Physical Activity and Health Promotion

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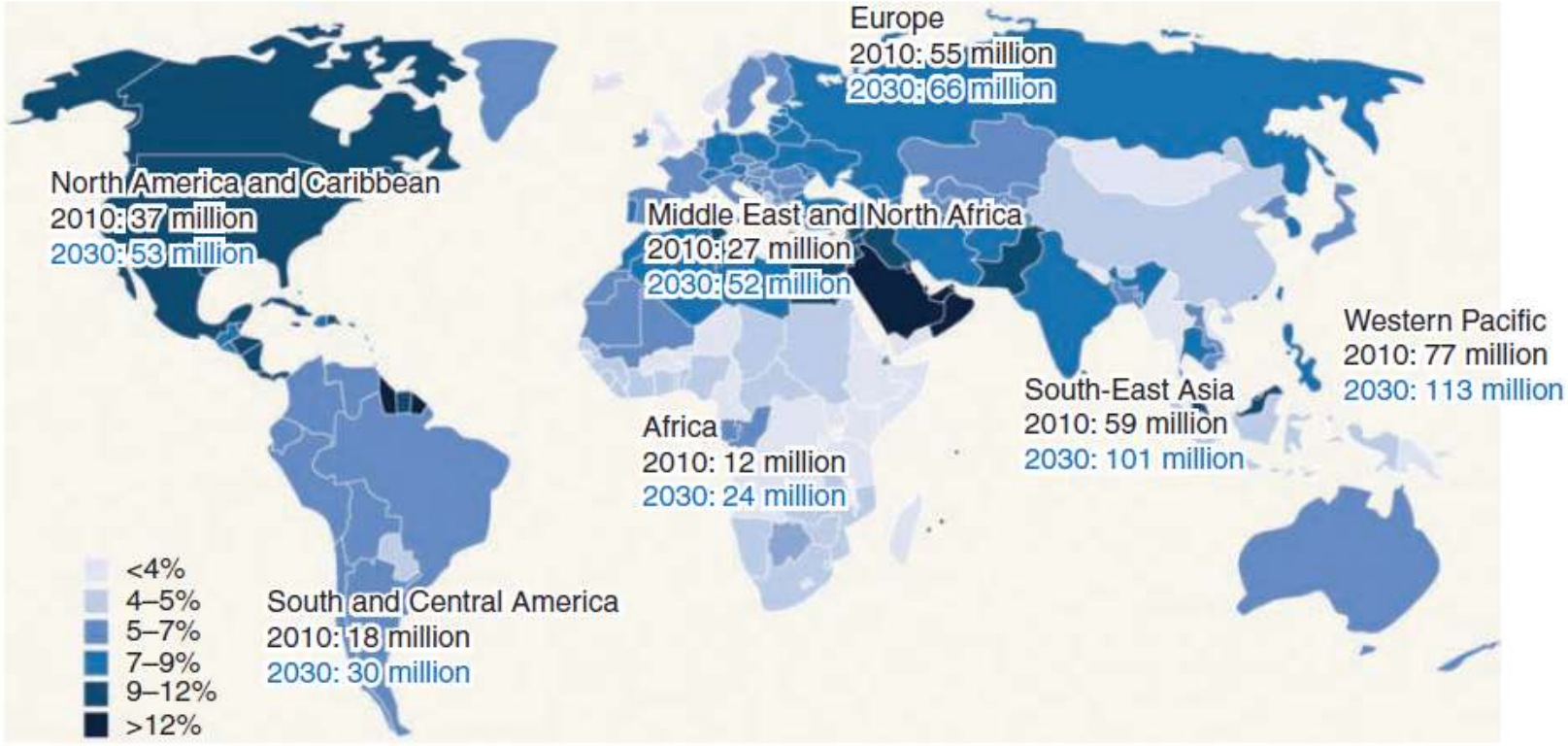
Metabolic Syndrome
And
Diabetes Mellitus

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include

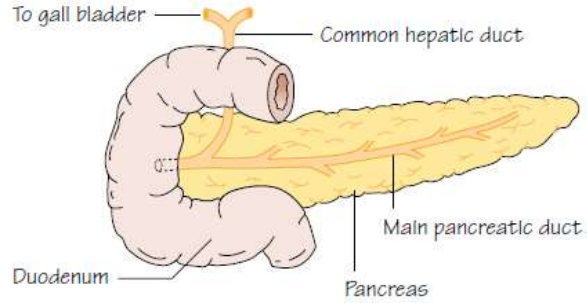
- **reduced insulin secretion**
- **decreased glucose utilization**
- **increased glucose production**.

The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system.

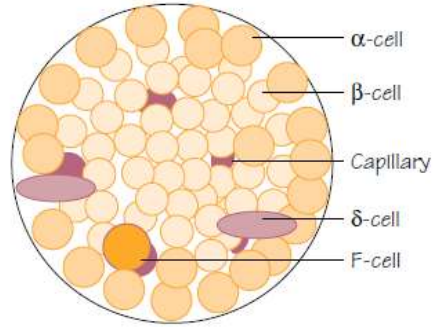
Worldwide prevalence of diabetes



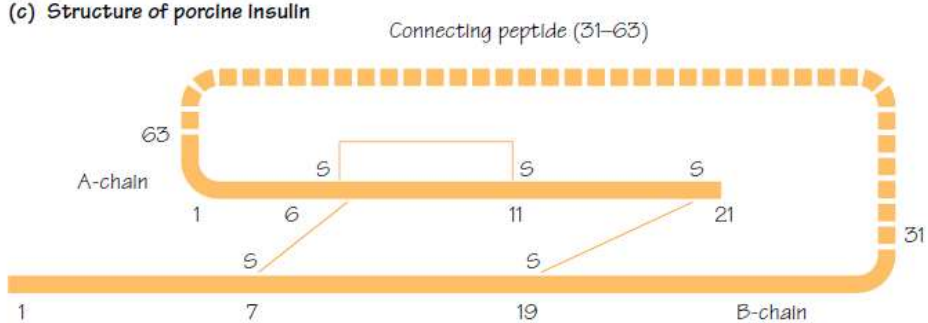
(a) The pancreas



(b) The pancreatic islet

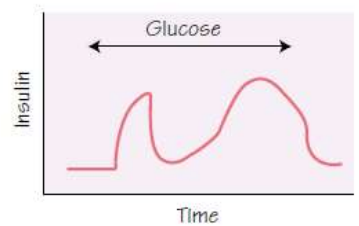


(c) Structure of porcine insulin



(d) Control of insulin secretion

Dietary	Hormonal	Neural
Glucose Amino acids Fatty acids Ketone bodies	Secretin Glucagon Gastrin Gastric inhibitory polypeptide Vasoactive intestinal peptide	Cholinergic – stimulates Adrenergic – mixed functions
All stimulate secretion		All stimulate secretion



ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

- **Type 1 diabetes** (beta cell destruction, usually leading to absolute insulin deficiency)
    - A. Immune mediated
    - B. Idiopathic
- **Type 2 diabetes** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
- **Other specific types** of diabetes
- **Gestational diabetes mellitus (GDM)**

Etiopathogenesis of Diabetes Mellitus

A

Genetic defects of **beta cell function** characterized by mutations in:

1. Hepatocyte nuclear transcription factor (HNF) 4α (**MODY*1**)
2. Glucokinase (**MODY 2**)
3. HNF-1α (**MODY 3**)
4. Insulin promoter factor-1 (IPF-1; **MODY 4**)
5. HNF-1β (**MODY 5**)
6. NeuroD1 (**MODY 6**)
7. Mitochondrial DNA
8. Subunits of ATP-sensitive potassium channel
9. Proinsulin or insulin

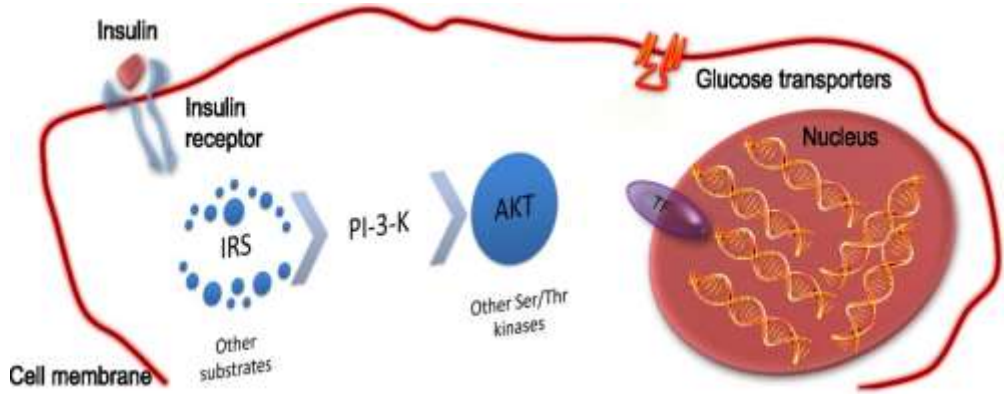
* **Maturity onset diabetes of the young**, (**MODY**)

Etiopathogenesis of Diabetes Mellitus

B

Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism*
3. Rabson-Mendenhall syndrome**
4. Lipodystrophy syndromes***



***Leprechaunism** derives its name from the hallmark elvish features (small stature, bulging eyes, thick lips, and upturned nostrils) exhibited by the affected individuals

** La **sindrome di Rabson-Mendenhall** is an uncommon genetic disease characterized by hypertrophy of pineal gland and insulin resistance

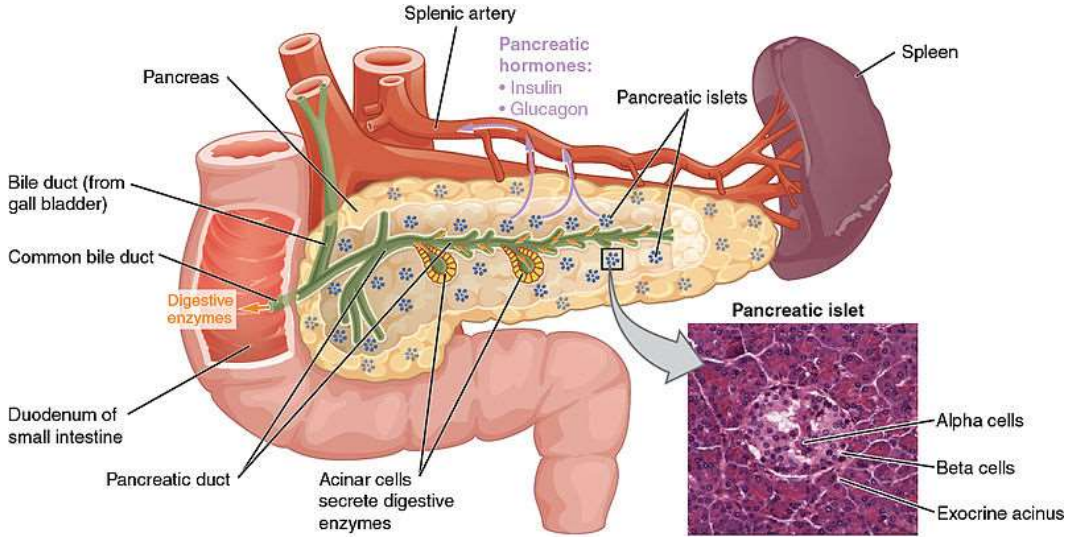
*** **Lipodystrophy** syndromes are a group of genetic or acquired disorders in which the body is unable to produce and maintain healthy fat tissue

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

C

Diseases of the exocrine pancreas

Pancreatitis,
Pancreatectomy
Neoplasia
Cystic fibrosis,
Hemochromatosis,
Fibrocalculous pancreatopathy,
Mutations in carboxyl ester lipase

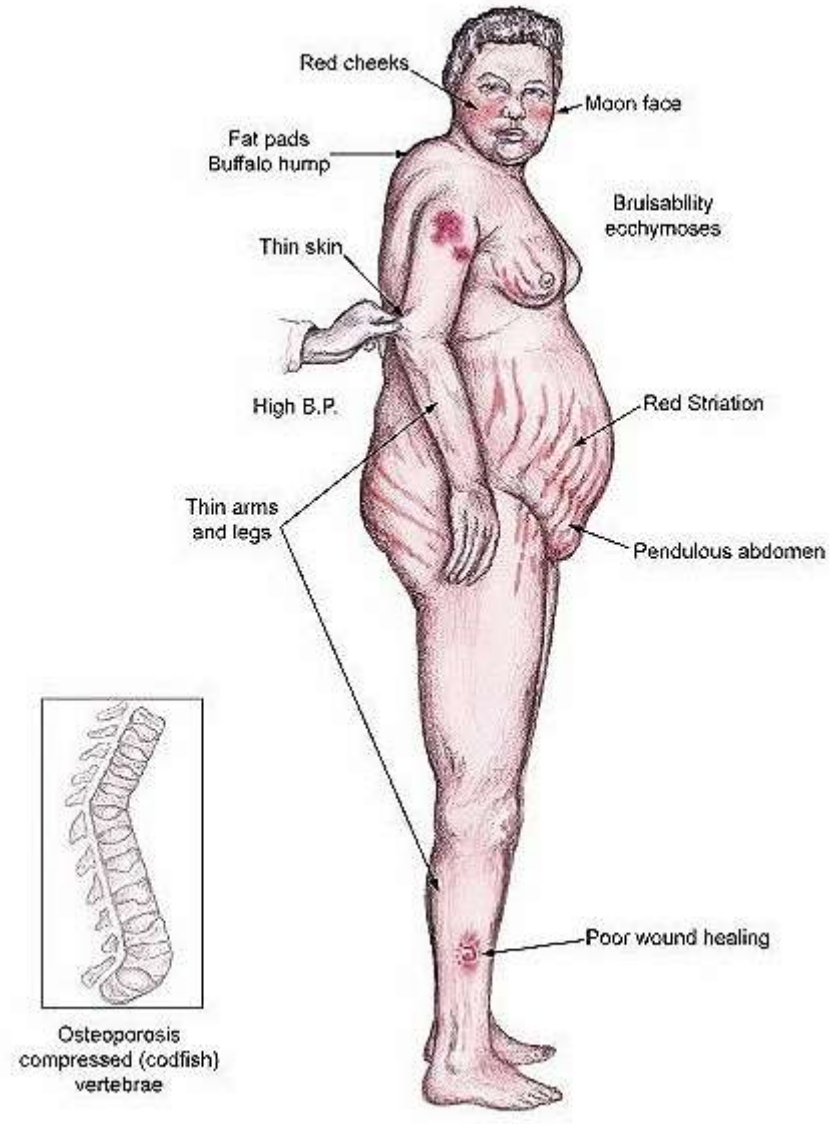


ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

D

Endocrinopathies

Acromegaly
Cushing's syndrome,
Glucagonoma
Pheochromocytoma
Hyperthyroidism,
Somatostatinoma,
aldosteronoma

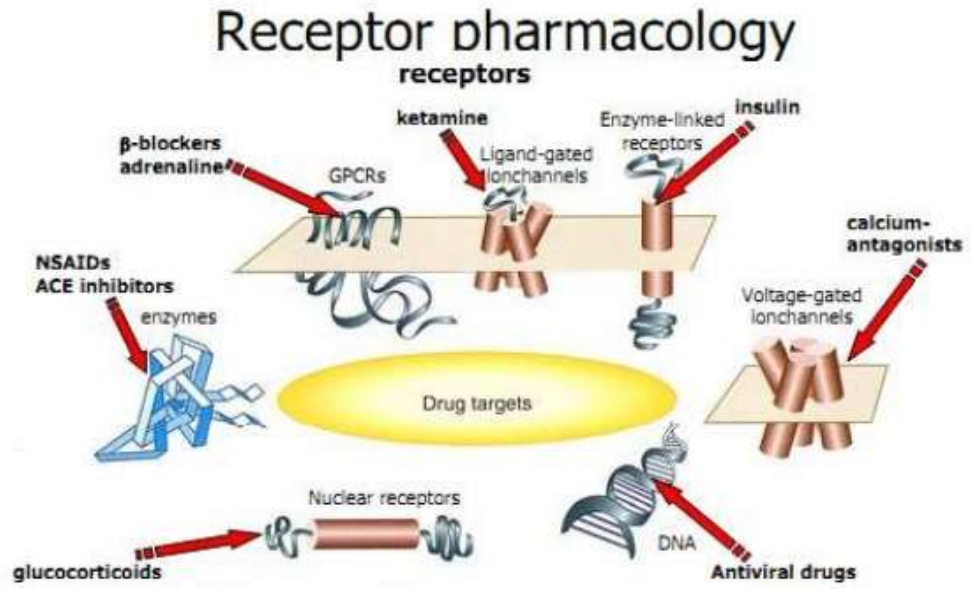


ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

E

Drug or chemical induced

Glucocorticoids
Vacor (a rodenticide),
Pentamidine,
Nicotinic acid,
Diazoxide,
β-adrenergic agonists,
Thiazides
Hydantoins,
Asparaginase
α-interferon
Protease inhibitors,
Antipsychotics (atypicals and others)
Epinephrine

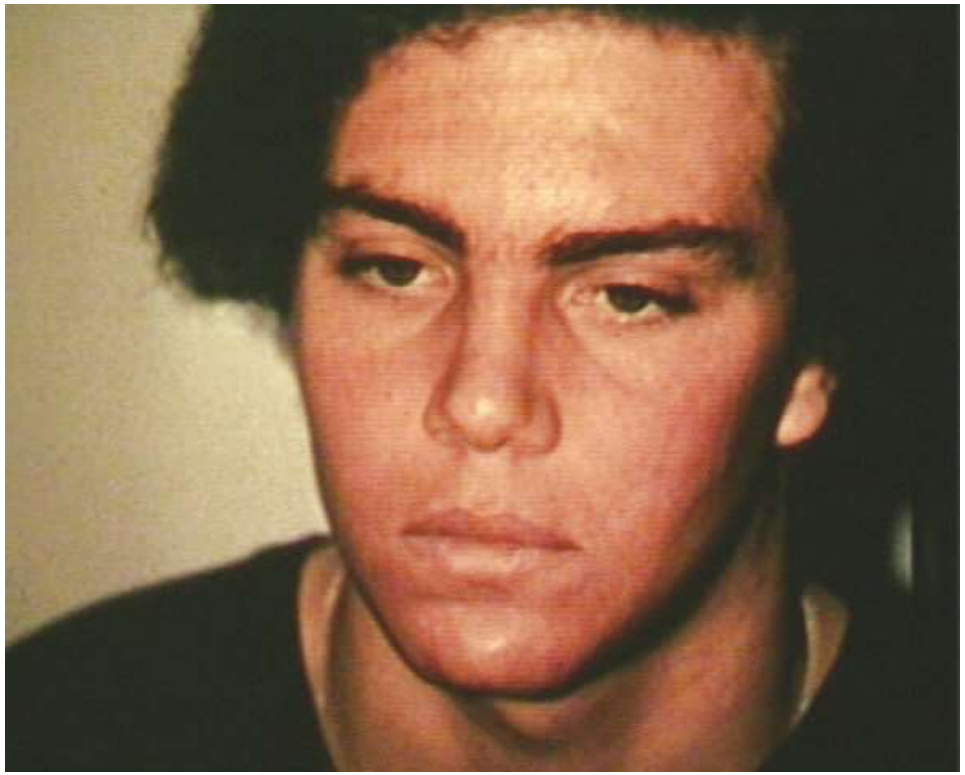


ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

F

Infections

Congenital rubella
Cytomegalovirus
Coxsackievirus

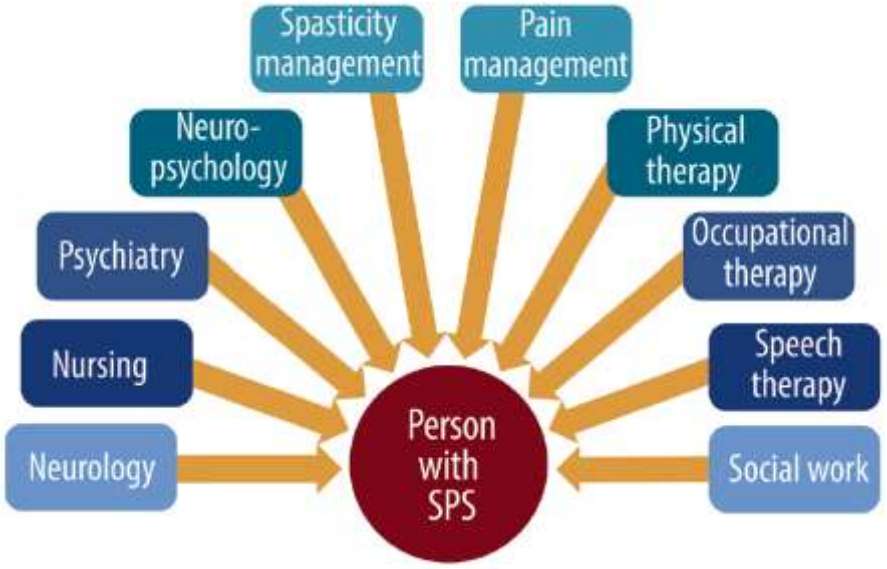


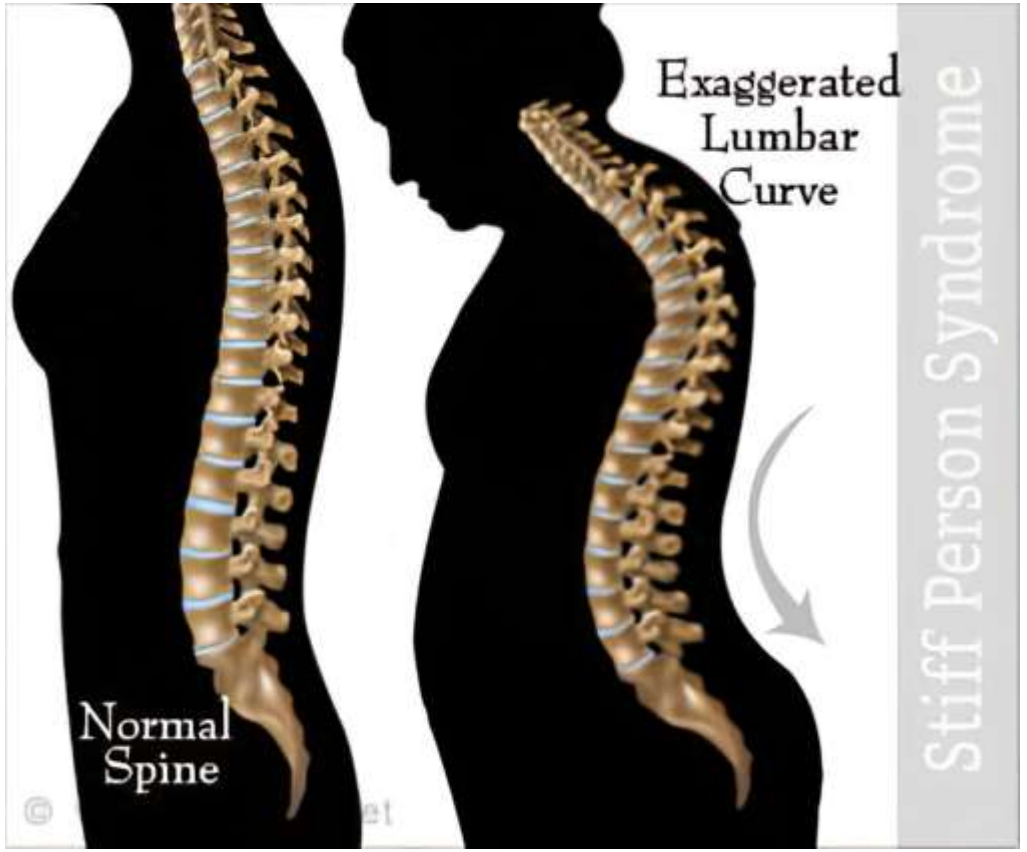
ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

G

Uncommon forms of immune-mediated diabetes

"stiff-person" syndrome
anti-insulin receptor antibodies



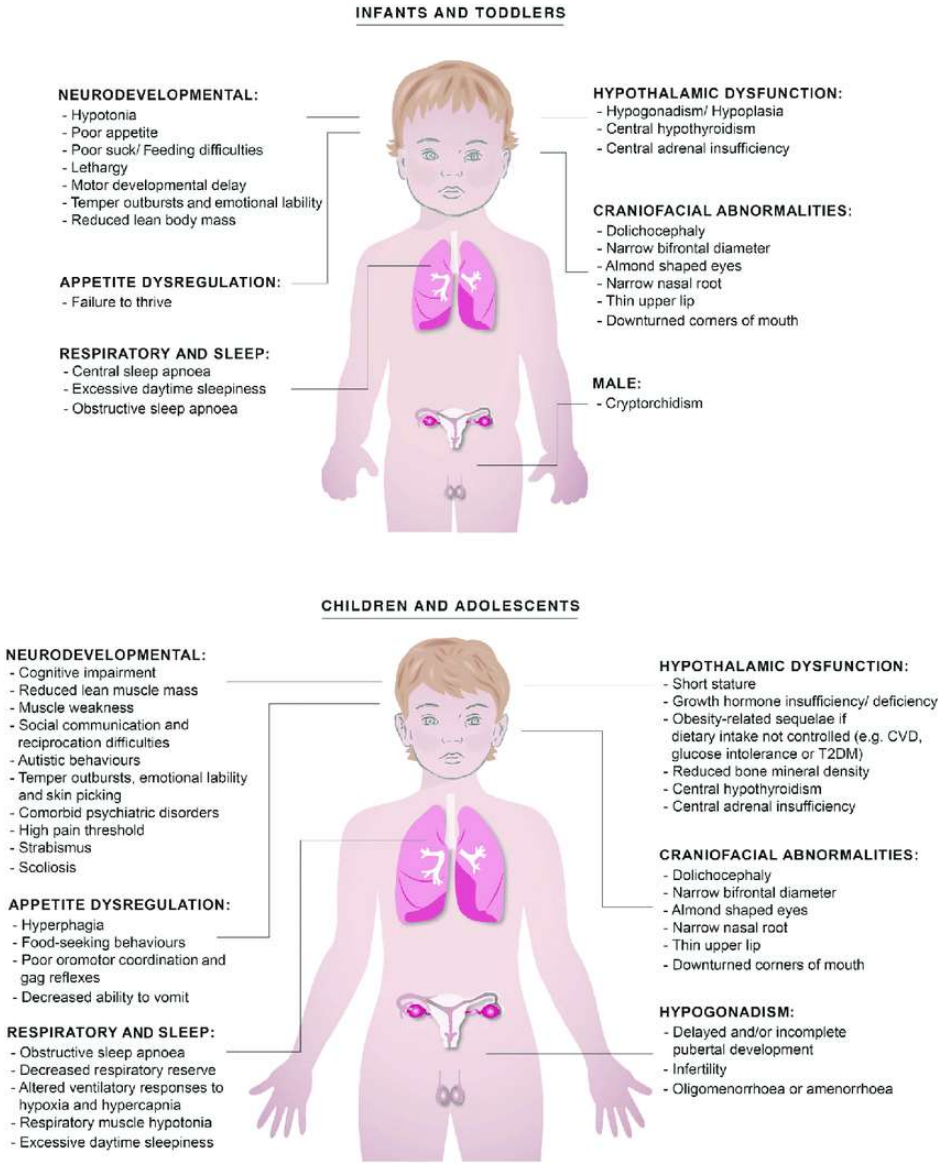


ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

E

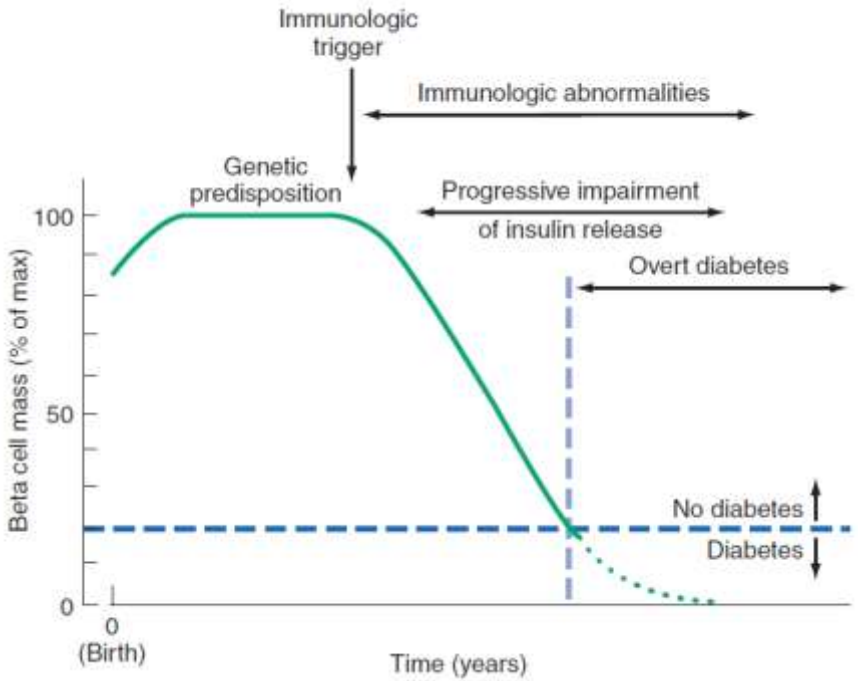
Other genetic syndromes sometimes associated with diabetes

Wolfram's syndrome
Down's syndrome,
Klinefelter's syndrome,
Turner's syndrome,
Friedreich's ataxia,
Huntington's chorea,
Laurence-Moon-Biedl syndrome
Myotonic dystrophy
Porphyria
Prader-Willi syndrome

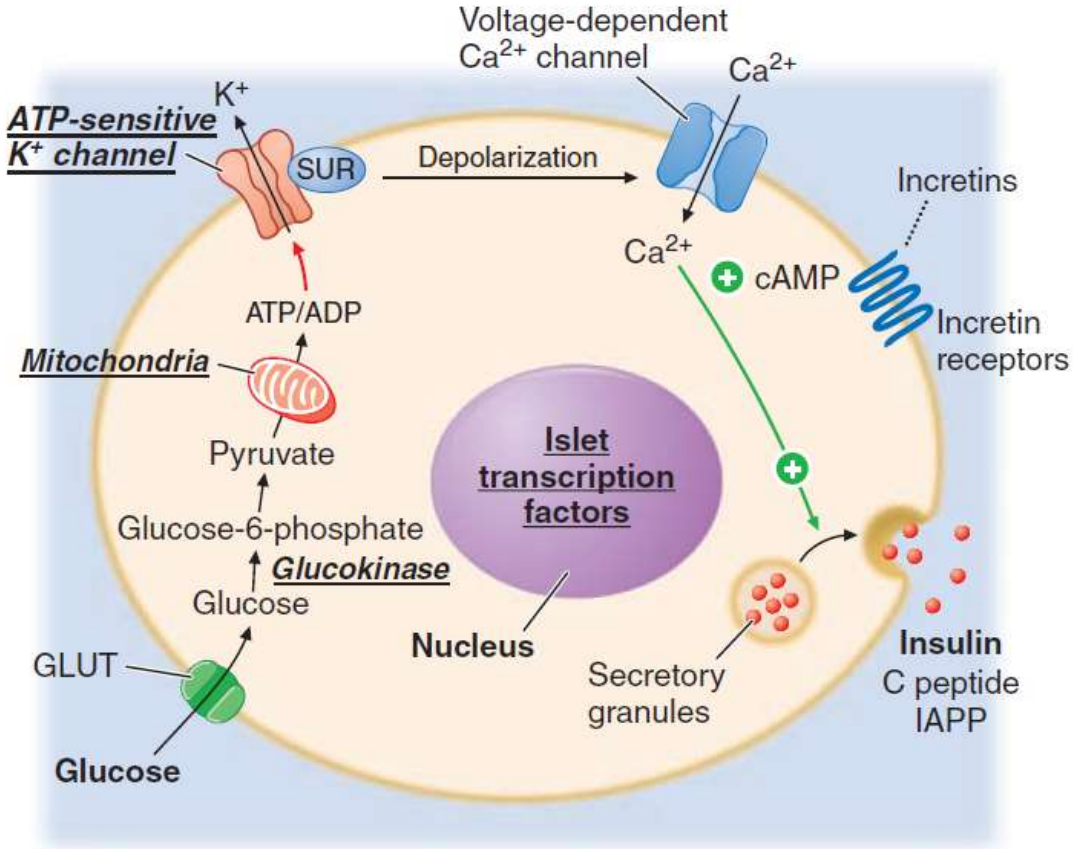


Glucose homeostasis diabetes and development of type1 Diabetes

Type of Diabetes	Normal glucose tolerance	Hyperglycemia		
		Pre-diabetes[a]	Diabetes Mellitus	
		Impaired fasting glucose or impaired glucose tolerance	Not insulin requiring	Insulin required for control / Insulin required for survival
Type 1				
Type 2				
Other specific types				
Gestational Diabetes				
Time (years)				
FPG	<5.6 mmol/L (100 mg/dL)	5.6–6.9 mmol/L (100–125 mg/dL)	≥7.0 mmol/L (126 mg/dL)	
2-h PG	<7.8 mmol/L (140 mg/dL)	7.8–11.0 mmol/L (140–199 mg/dL)	≥11.1 mmol/L (200 mg/dL)	
A1C	<5.6%	5.7–6.4%	≥6.5%	

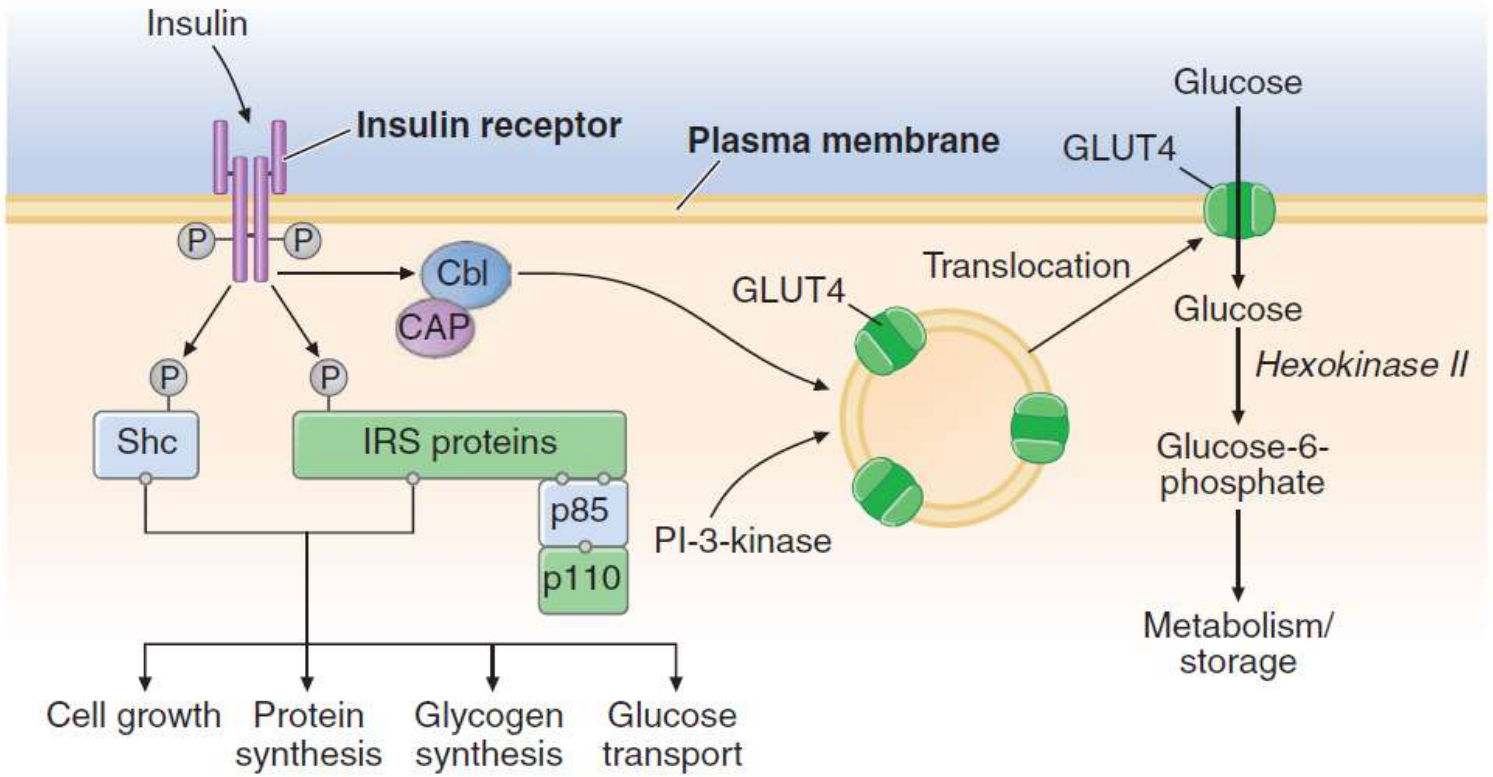


The spectrum from normal glucose tolerance to diabetes in type 1 DM, type 2 DM, other specific types of diabetes, and gestational DM is shown from left to right. In most types of DM, the individual traverses from normal glucose tolerance to impaired glucose tolerance to overt diabetes (these should be viewed not as abrupt categories but as a spectrum). Arrows indicate that changes in glucose tolerance may be bidirectional in some types of diabetes. For example, individuals with type 2 DM may return to the impaired glucose tolerance category with weight loss; in gestational DM, diabetes may revert to impaired glucose tolerance or even normal glucose tolerance after delivery. The fasting plasma glucose (FPG), the 2-h plasma glucose (PG) after a glucose challenge, and the A1C for the different categories of glucose tolerance are shown at the lower part of the figure. These values do not apply to the diagnosis of gestational DM. The World Health Organization uses an FPG of 110–125 mg/dL for the prediabetes category. Some types of DM may or may not require insulin for survival. *a* Some use the term "increased risk for diabetes" (ADA) or "intermediate hyperglycemia" (WHO) rather than "prediabetes." (*Adapted from the American Diabetes Association: Diabetes Care 30:S4, 2007*



Mechanisms of glucose-stimulated insulin secretion and abnormalities in diabetes.

Glucose and other nutrients regulate insulin secretion by the pancreatic beta cell. Glucose is transported by a glucose transporter (GLUT1 in humans, GLUT2 in rodents); subsequent glucose metabolism by the beta cell alters ion channel activity, leading to insulin secretion. The SUR receptor is the binding site for some drugs that act as insulin secretagogues. Mutations in the events or proteins underlined are a cause of maturity-onset diabetes of the young (MODY) or other forms of diabetes. ADP, adenosine diphosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; IAPP, islet amyloid polypeptide or amylin; SUR, sulfonylurea receptor.



Insulin signal transduction pathway in skeletal muscle.

The insulin receptor has intrinsic tyrosine kinase activity and interacts with insulin receptor substrates (IRS and Shc) proteins. A number of “docking” proteins bind to these cellular proteins and initiate the metabolic actions of insulin [GrB-2, SOS, SHP-2, p110, and hosphatidylinositol-3’-kinase (PI-3-kinase)]. Insulin increases glucose transport through PI-3-kinase and the Cbl pathway, which promotes the translocation of intracellular vesicles containing GLUT4 glucose transporter to the plasma membrane.

CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS

- Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL)[a] *or*
- Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)[b] *or*
- A1C >6.5%[c] *or*
- Two-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[d]

[a]Random is defined as without regard to time since the last meal.
[b]Fasting is defined as no caloric intake for at least 8 h.
[c]The test should be performed in a laboratory certified according to A1C standards of the Diabetes Control and Complications Trial.
[d]The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, not recommended for routine clinical use.
Note: In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.
Source: American Diabetes Association: Diabetes Care 34:S11, 2011.

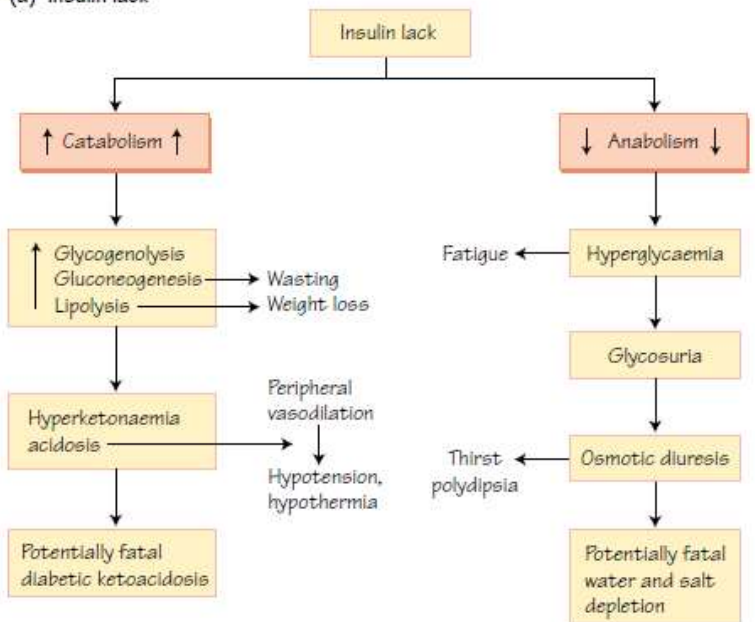
RISK FACTORS FOR TYPE 2 DIABETES MELLITUS

Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
Obesity (BMI ≥25 kg/m^2)
Physical inactivity
Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
Previously identified with IFG, IGT, or an A1C of 5.7–6.4%
History of GDM or delivery of baby >4 kg (9 lb)
Hypertension (blood pressure ≥140/90 mmHg)
HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
Polycystic ovary syndrome or acanthosis nigricans
History of cardiovascular disease

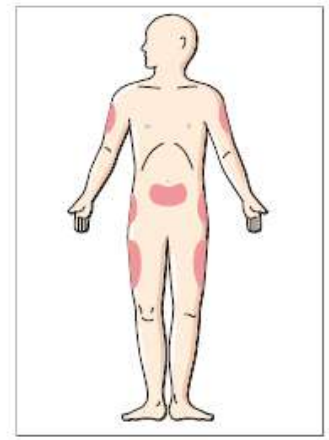
Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
Source: Adapted from American Diabetes Association: Diabetes Care 34:S11, 2011.

Type 1 diabetes

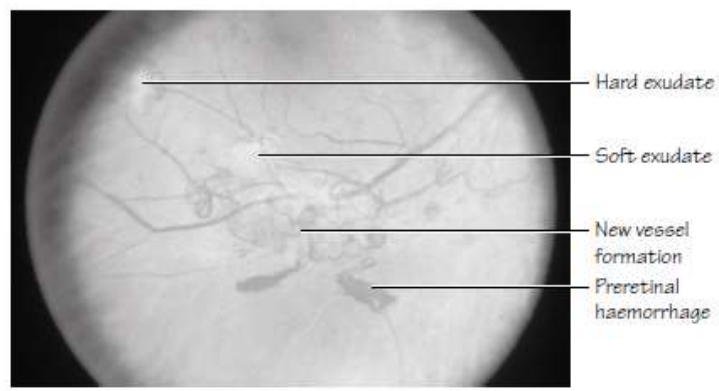
(a) Insulin lack



(b) Recommended sites for insulin injection

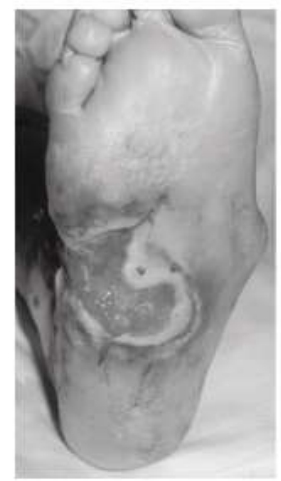


(c) Proliferative diabetic retinopathy

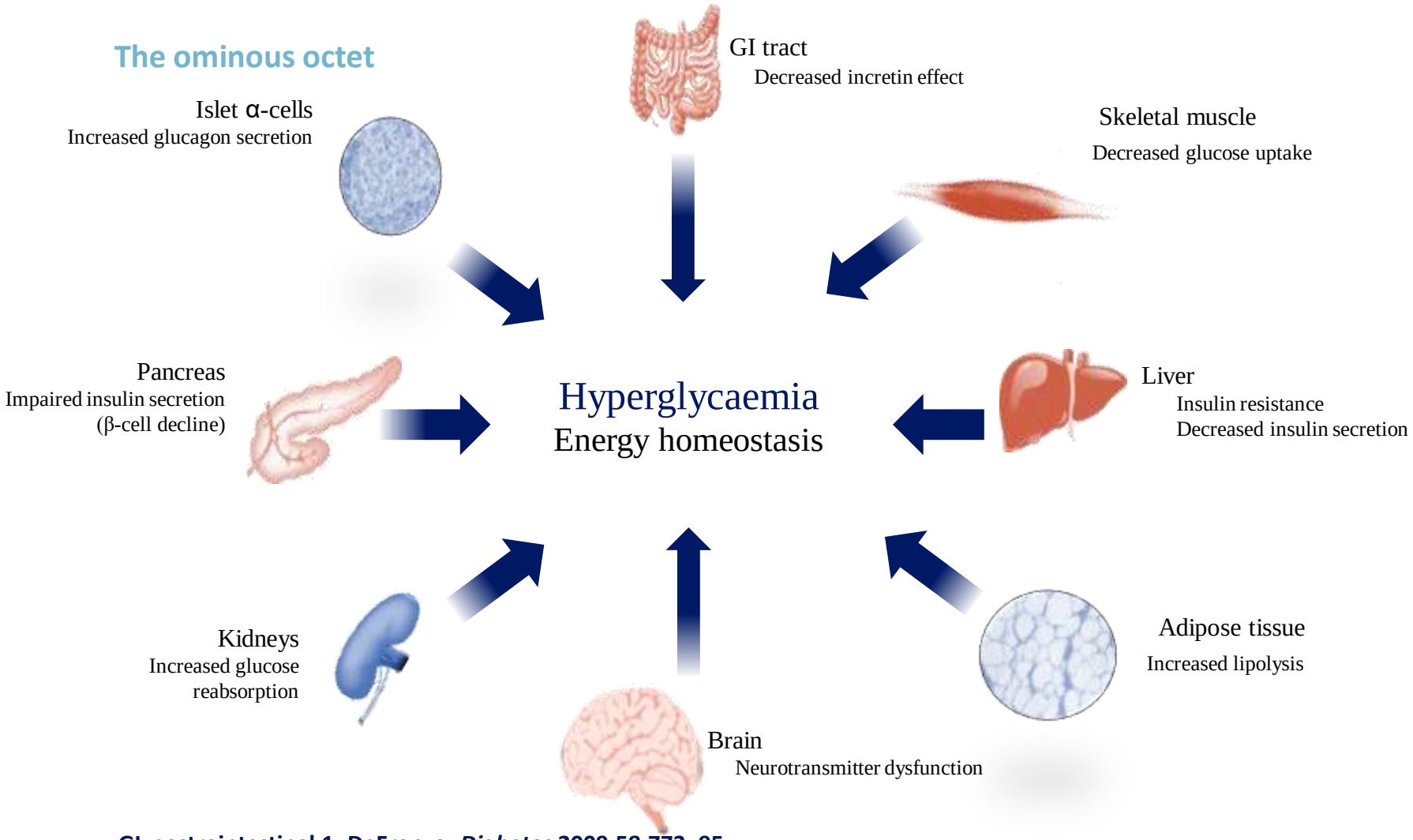


(d) Charcot's arthropathy

Charcot's arthropathy is a more unusual manifestation of diabetic neuropathy in which the joints of the foot become completely disorganized and collapse of the arches of the foot further predisposes to ulceration



Pathogenesis of type 2 diabetes and obesity



GI, gastrointestinal 1. DeFronzo. *Diabetes* 2009;58:773–95

Hormonal Responses to Exercise (non-diabetic)

Insulin Secretion

↓↓

Counterregulatory Hormone Secretion

↑

(Epi/Nepi • Glucagon • GH, Cortisol)

<u>Substrate Breakdown</u>

• Glycogenolysis

• Lipolysis

• A.A. Utilization

BG Holds *Steady* Despite

↑ Glucose Utilization by Muscle

Hormonal Responses to Exercise

Insulin Levels
⇗ or ⇔

Counterregulatory Hormone Action Suppressed

Substrate Breakdown Blocked
Glucose Uptake Accelerated

Hypoglycemia May Result

Insulin Adjustment Based on Timing and Duration

	Activity Within 2 Hours After Meal	Activity Before or Between Meals
Short Duration (<90 Minutes)	↓ Mealtime Bolus	Snack Prior to Activity

Diabetes Care, vol. 24, no. 4, 4/2001, 625-630.

Insulin Adjustment Based on Timing and Duration

	Activity Within 2 Hrs After Meal	Activity Before or Between Meals
Long Duration (>90 Minutes)	↓ Mealtime Bolus ↓ Basal Rate Snack at regular intervals Watch for delayed-onset hypoglycemia	Snack Prior to Activity ↓ Basal Rate (if using pump) Snack at regular intervals Watch for delayed-onset hypoglycemia

Insulin Adjustments

Meal Bolus Adjustment

(for post-meal activity)

▶ Low Intensity Cardio	↓ 25%
▶ Mod. Intensity Cardio	↓ 33%
▶ High Intensity Cardio	↓ 50%
▶ Competitive/Anaerobic	

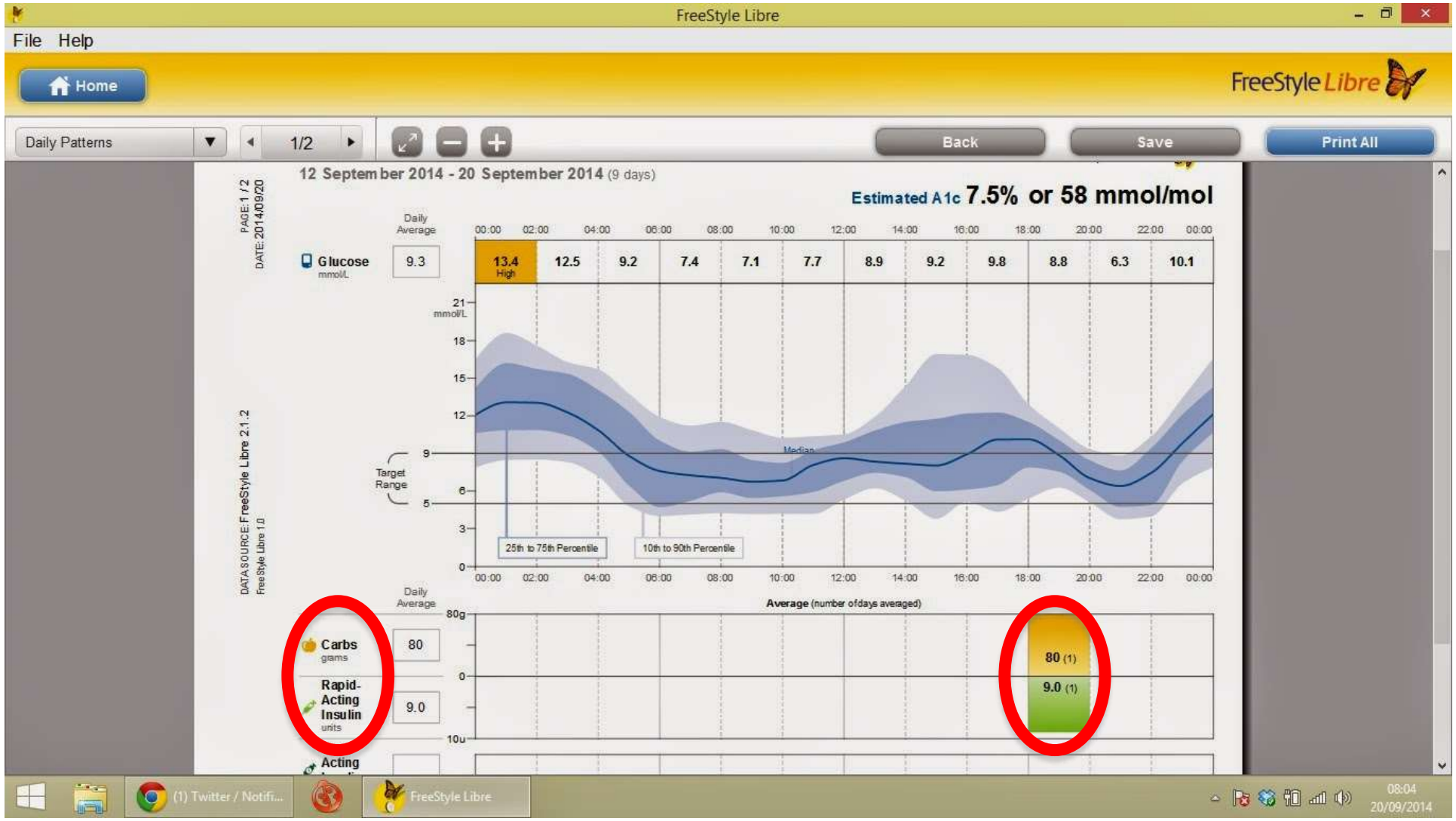
Diabetes Care, vol. 24, no. 4, 4/2001, 625-630.


6.2


109
mg/dL
Sensor
Smart Transmitter
Mobile App


iHealth
Manage
Logbook
Statistics
Trends


110
Lisa
10:09
110
mg/dL


FreeStyle Libre
File Help
Home
FreeStyle Libre
Daily Patterns
1/2
Back
Save
Print All
12 September 2014 - 20 September 2014 (9 days)
Estimated A1c 7.5% or 58 mmol/mol
PAGE: 1 / 2
DATE: 2014/09/20
DATA SOURCE: FreeStyle Libre 2.1.2
FreeStyle Libre 1.0
Daily Average
Glucose
mmol/L
9.3
13.4
High
12.5
9.2
7.4
7.1
7.7
8.9
9.2
9.8
8.8
6.3
10.1
21
mmol/L
18
15
12
9
6
5
3
0
Target Range
Median
25th to 75th Percentile
10th to 90th Percentile
00:00 02:00 04:00 06:00 08:00 10:00 12:00 14:00 16:00 18:00 20:00 22:00 00:00
Daily Average
Average (number of days averaged)
Carbs
grams
80
Rapid-Acting Insulin
units
9.0
80g
0
10u
80 (1)
9.0 (1)
Acting
(1) Twitter / Notifi...
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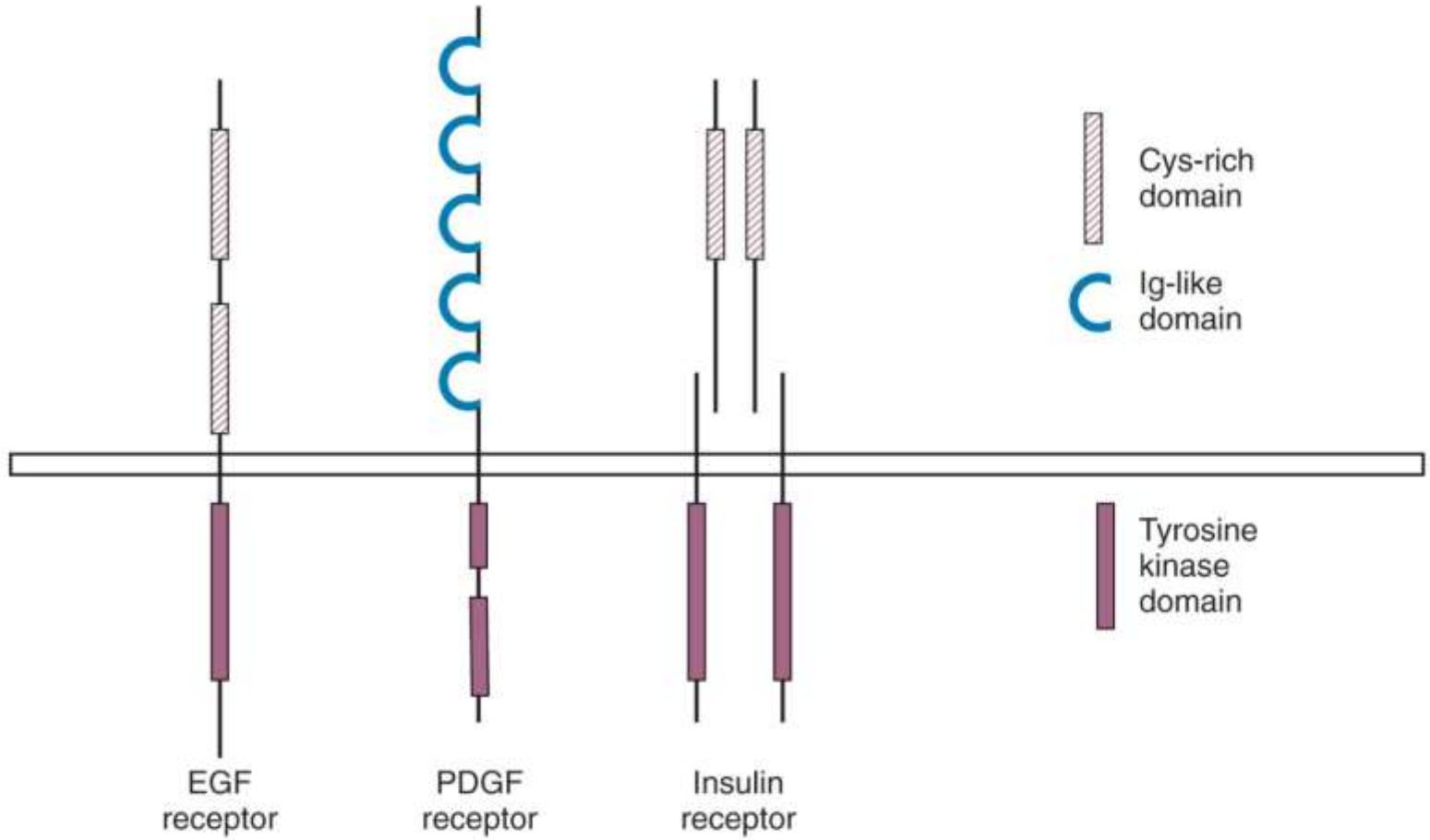
20/09/2014

Regulation of insulin release. Glucose is the principal stimulus for insulin release from the pancreatic β-cell. Glucose enters the β-cell by a specifi c glucose transporter protein (GLUT 2) undergoes glycolysis leading to generation of ATP. The increased ATP/ADP ratio leads to inhibition and closure of the ATP-sensitive K + channels (the target of sulfonylurea drugs), resulting in plasma membrane depolarization and opening of the voltage-dependent Ca 2+ channels. The increased Ca 2+ infl ux coupled with mobilization of Ca 2+ from intracellular stores leading to the fusion of insulincontaining secretory granules with the plasma membrane and the release of insulin (and C-peptide) into the circulation. Addition factors can also stimulate insulin release from the β -cell, including hormones (glucagon-like peptide 1) and neurotransmitters (acetylcholine). Glucose synergizes with these mediators and enhances the secretory response of the β -cell to these factors. AC, adenylate cyclase; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CCK, cholecystokinin; GLP 1, glucagonlike peptide-1; PLC, phospholipase C. (Modifi ed, with permission, from Fajans SS, Bell GI, Polonsky KS. Mechanisms of disease: molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Engl J Med*. 2001;345:971.)


Cys-rich domain
Ig-like domain
Tyrosine kinase domain
EGF receptor
PDGF receptor
Insulin receptor