

Pathophysiology of carbohydrates
metabolism.

D i a b e t e s m e l l i t u s .

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Carbohydrates

= Easy energy

Whatever they say, it's the ... energy!

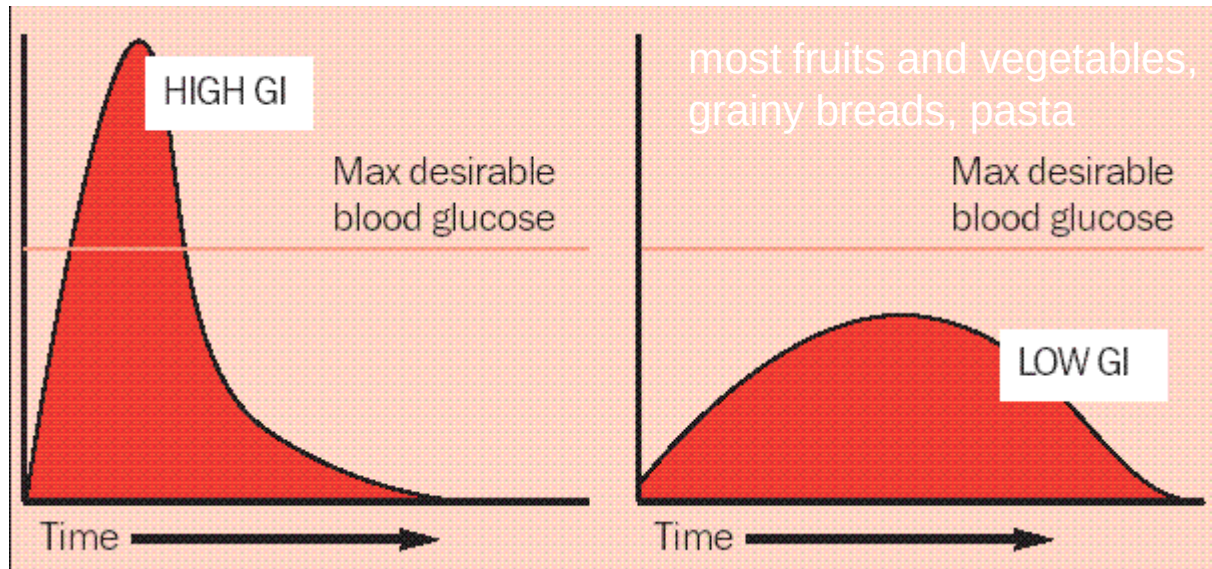


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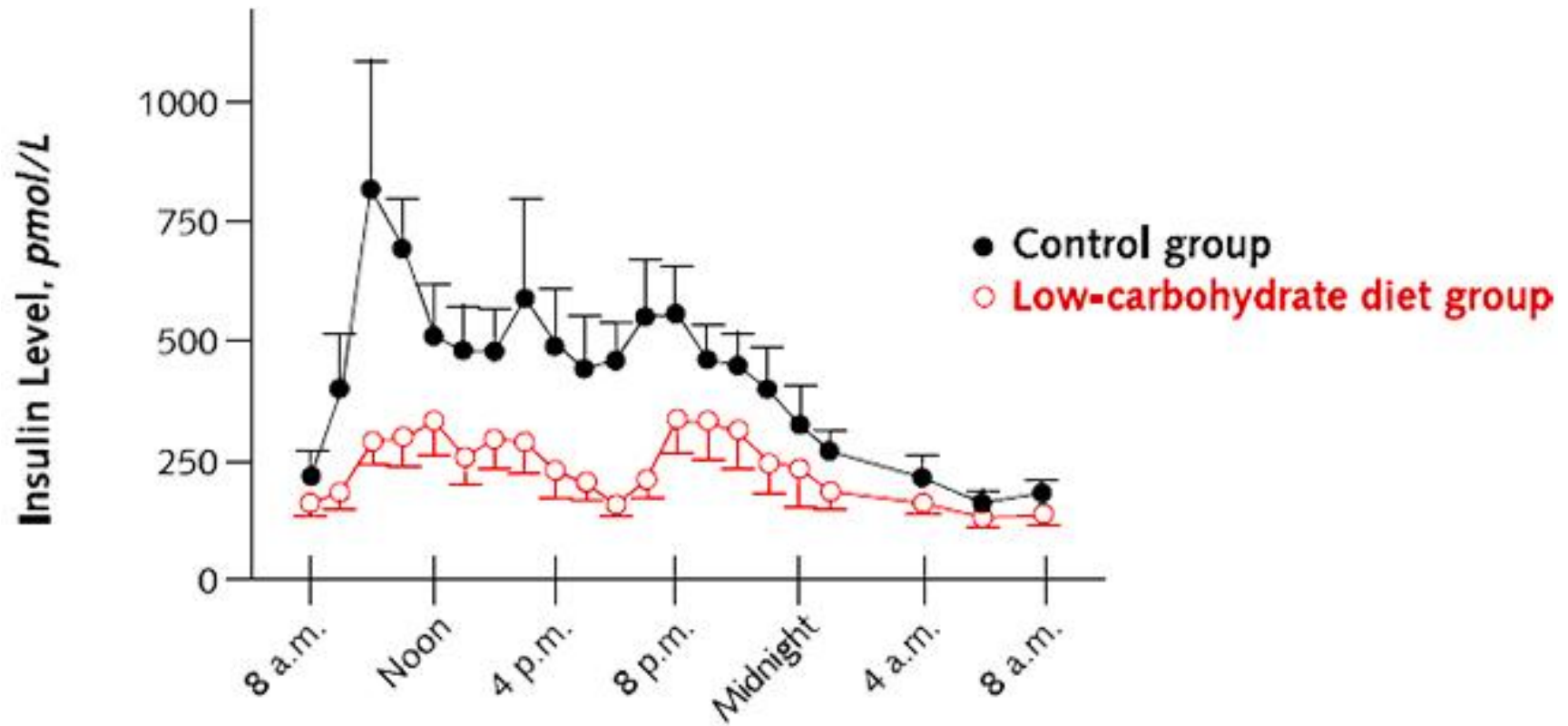


Glycemic index (GI)

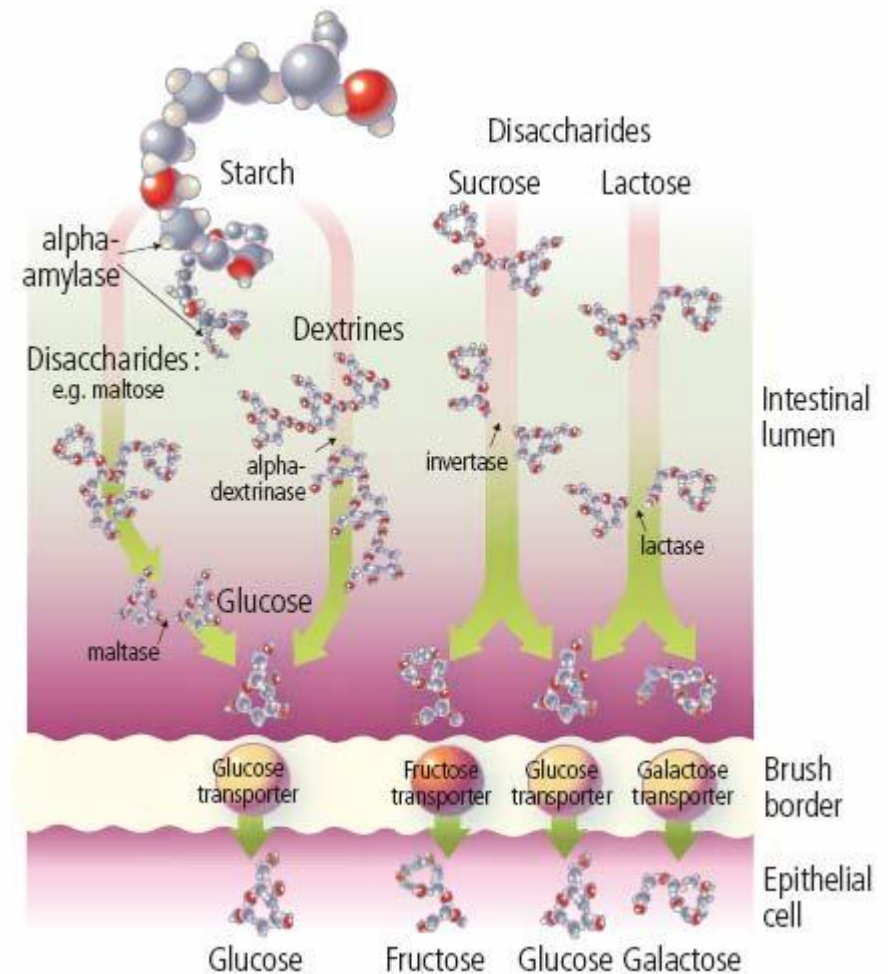
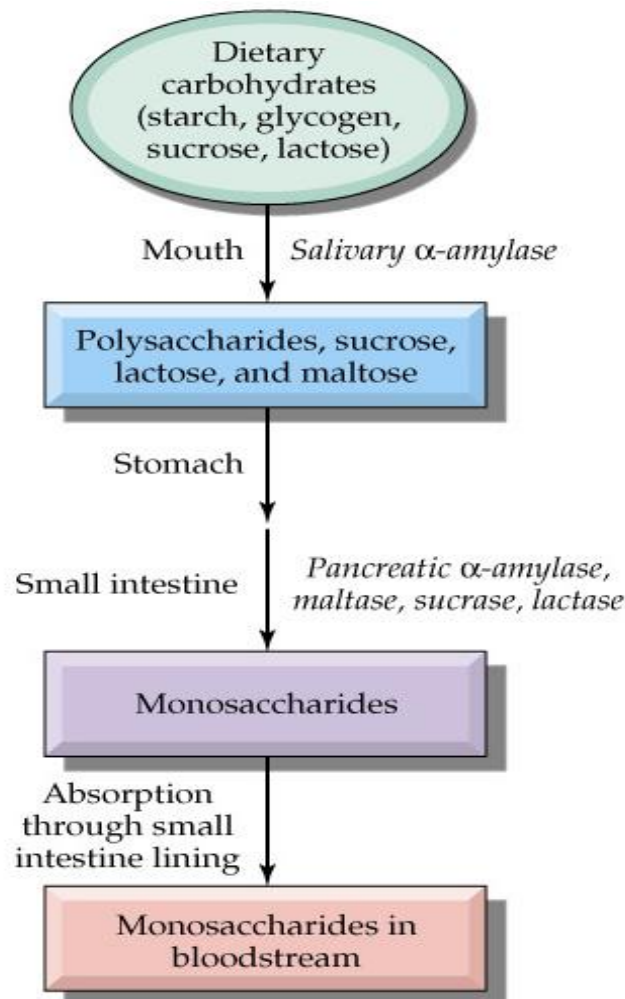
- **GI** is a measure of the effects of carbohydrates on blood sugar levels. Carbohydrates that break down quickly, releasing glucose rapidly, have a high GI; carbohydrates that break down more slowly, releasing glucose more slowly and steadily, have a low GI.
- For most people, *foods with a low GI* have significant health benefits.



Why the Glycemic Index matters



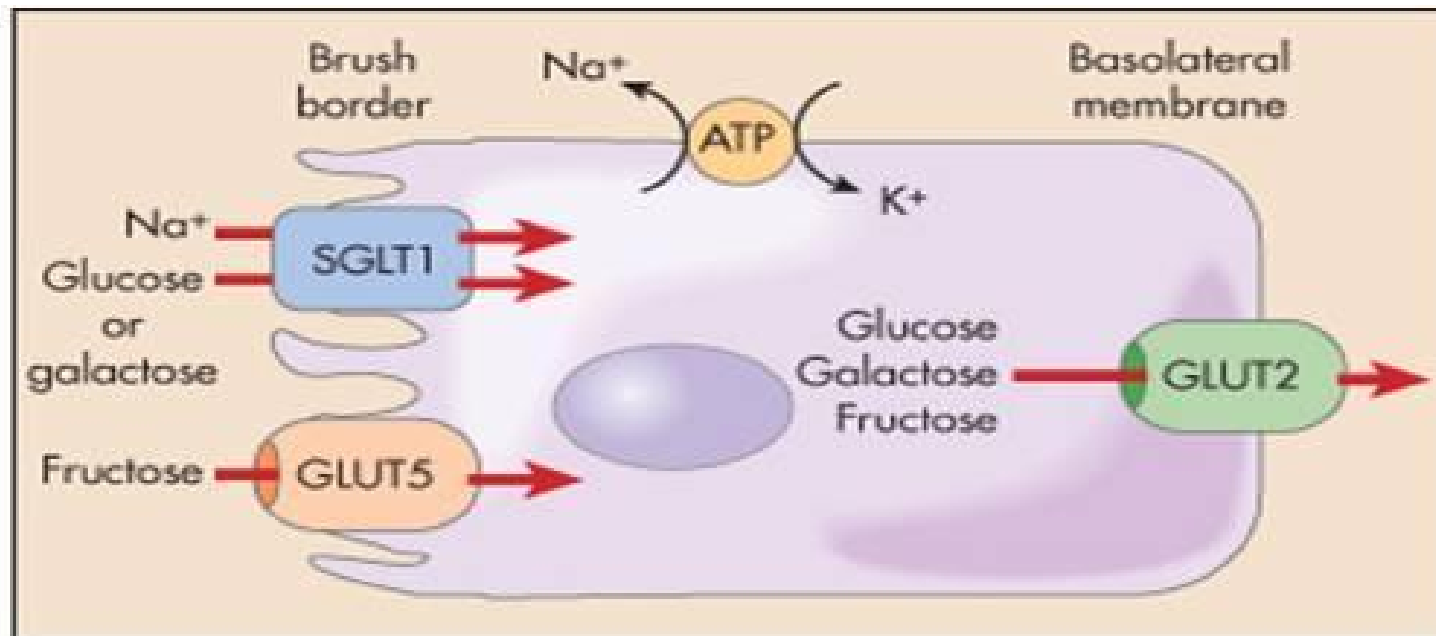
Digestion of carbohydrates



Absorption of monosaccharides



... unless you are Fructose!



What may go wrong?



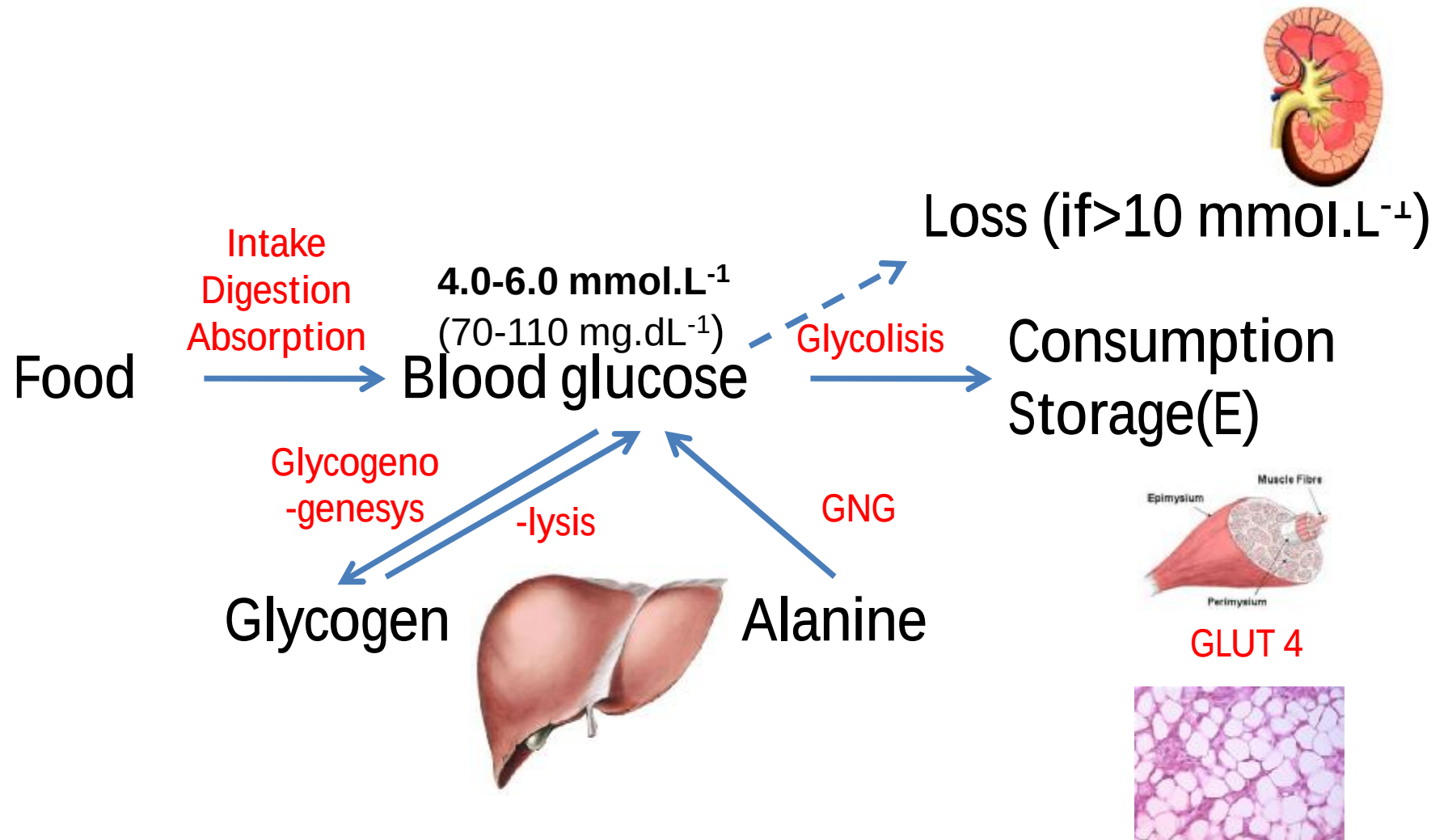
- Reduced salivary α -amylase (hyposalivation)
- Reduced pancreatic enzymes (chronic pancreatitis)
- Accelerated food passage (dumping syndrome)
- Reduced absorption area
- Hyponatremia (Addison disease)
- Disaccharidase insufficiency - acquired or genetic (lactase deficiency – most common).

When it goes wrong?

- n Increased level of osmotic molecules (undigested CH molecules)
- n Attract water and increase intestinal content
- n Bacterial fermentation in colon
- n Diarrhea



The Glucose flow



“I stand alone”

* Insulin

VS

- Glucocorticosteroids
- Adrenocorticotrophic hormone
- Glucagon (fast)
- Catecholamines (fast)
- Thyroid hormones (T_3 and T_4)
- Growth hormone



Peptide hormones – $\uparrow$ glycogenolysis and $\downarrow$ glycogenesis

Steroid hormones - $\downarrow$ glucose utilization and $\uparrow$ insulin resistance (postreceptor)

Glucose metabolism

summary

The liver's uptake and output of glucose and the use of glucose by peripheral tissues depend on the physiologic balance of several hormones that:

- Lower blood glucose level - insulin
- Rise blood glucose level - glucagon, adrenaline, GH, glucocorticoids...

(termed contrainsular hormones)

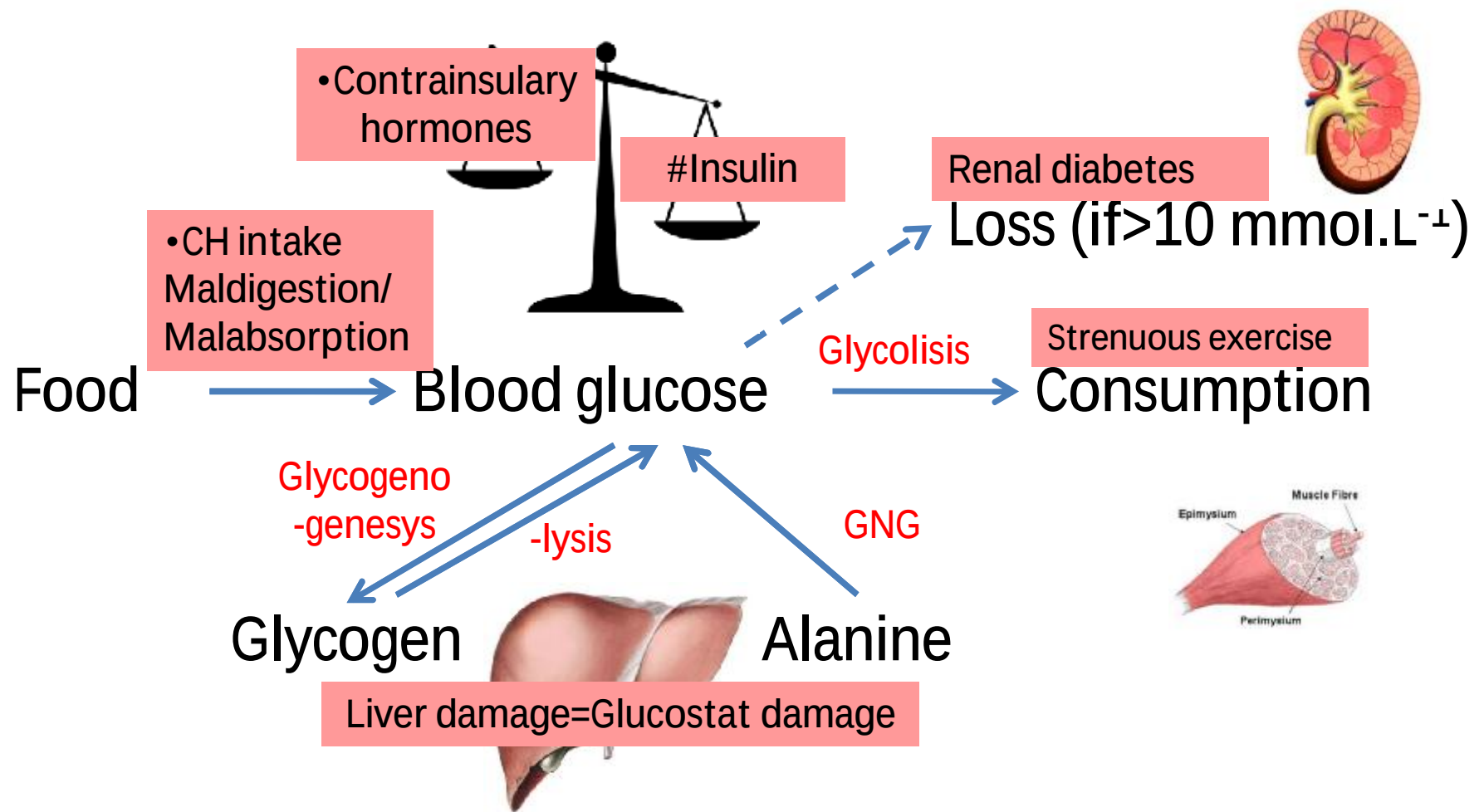
Insulin responsibilities

- Decreases blood glucose
- Enhances cellular import of α -AA, α -KA, electrolytes (K^+)
- Induces the synthesis of anabolic enzymes
- Stimulates growth, cell division, DNA synthesis
- Anticatabolic effect (via gene transcription regulation)

NB! Glycogenosynthesis $\uparrow$, Proteosynthesis $\uparrow$,
Liposynthesis $\uparrow$

Hypoglycemia

Decreased plasma glucose levels



Hypoglycemia

A list

- Physiologic state
- Pathologic condition
 - Decreased carbohydrates (CH) intake
 - Maldigestion/ Malabsorption of CH
 - Altered CH metabolism in the liver (cirrhosis, glycogenoses)
 - C₂H₅OH
 - Reactive hypoglycemia
 - Strenuous exercise
 - Renal diabetes (urinary loss)
 - Defective regulation of glucose level
 - Contrainsular hormones deficiency
 - Increased insulin levels (insulinomes, yatrogenic)

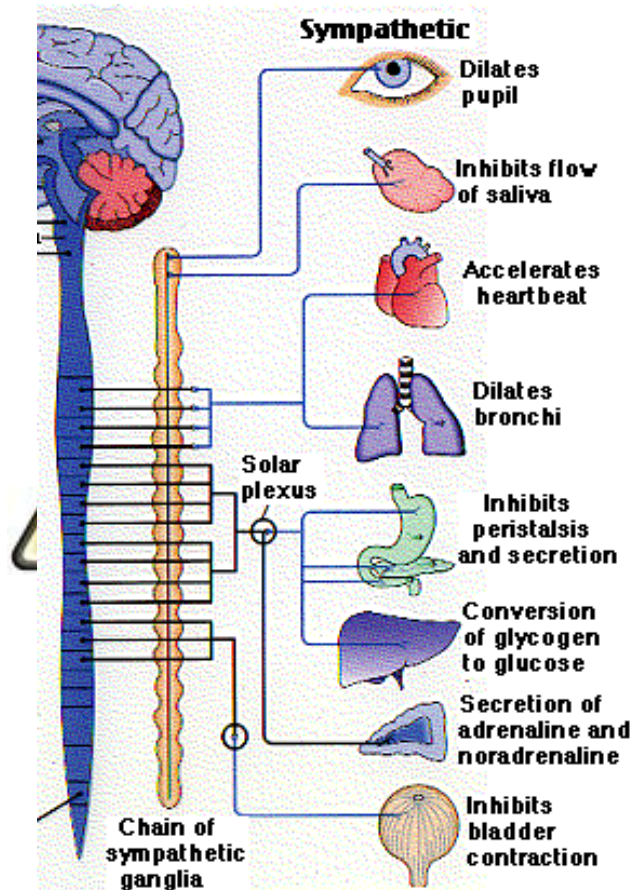
Hypoglycemia symptoms or when **Nothing else matters ...but glucose**

- Life-threatening condition
- Hunger and S-Adr activation

- mydriasis
- pallor
- sweating
- trembling
- tachycardia

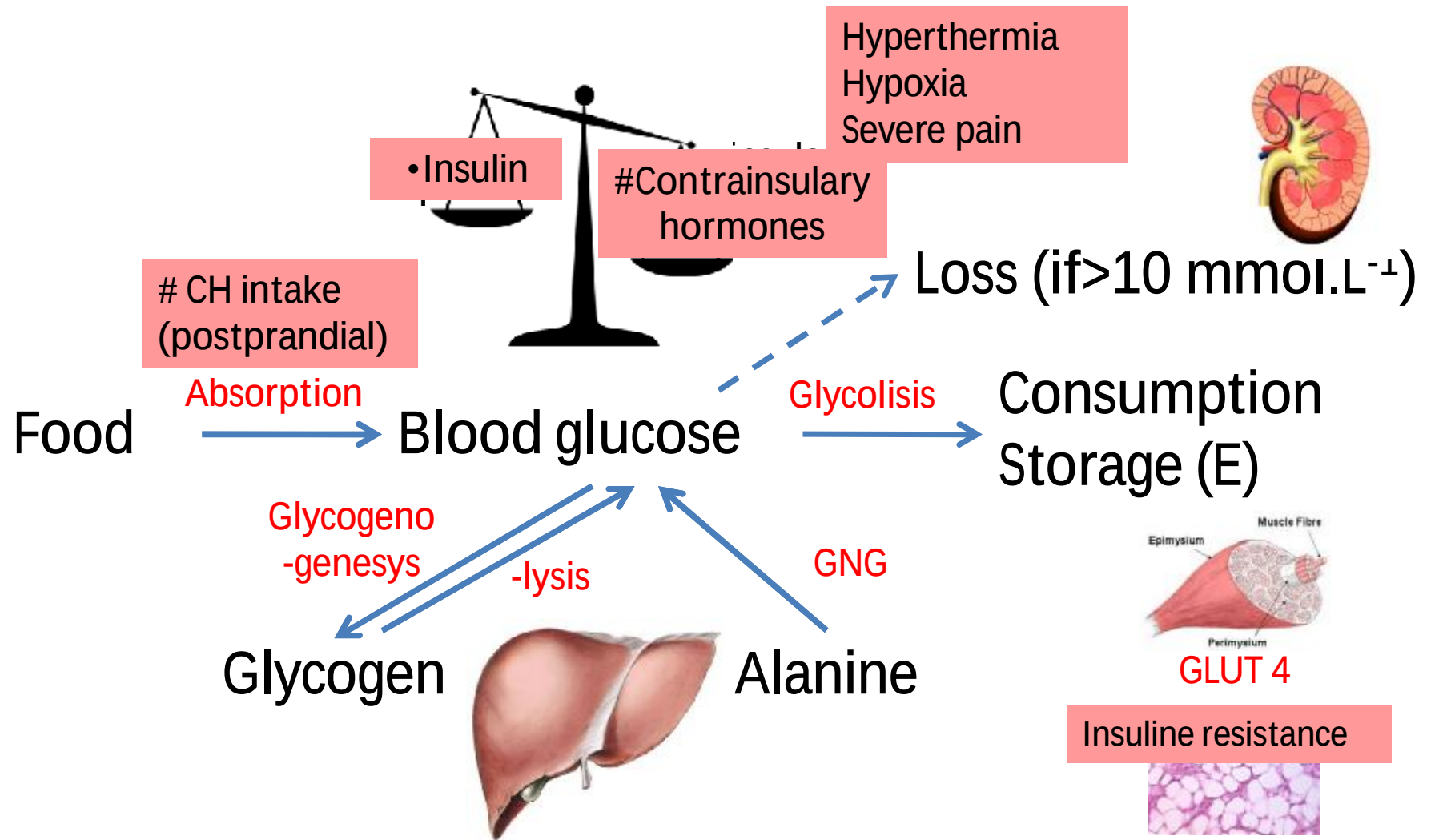
- Brain hypoenergetic shutdown

- drowsiness, mental confusion, seizures and coma



Hyperglycemia

Increased in plasma glucose levels



Hyperglycemia

A list

- Alimentary
- High levels of contrainsular hormones
- Due to insulin deficiency or insulin resistance (Diabetes mellitus)
- Miscellaneous
 - Hyperthermia
 - Hypoxia
 - Severe pain

Diabetes mellitus

Definition

Diabetes mellitus is a heterogeneous primary disorder of carbohydrate metabolism with multiple etiologic factors that **generally involve absolute or relative insulin deficiency** or both and is characterized by **metabolic disorders of carbohydrates, lipids and proteins.**



Diabetes mellitus

New Classification*

- n Type I Diabetes Mellitus (former IDDM)
- n Type II Diabetes Mellitus (former NIDDM)
- n Other specific (former Secondary DM)
 - n Genetic defects (β -cells, insulin)
 - n Destructive diseases of the pancreas
 - n Endocrinopathies
 - n Drug induced (iatrogenic)
- n Gestational diabetes

MODY – maturity onset diabetes of the young

LADA - latent autoimmune diabetes in adults

*American Diabetic Association 2012

Terminology key points

In the new classification:

- Terms IDDM and NIDDM are **not used**
- Terms Primary and Secondary DM are **not used**

New classification also introduces new terms:

- * impaired glucose tolerance (IGT)
- * impaired fasting plasma glucose (IFG)

Impaired fasting glucose (IFG)

Condition in which the fasting blood glucose is elevated above what is considered normal levels (5.4 to 6.9 mmol/L) but is not high enough to be classified as diabetes mellitus. It is considered a pre-diabetic state, associated with insulin resistance.

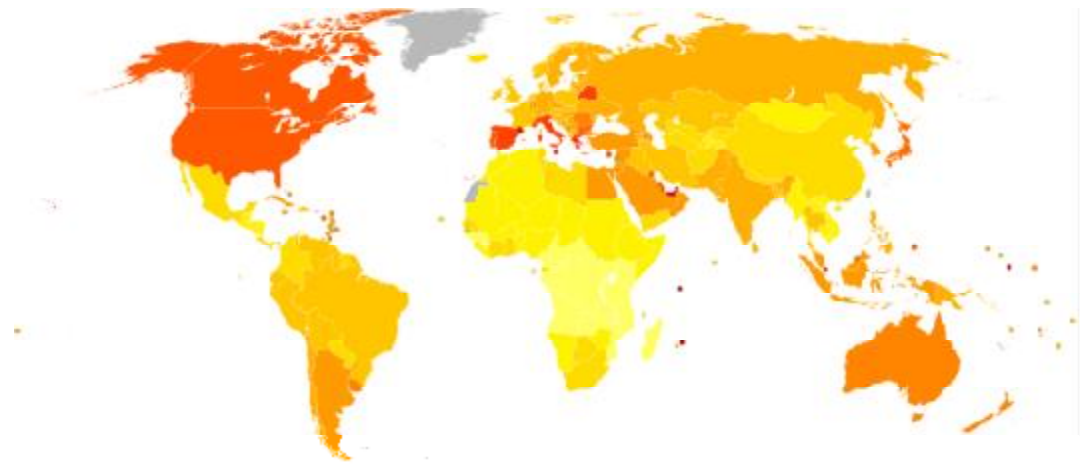
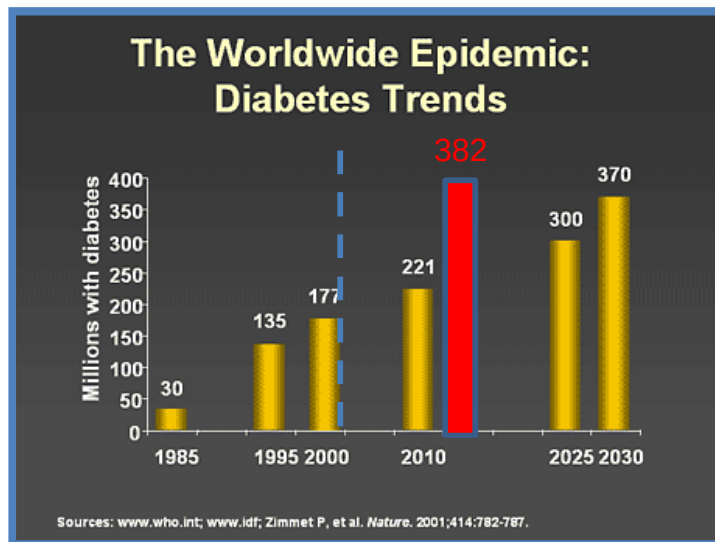
Impaired glucose tolerance (IGT)

Impaired Glucose Tolerance (IGT) is a pre-diabetic state of dysglycemia (6.8 to 11.0 mmol/L), that is associated with insulin resistance and increased risk of cardiovascular pathology.

Diabetes mellitus

Epidemiology and Pessimism

- 382 mln people worldwide (2013) – 8.3% of the population (♂=♀)
- 85-90% cases are Type II
- up to 30% undiagnosed
- 1.5 mln deaths per year (8th in “serial killers” list)

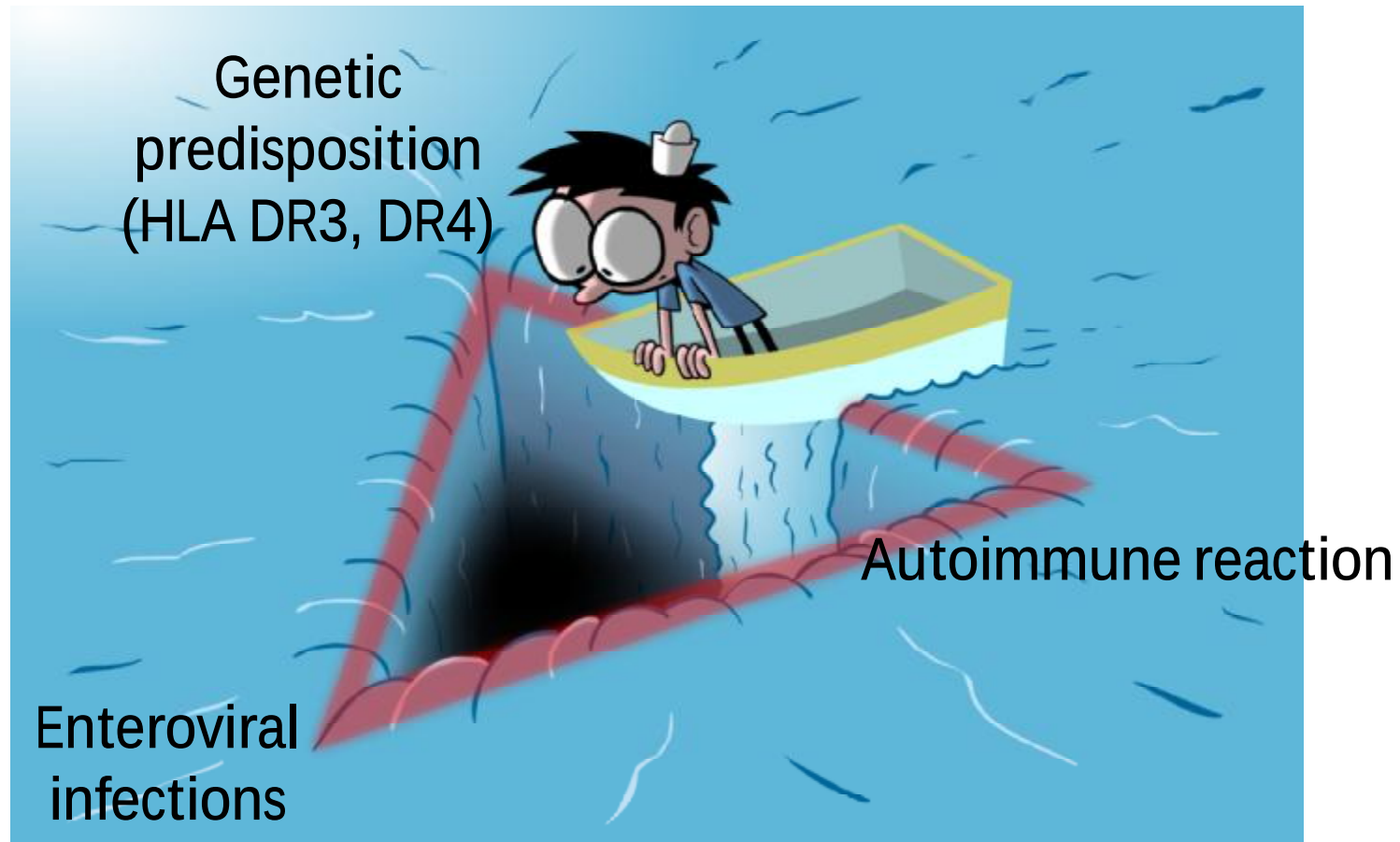




KEEP
CALM
AND
EAT
CHOCOLATE

Diabetes Mellitus Type I

Former Insulin dependent diabetes mellitus (IDDM)



The result of beta cells destruction:

- Absolute insulin deficiency ensues
- Glucagon is present in relative excess
- Individuals are prone to ketoacidosis
- Insulin resistance is rare
- Patients are insulin **dependent**

Signs and symptoms of DM type 1 and their respective pathogenesis

- § Hyperglycemia
- § Glycosuria
- § Polyuria – osmotic diuresis
- § Polydipsia – hyperosmolarity and dehydration
- § Polyphagia – cellular fasting
- § Weight loss – #catabolism, negative E balance
- § Fatigue – metabolic changes
- § Poor wound healing – alterations in local
- § Infections – and general immunity

LADA – characteristics

(Latent autoimmune diabetes in adults)

- § Called Type 1.5 DM or slowly progressing insulin-dependent diabetes
- § T cell mediated autoimmune disease
- § Adult age at diagnosis (range 30-70year)
- § Lean or non-obesity
- § The presence of diabetes-associated autoantibodies (IA2, ICA, GAD)
- § Delay (at least half year) from diagnosis in the need for insulin therapy to manage hyperglycemia
- § Having type 1 DM's predisposing genes (such as HLA-DR3,HLA-DR4, BW54, DQ-131-57-NON-ASP)
- § Often accompanied by thyroid and gastric parietal cells organ specific antibodies

Diabetes Mellitus Type II

(Former Non-insulin dependent diabetes mellitus NIDDM)

- At the beginning-predominance of **insulin resistance and relative deficit of insulin** (normo- or hyper -insulinemia),
- Later on - combination of **impaired insulin secretion and simultaneous insulin resistance** (hypoinsulinemia, insulin resistance)

Diabetes Mellitus Type II

1. Primary disturbance:

§ ↓ biological activity of insulin

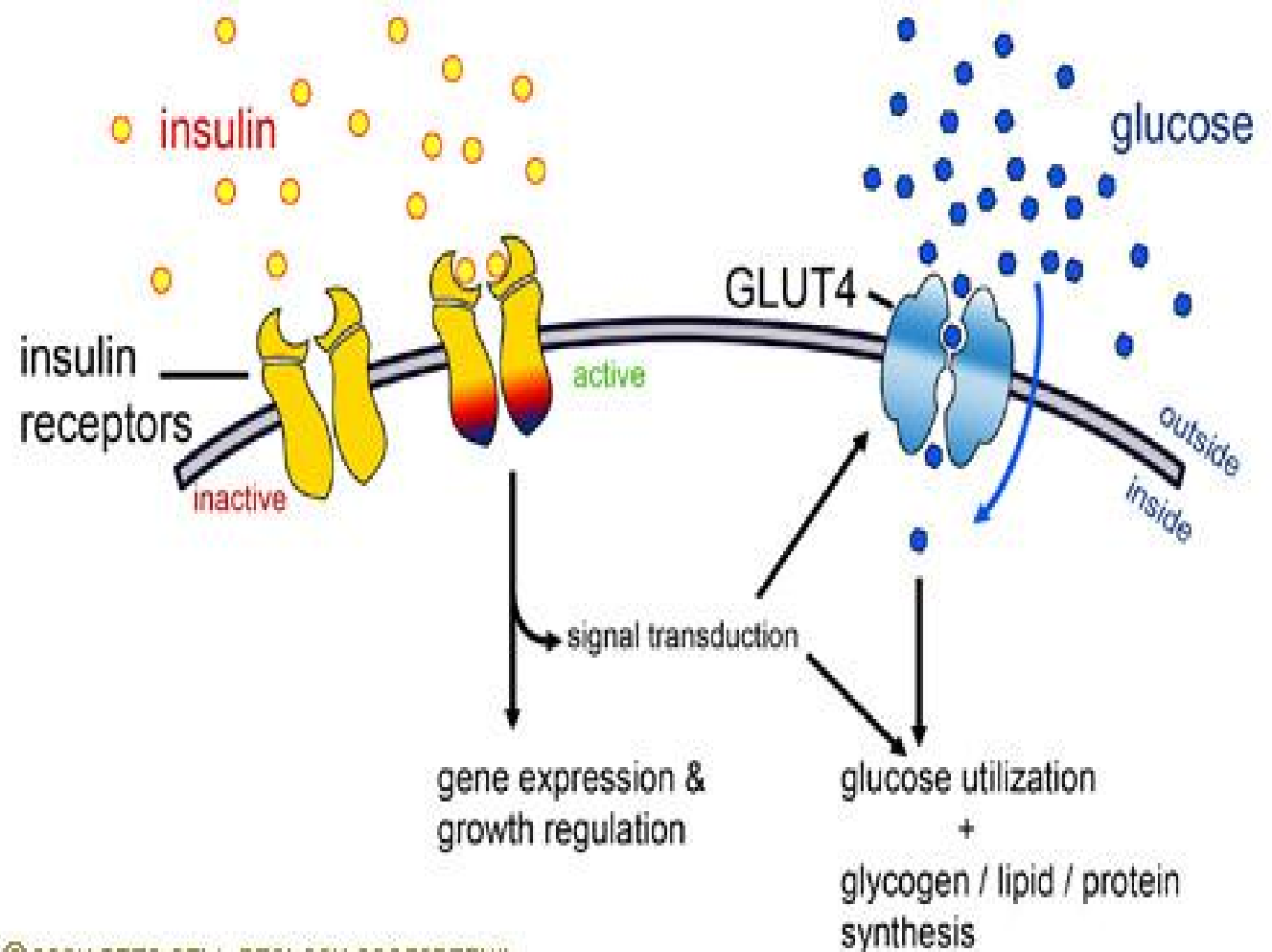
2. Compensatory hyperinsulinemia

§ due to ↑ concentration of blood glucose

3. Insulin resistance:

§ ↓ ability of insulin to inhibit production of glucose in liver → ↑ glucose production

Mechanism of insulin action



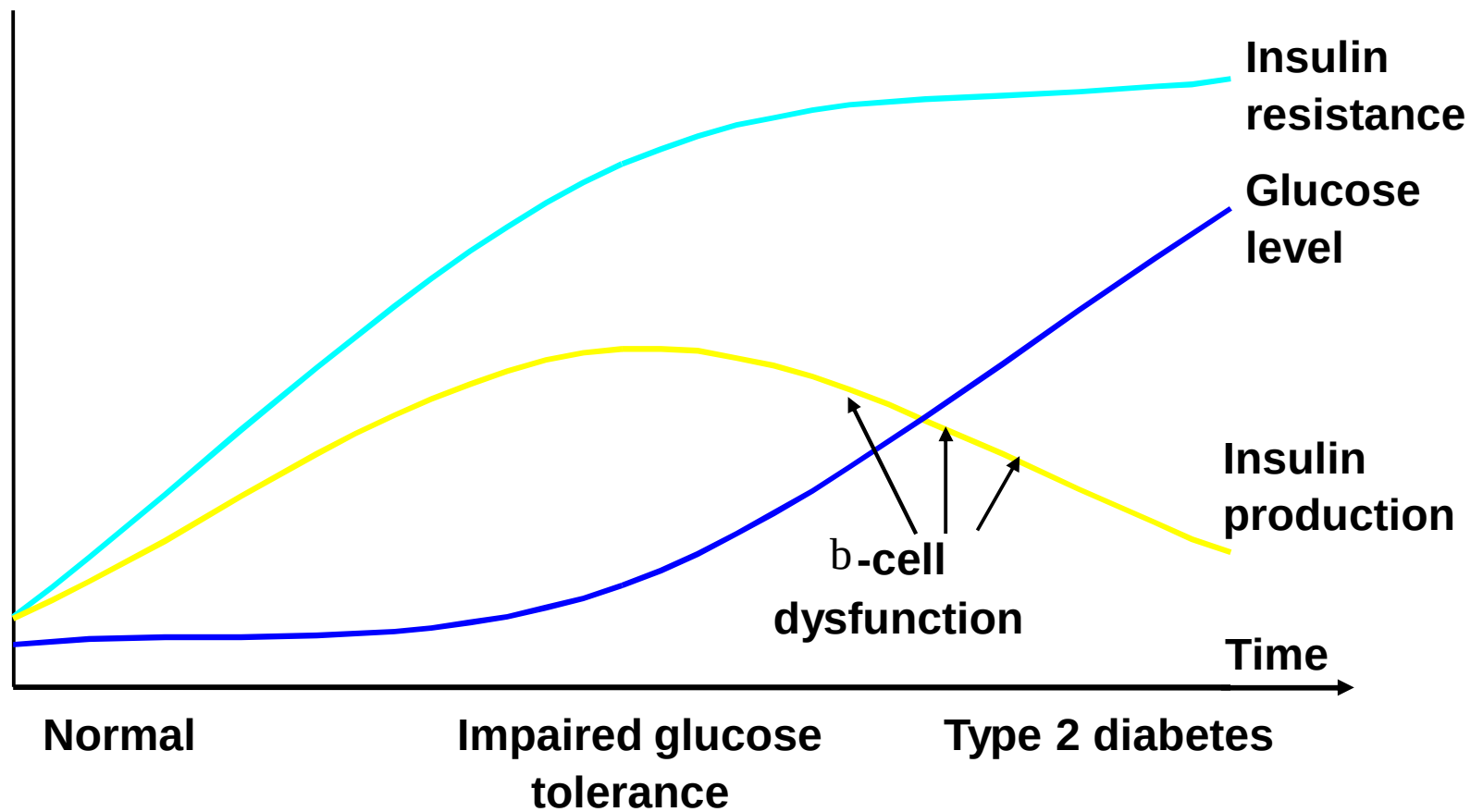


Insulin Resistance (IR)

Causes

1. Autoimmune reactions
 - § development of anti-insulin antibodies
 - § development of anti-insulin receptor antibodies
2. Defects in the insulin receptor at the cell surface
 - a) defect in receptor processing
 - b) decrease in receptor number
3. Defective signal transduction (from the receptor to the plasma of cell)
4. Postreceptor defect
5. Increased concentration of anti-insulinic hormones

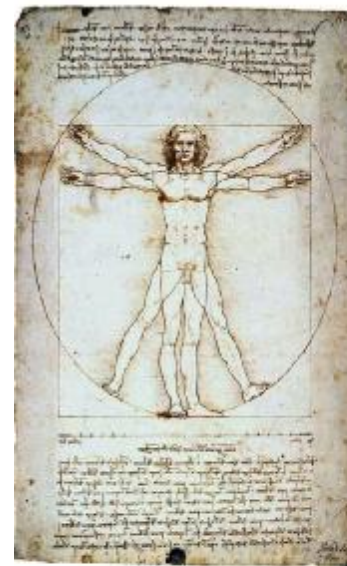
Natural History of Type II Diabetes



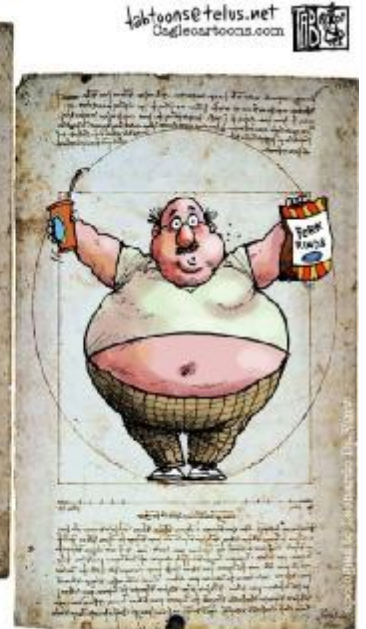
WHEN? ... not “If”

- Genetic predisposition
- Obesity
- Stress
- Insufficient/disturbed sleep
- Chemistry

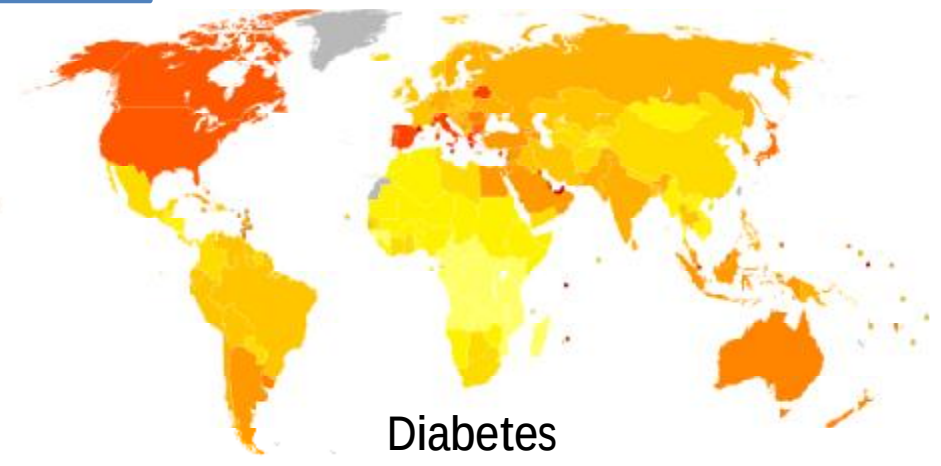
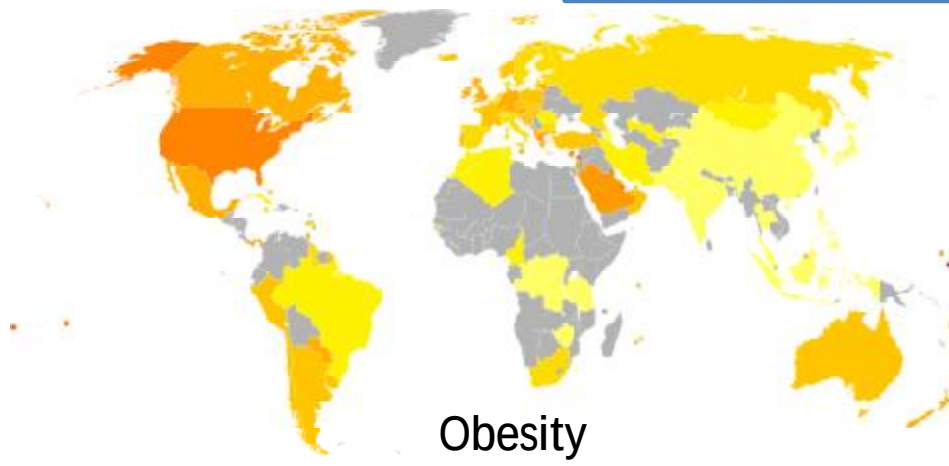
1 kg weight=+5% risk



THEN..



NOW..

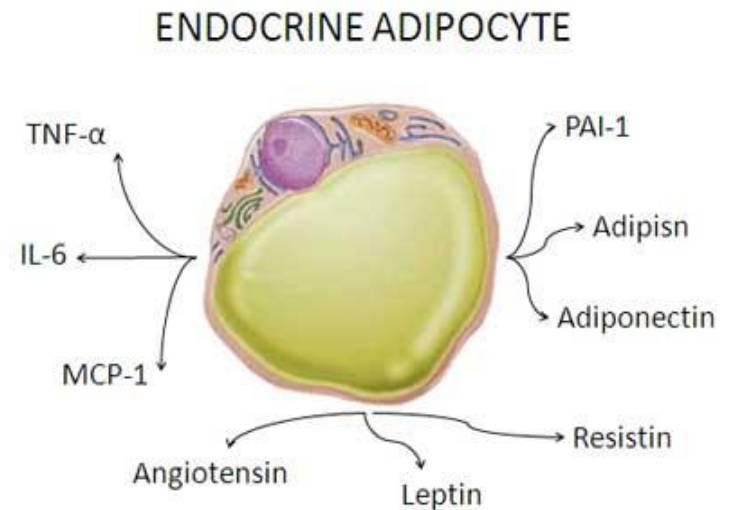


Syndrome X (metabolic syndrome)

Frequently occurs in people suffering from visceral obesity

Characteristic features:

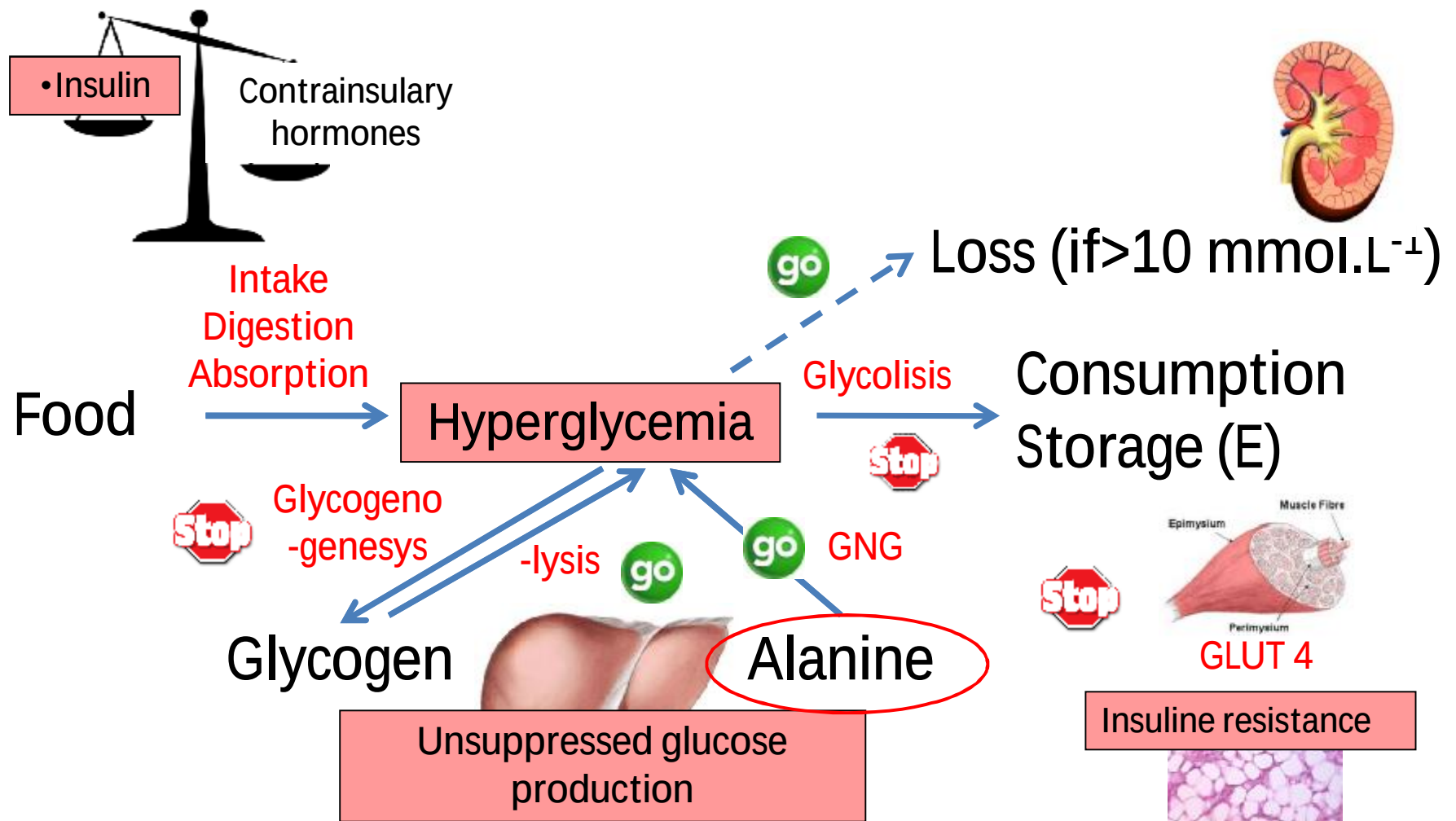
- § insulin resistance
- § compensatory hyperinsulinemia
- § visceral obesity
- § dyslipidemia (- LDL, - TG, $\uparrow$ HDL)
- § systemic hypertension



Increased probability of DM - type2 development

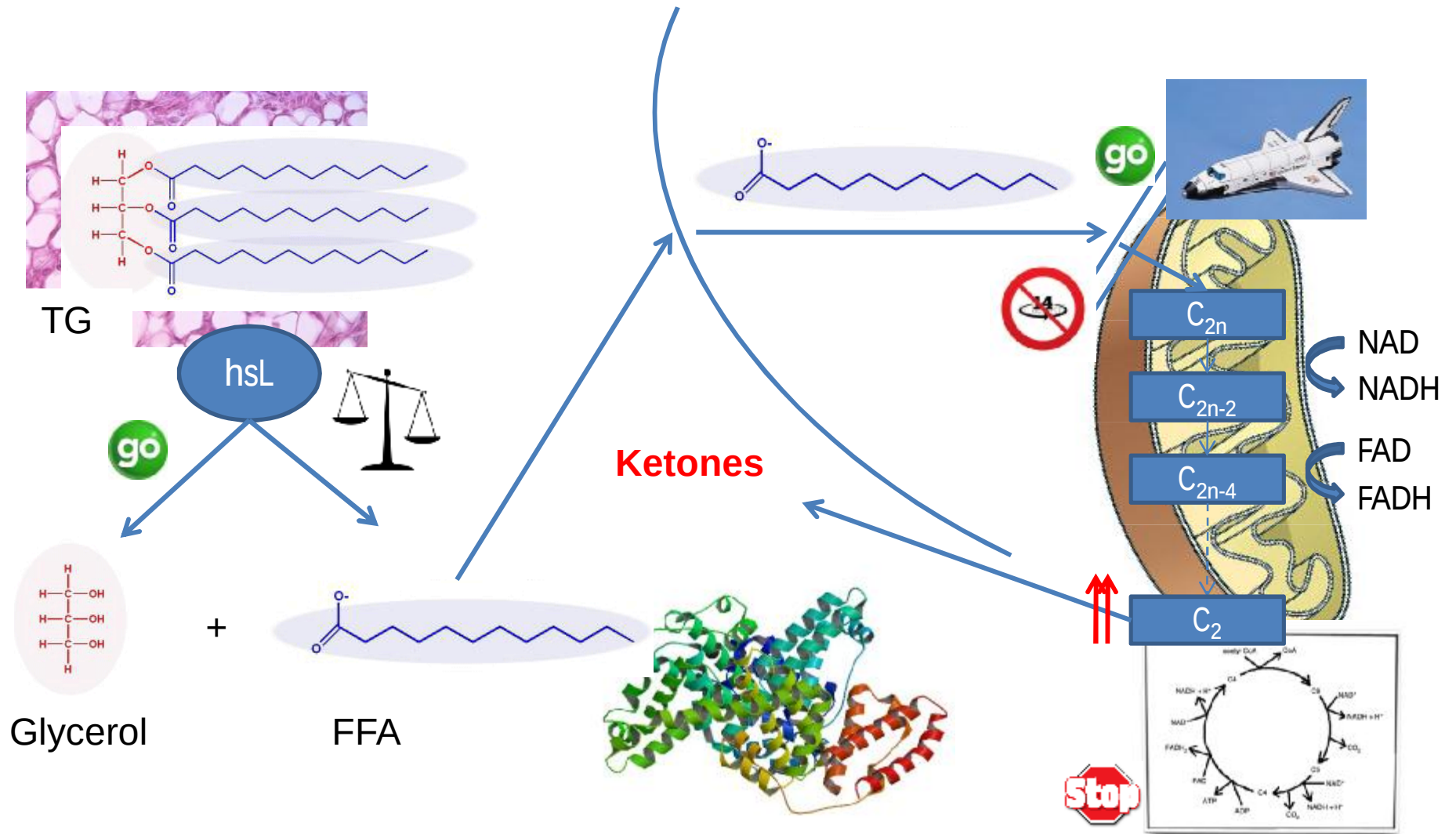


Pathobiochemistry of DM (CH and Protein)





Do not forget the lipids!



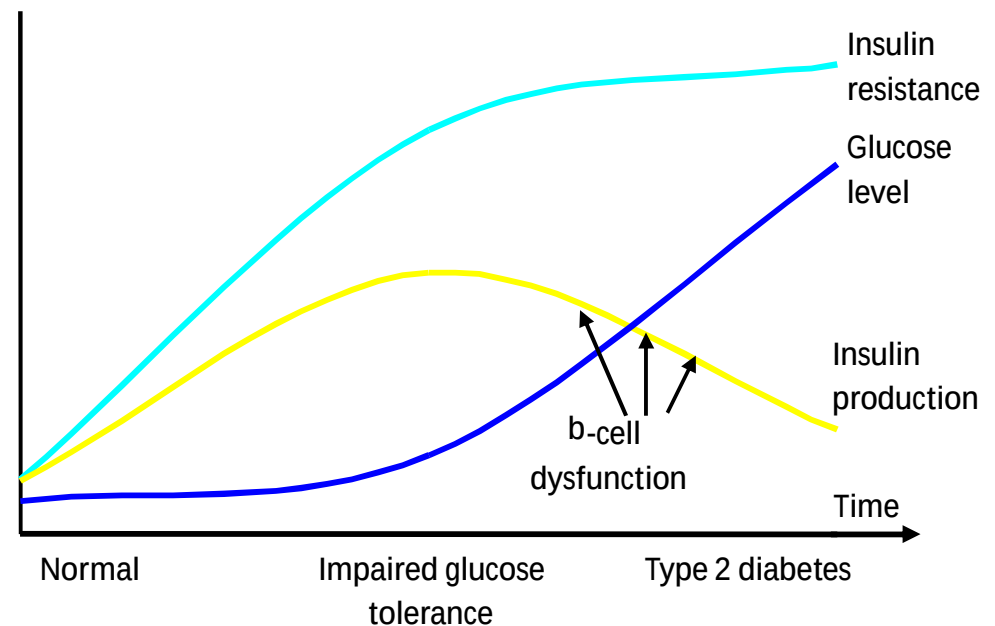
Signs and symptoms of DM type 2 ... and their absence

Mild polyuria

Mild polydipsia

Mild polyphagia

Genital itching



The symptoms of complications

Acute Complications

- Hypoglycemia and hypoglycemic coma
- Diabetic Ketone acidosis (DKA)
- Hyperosmolar diabetic coma (HDC)



Characteristics of ketoacidic and hyperosmolar coma

Characteristics	Ketoacidic coma	Hyperosmolar coma
•Type diabetes •Primary alteration •Treatment •Age •Trigger •Prognosis	Type 1 Excessive ketoacidosis Ketones >3 mmol/L; pH <7.25 Insulin + rehydration Young Infection, stress, trauma Poor (50:50); 5% in DKA	Type 2 Excessive hyperglycemia + Osmolarity > 330 mOsm/L Rehydration (hypovolemia!) Elderly Inadequate water intake Pessima

Chronic complications

(micro- & macrovascular)

§ Macrovascular (CAD, CVD (stroke), PVD)

Macrovascular disease - atherosclerotic lesion

of larger arteries (coronary arteries, brain arteries, peripheral arteries)

§ Microvascular (kidney, reticular, nerve)

Microvascular disease - specific lesion of DM that affect capillaries and arterioles of **the retina, renal glomeruli, peripheral nerves, muscles and skin**

- thickening of the capillary basement membrane

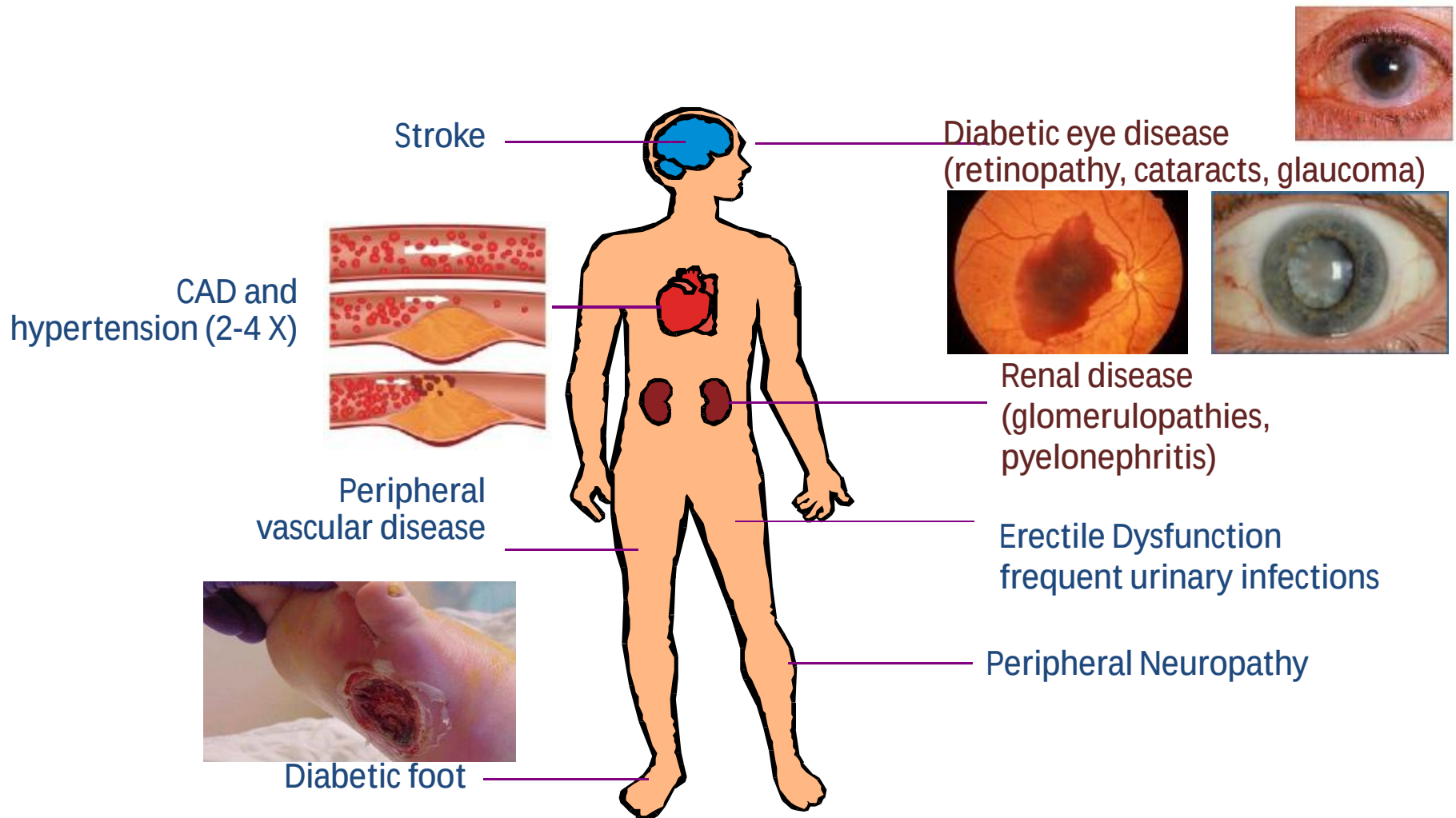
Chronic complications

Autonomic neuropathy

- Cardiovascular Autonomic Neuropathy
 - orthostatic hypotension
 - lack of normal variation in heart rate with breathing, tachycardia
- Gastrointestinal Autonomic Neuropathy
 - gastroparesis: nausea, bloating, vomiting
 - diarrhea: often nocturnal
- Erectile dysfunction
 - absent nocturnal and morning erections
 - more common than diagnosed



“Take no prisoners!”

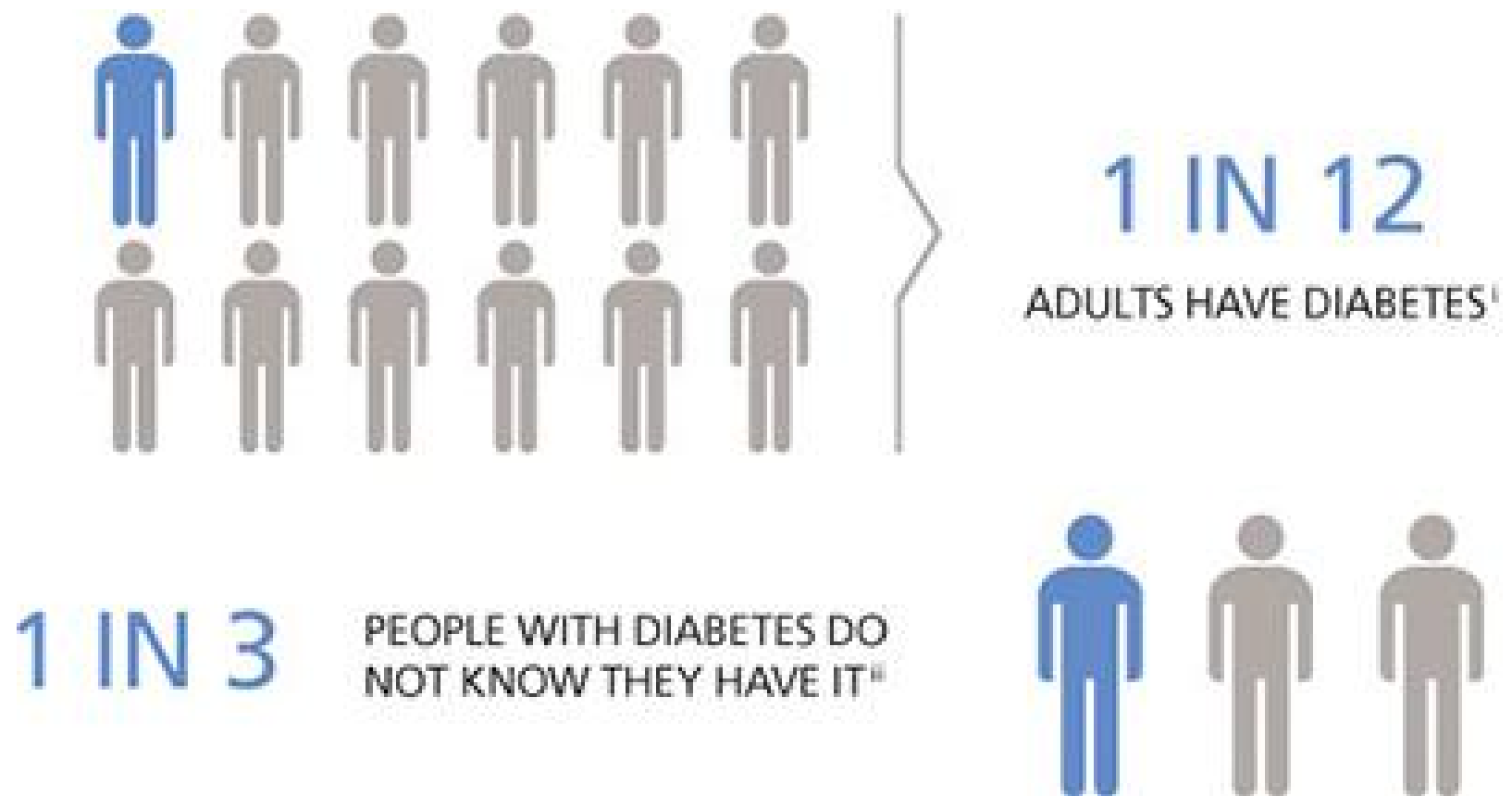




Characteristics of two main types of diabetes

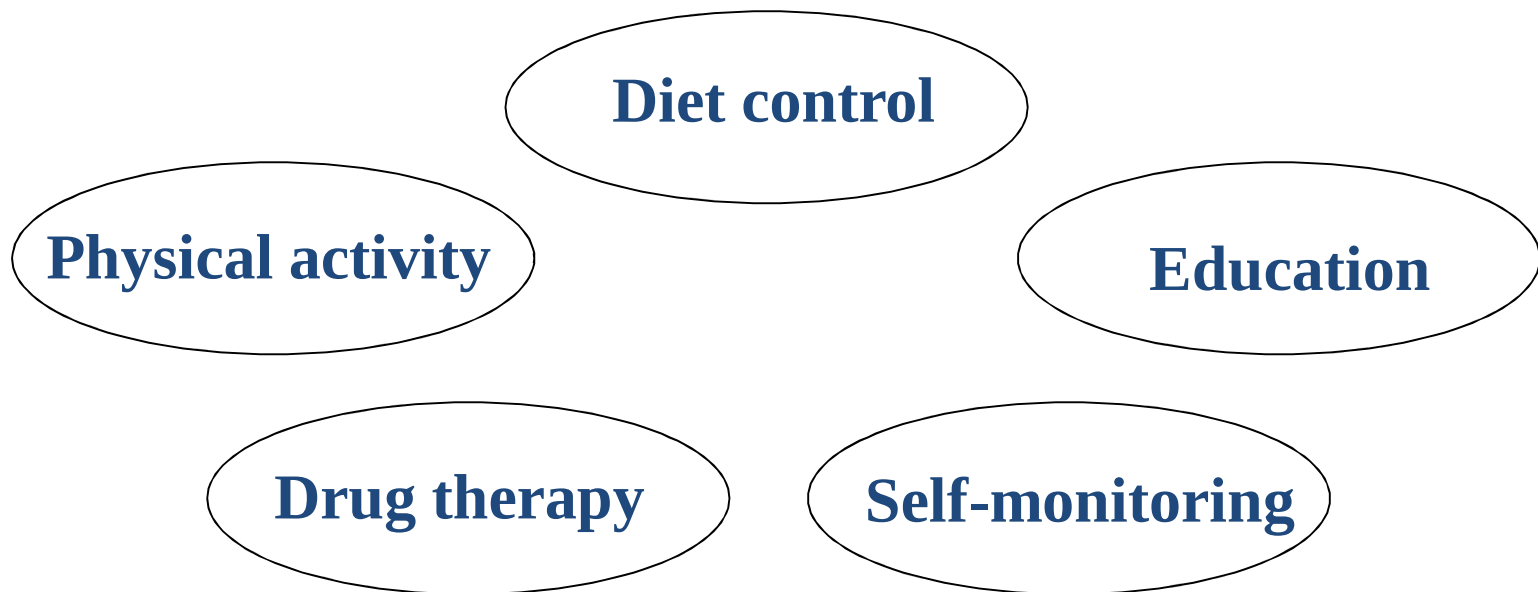
Main pathogenetic link	Absolute insulin deficiency	Relative insulin deficiency
Heredity	50% concordance	100% concordance
Mode of onset	Acute	Chronic
Age of onset	Young (<25 y, 12-14y)	>40 years old (60-65y)
Clinical feature	typical and severe (fragile)	Light or asymptomatic
Insulin or C-peptide release test	Low or Deficiency	peak value delay or absence
Body weight at onset	Normal	Overweight or obesity
Acute complication	Ketoacidosis	Hyperosmolar coma
Chronic impairment	Nephropathy(35%-40%---- mainly death cause)	Cardiovascular Disease(>70%--- mainly death cause)
Treatment	insulin	Diet/Oral hypoglycemic agents/insulin

Disease Burden of Diabetes Mellitus



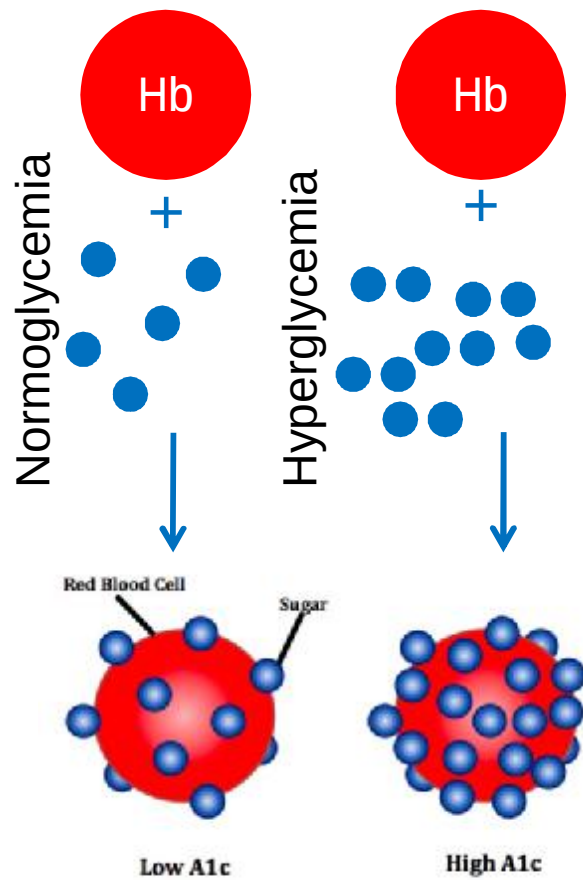
Diabetes - management

Early, long term, integrated, individualized





HbA_{1c} – ultimate goal



A1C	FPG	GTT
DIABETIC > 6.5	DIABETIC > 7.0	DIABETIC > 11.1
PRE-DIABETIC 5.7 - 6.5	PRE-DIABETIC 5.6 - 7.0	PRE-DIABETIC 7.8 - 11.1
NORMAL < 5.7	NORMAL < 5.6	NORMAL < 7.8



Indication for insulin therapy

1. Type I DM
2. Type II DM:
 - Acute complication: HDC, DKA
 - End stage of chronic complication
 - Stress
 - Pregnancy
 - Severe weight loss
 - Cortisol therapy



Thank you !

