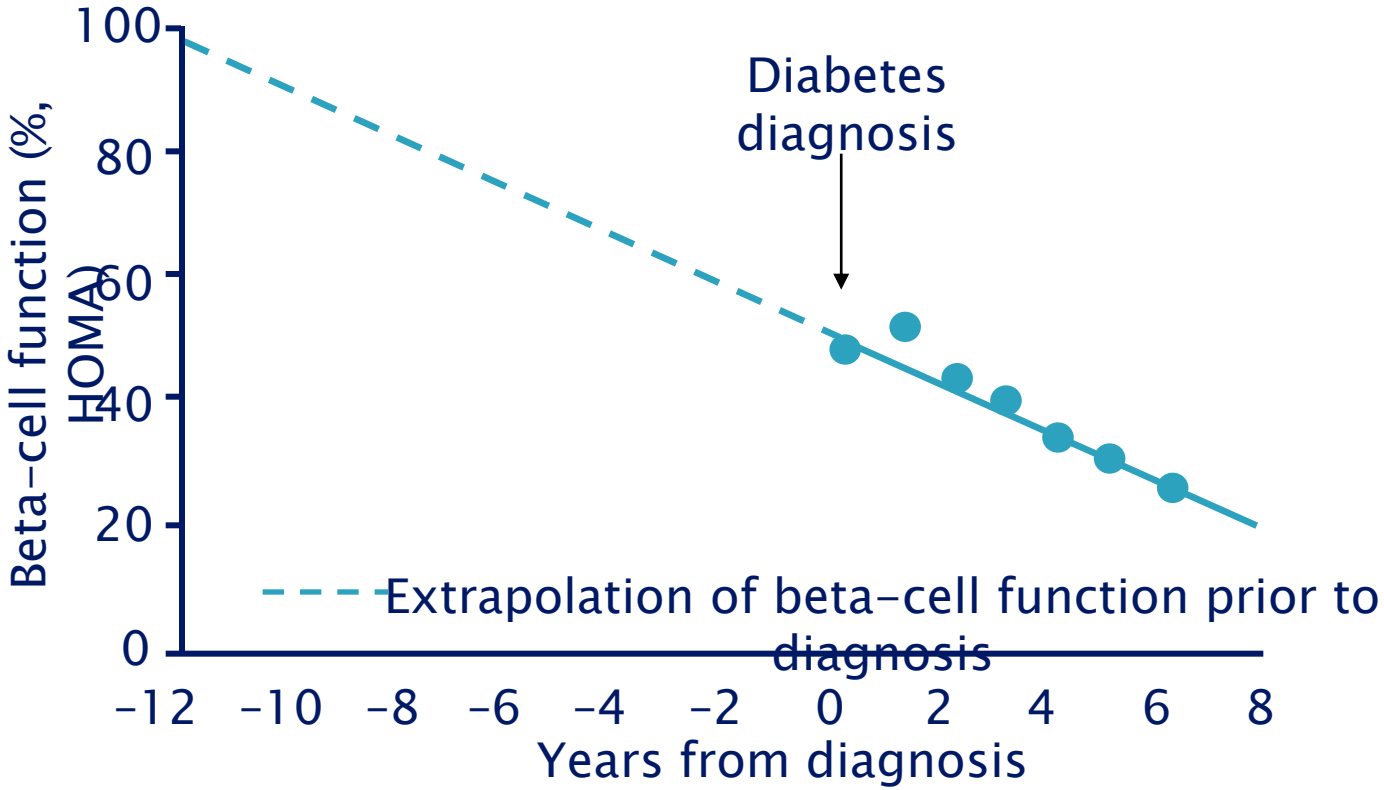
5•T1DM: +GAD, tyrosine phosphatase (IA2), and/or insulin Abs
Up to 30 % of T2DM have + Abs

Development of Type 2 Diabetes: A Long-term Process



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

Beta-cell function progressively declines

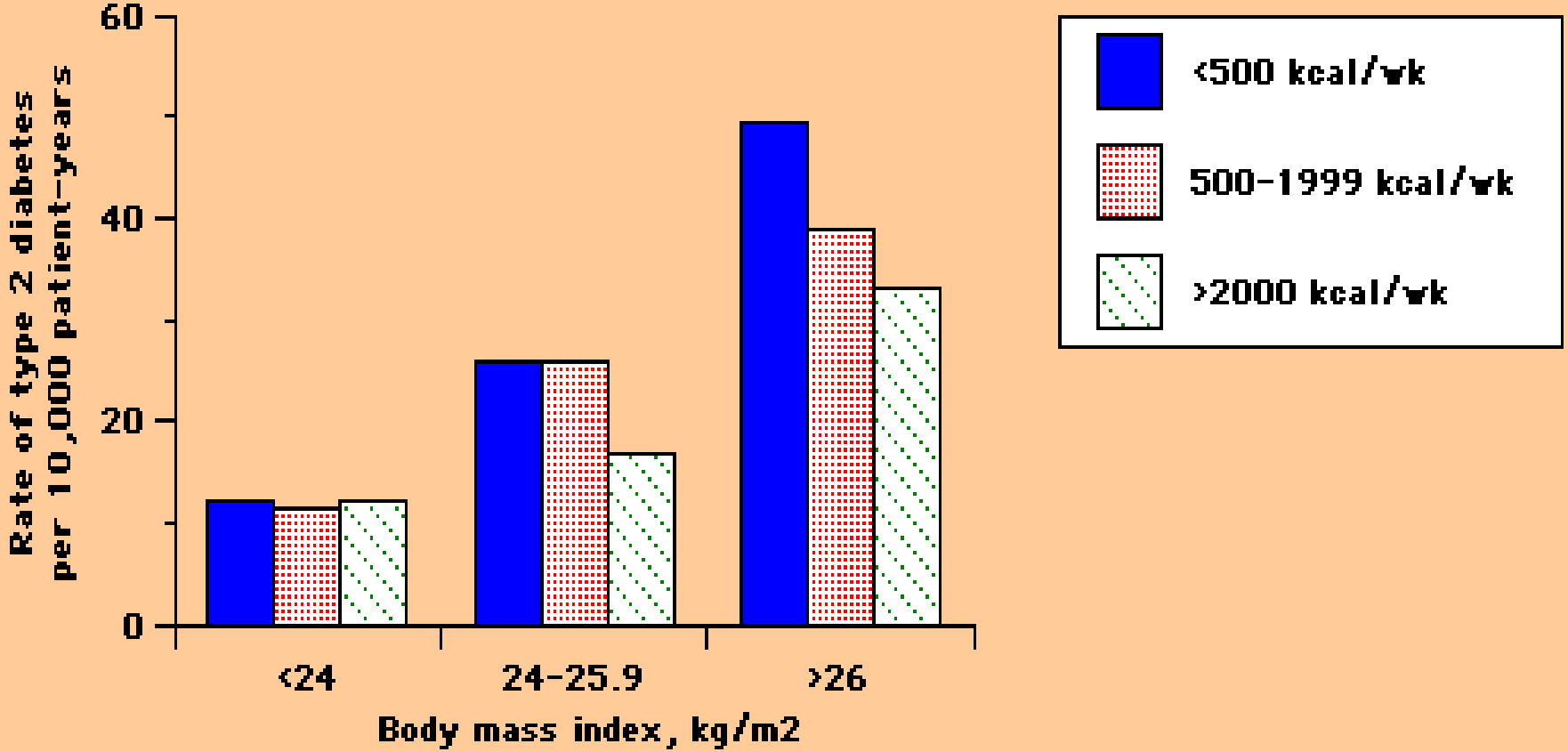


HOMA: homeostasis model assessment

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

ROLE OF DIET, OBESITY, AND INFLAMMATION

- 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.

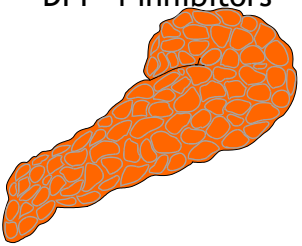
Management of Type2DM

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

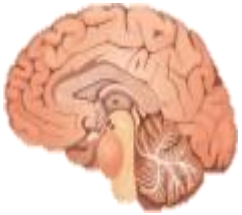
Pharmacological Actions of Diabetes Drugs*

Pancreas

Glucagon Suppression
GLP-1 agonists
DPP-4 inhibitors



Insulin Secretion
Sulfonylureas
Glinides
GLP-1 agonists
DPP-4 inhibitors



Brain

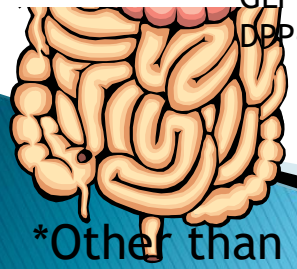
Circadian Rhythm
Bromocriptine QR

Liver

Hepatic Glucose Production
Metformin
GLP-1 agonists
DPP-4 inhibitors

HYPERGLYCEMIA

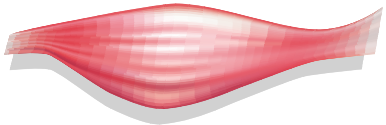
Intestine



GI Motility/Satiety
GLP-1 agonists

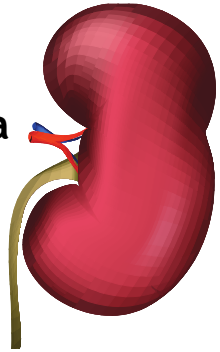
Skeletal Muscle

Insulin Sensitivity
TZDs



Kidney

Glucosuria
SGLT2 inhibitors



*Other than insulin

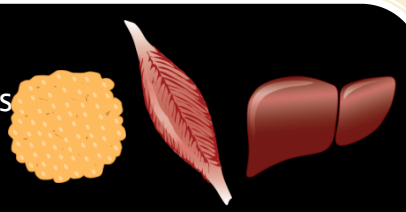
Existing and novel mechanisms to reduce hyperglycaemia in Type 2 diabetes[1–4]

Insulin-dependent mechanisms

1

Insulin action

- Thiazolidinediones
- Metformin



Adipose tissue, muscle and liver

2

Insulin release

- SUs
- GLP-1R agonists*
- DPP4 inhibitors*
- Meglitinides

Pancreas

3

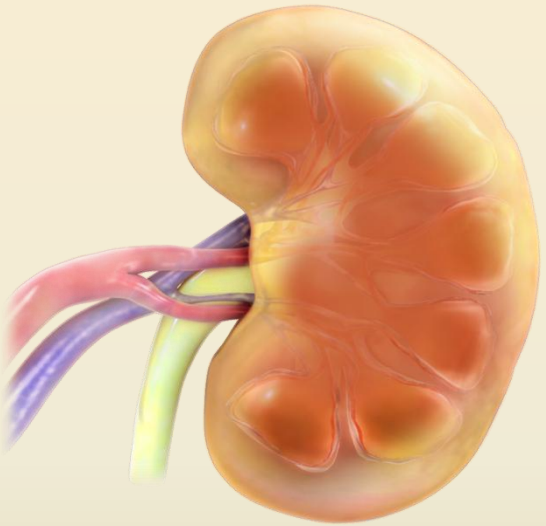
Insulin replacement

- Insulin

Glucose utilisation

Insulin-independent mechanism

SGLT2 inhibition



Glucose excretion/caloric loss

*In addition to increasing insulin secretion, which is the major mechanism of action, GLP-1R agonists and DPP4 inhibitors also act to decrease glucagon secretion.

DPP4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor; SUs, sulphonylureas.

1. Washburn WN. *J Med Chem* 2009;52:1785–94; 2. Bailey CJ. *Curr Diab Rep* 2009;9:360–7; 3. Srinivasan BT, *et al. Postgrad Med J* 2008;84:524–31; 4. Rajesh R, *et al. Int J Pharma Sci Res* 2010;1:139–47.

Current available Therapy

- 1. Biguanides: Metformin
- 2. Sufonylureas and Meglitinides: Glibenclamide, Repagnilide
- 3. Alpha- glucosidase inhibitors: Acarbose
- 4. Thiazolidinediones: Pioglitazones,Rosiglitazones

Drug therapy

- 5. Incretin based therapy:
- **a. DPP4 Inhibitors**
- **b. GLP1 agonists**:
- **Exenetide, Liraglutide** :

- 6. **Amylin analogues**: PRAMLINTIDE
- peptide that is co-secreted with insulin .

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

7. SGLT2 inhibitors : empagliflozin
8. Dopamine agonist: Bromocriptine

Insulins

- Ultra-short acting : Aspart-Lispro-Glulisine
- Short acting: Regular
- Intermediate acting : NPH
- intermediate—long : Insulin Detimir
- Long acting : Insulin Glargine

Thank You