Overview

of Diabetes Mellitus (DM)

AHLAM HAMDI DAHADHA

What do we know about …

Diabetes epidemiology-Prevalence

- In 2017 there was **451** million (age 18-99 years) people with diabetes worldwide; almost **50%** are undiagnosed.

- These figures are expected to increase to **693** million by 2045.

- About **1 in 11** adults have DM (90% have type 2 diabetes mellitus (T2DM)), and **Asia has the highest level.**

- The global prevalence of DM among adults > 18 years of age has risen from **4.7%** in 1980 to **8.5%** in 2014

(WHO,2018) , (Zheng et al,2018) , (IDF, 2018)

Diabetes epidemiology-Prevalence

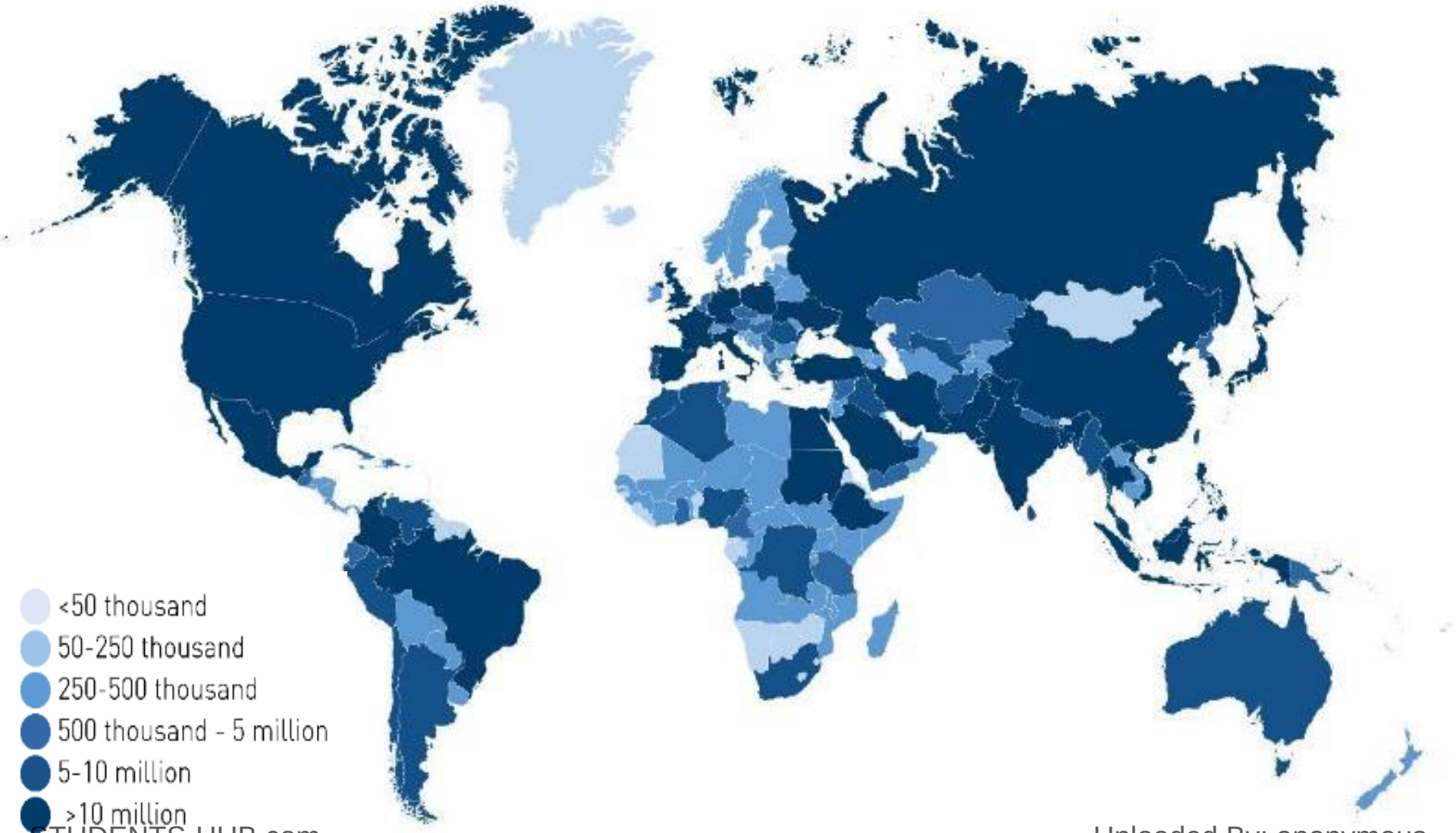
- Diabetes prevalence has been rising more rapidly in **middle- and low-income countries**.

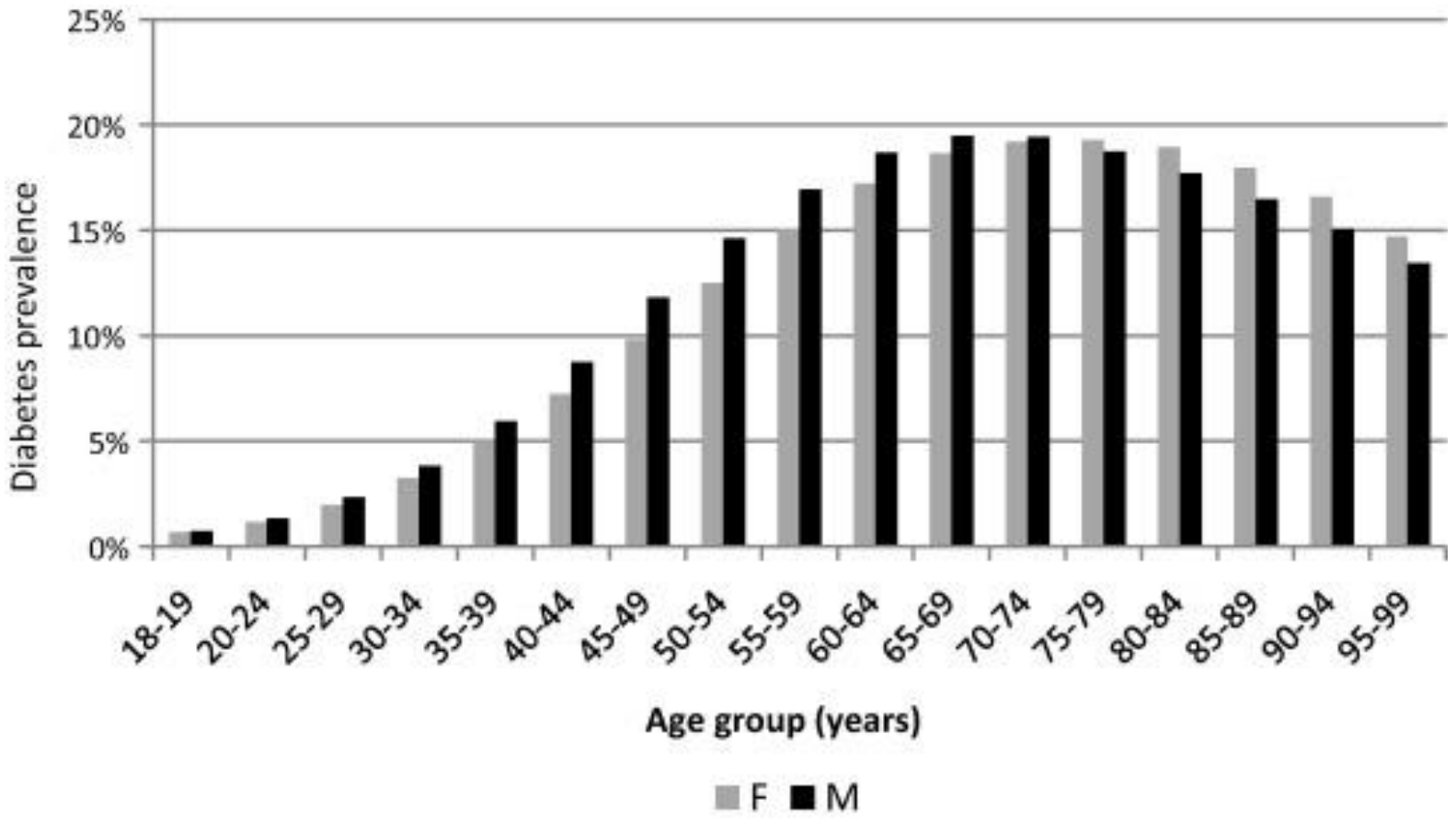
- In Palestine, prevalence of DM in adults is **7.0 %** , with total cases of around 168,800.

→ Reasons of increasing worldwide rate is sedentary lifestyle and urbanization.

(IDF, 2018)

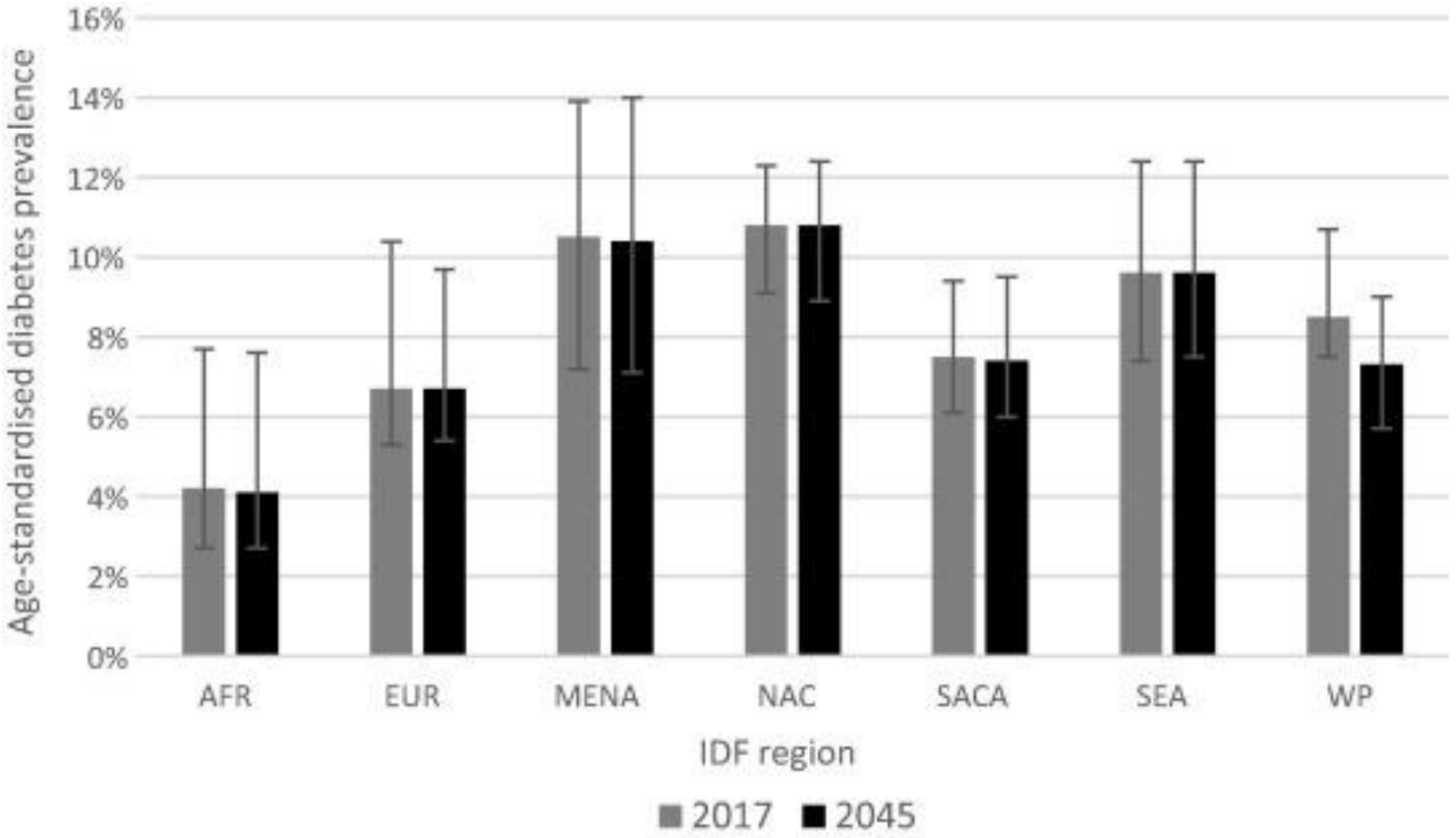
Estimated total number of adults (20-79 years) living with diabetes, 2017





Prevalence (%) of people with diabetes by age and sex, 2017.

(IDF, 2018)



Age-standardised prevalence of diabetes per IDF region for 2017 and 2045 (18–99years).

(IDF, 2018)

Diabetes epidemiology- IGT

- **Impaired glucose tolerance (IGT) –** 374 million in 2017

→69.2% in middle- and low-income countries.

→ Almost half (47.8%) <50 years of age.

- Diabetes in pregnancy –

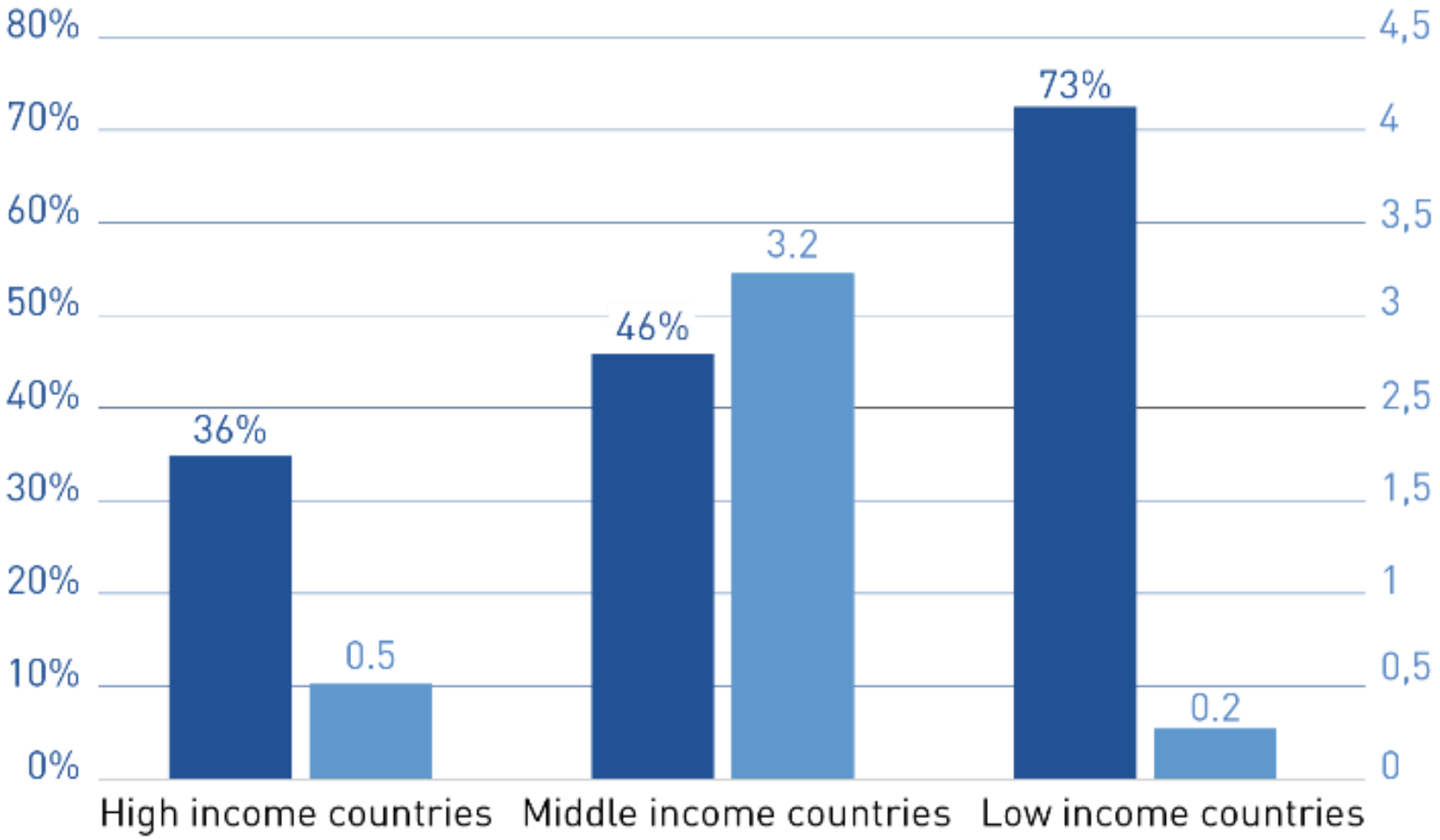
21.3 million live births (16.2%) with hyperglycemia.

Diabetes epidemiology- Mortality

- Approximately 5 million deaths worldwide were attributable to diabetes in the 20-99 years age range.

- **Almost HALF are under the age of 60.**

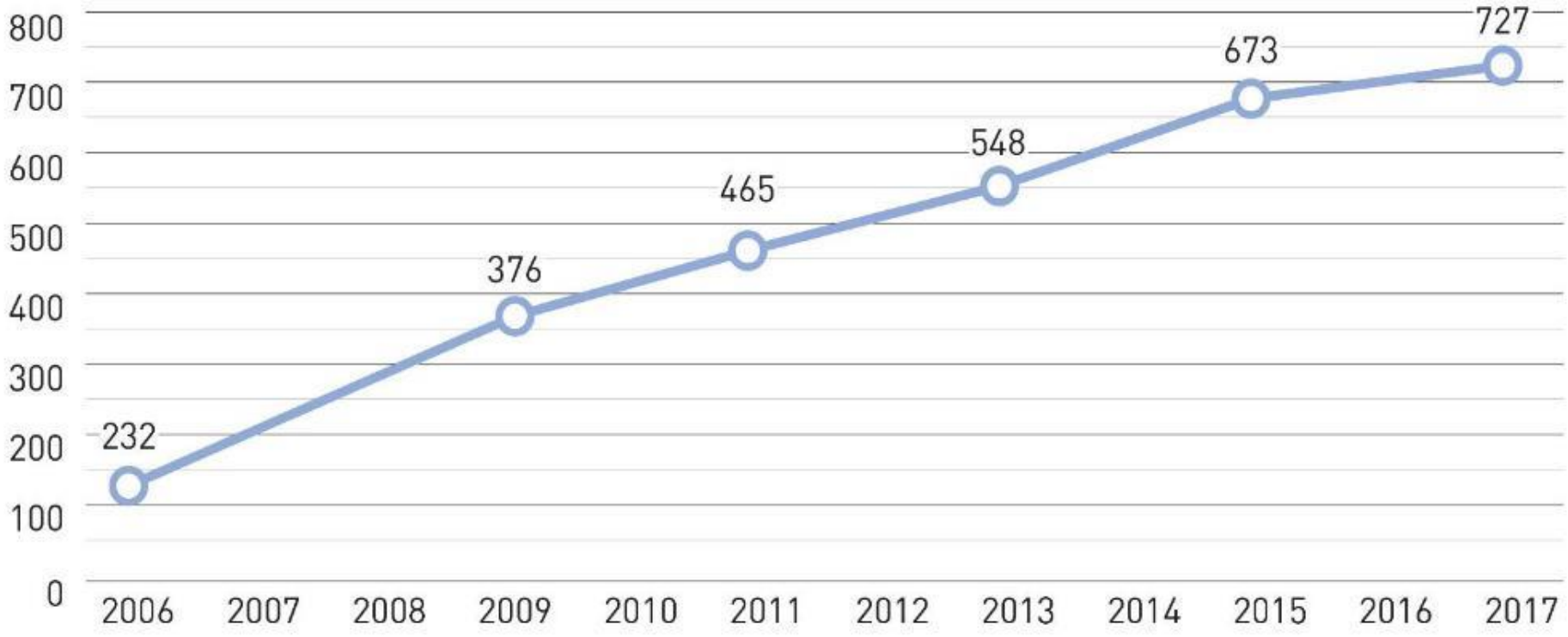
Deaths attributable to diabetes by age (20-79 years)



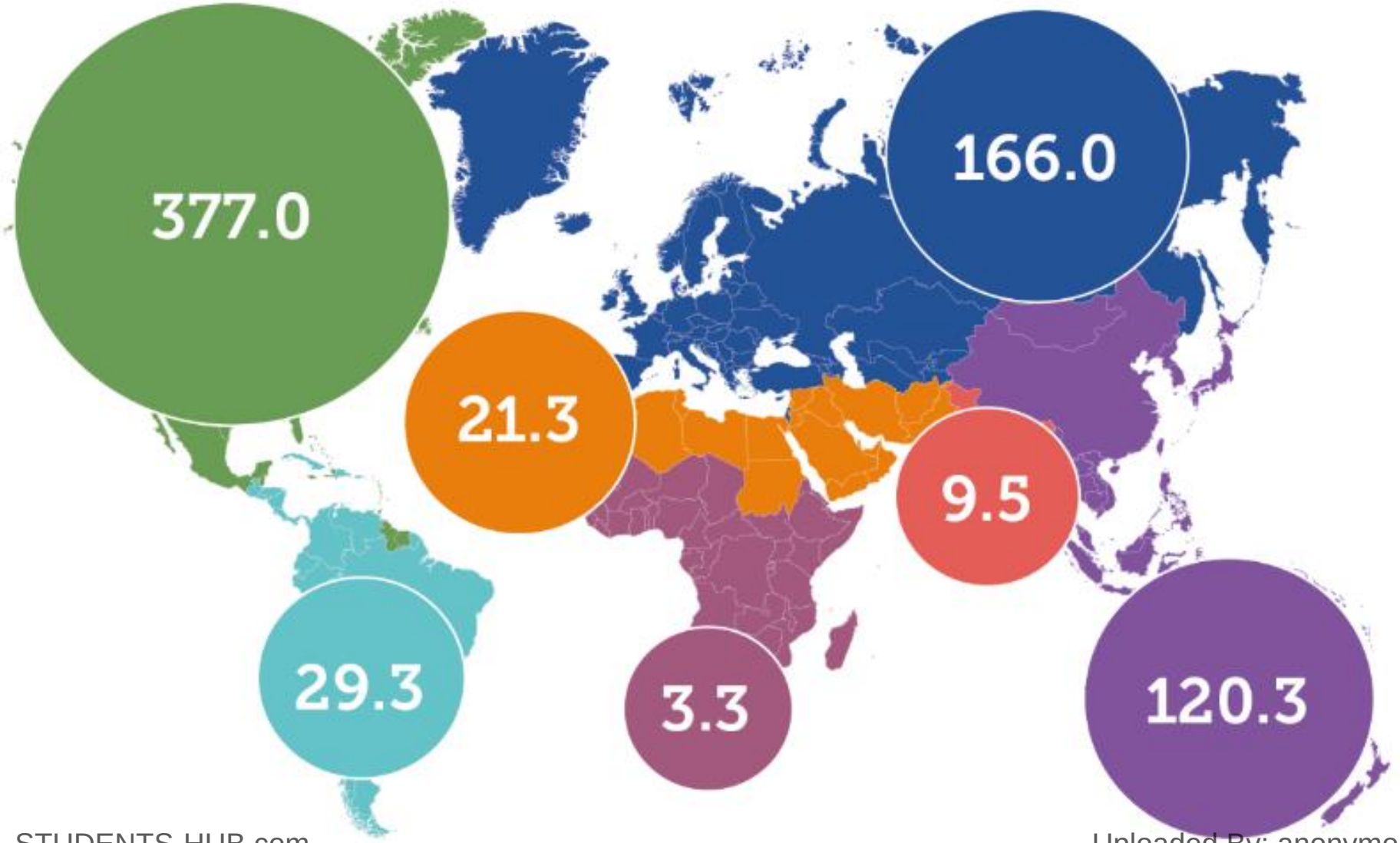
Healthcare Expenditure

"USD 54 billion more is spent on diabetes than 2015"

Total healthcare expenditure by people with diabetes (20-79 years)



Diabetes-related healthcare expenditure in adults (20-79 years) in 2017 per IDF region



Diabetes Mellitus in history

- **1500 BC:**

  " A disease characterized by too much emptying of the urine"

→ Indian physicians called it 'honey urine' because it attracted ants.

Diabetes Mellitus in history

- **400-500 AD**:

  Aretaeus the Cappadocian the first to use the word diabetes; in Greek means ‘siphon’>

  → “… no essential part of the drink is absorbed by the body while great masses of the flesh are liquefied into urine,,

- **1675 :**

  The word ‘Mellitus’ was added to diabetes and it means ‘honey’ in latin.

Diabetes Mellitus in history

- **1869:**

  Paul Langerhans identified a cluster of cells later known as **'Islets of Langerhans'**

- **1889:**

  Von Mering nd Minkowski found the **removal of pancreas** from dogs led to diabetes.

Insulin discovery

- **Before insulin** : people diagnosed with DM I died within weeks to years of disease onset.

- **1921:** insulin was discovered by the Canadian surgeon **Banting and his assistant Best** → a breakthrough in Medicine.

- **1950**: the first oral antidiabetic drugs (sulphonylureas) were added to the treatment of DM.

- **1960s and 70s :** Syringes were used ; made first of glass then transformed to **plastic syringes** → to prevent infections.

- **1980s:** the first human insulin was manufactured by **Graham Bell**, and two years later the first biosynthetic insulin (humulin) was developed.

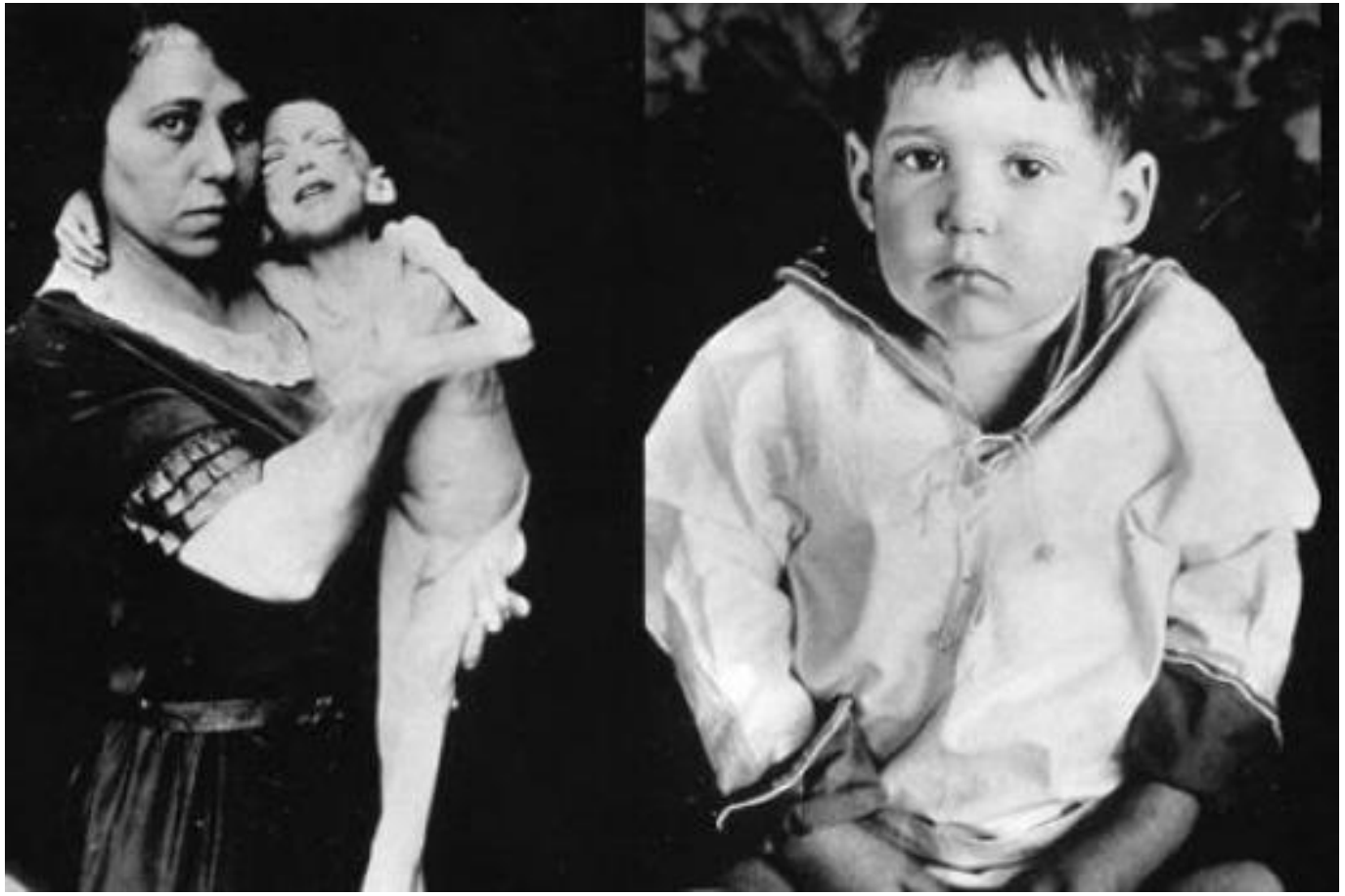
- **Later on:** Other forms of insulin were used , such as: inhaled insulin and oral sprays in addition to the use of insulin pumps.

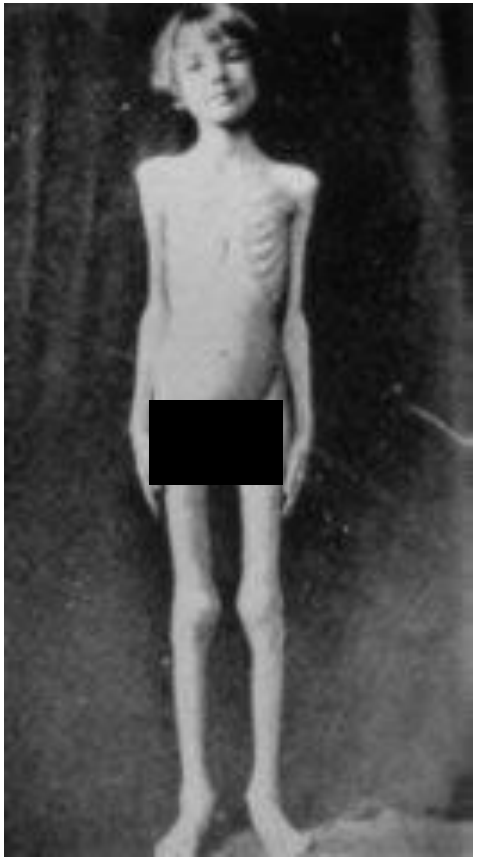
(Lakhtakia, 2013)

1922

The first patient to receive insulin

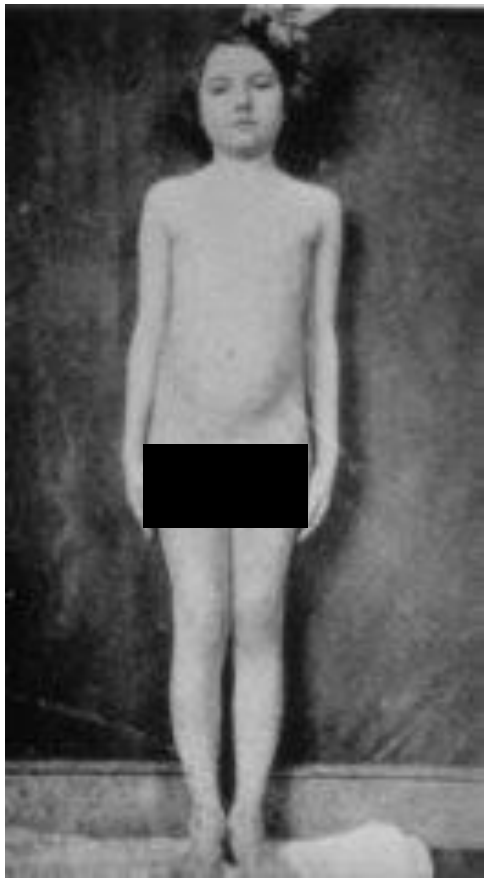
Leonard Thomson





Photographed in 1922, she was 152cm and weighed 20 kg

Placed on insulin and a diet of bread potatoes, macaroni cheese and a pint of cream daily



Gained 4 kg in 5weeks and continued at 1 kg a week increase

Elizabeth Evans Hughes

Diagnosed diabetic 1918 age 11

Died of a heart attack 1981 age 74 years

Definition of Diabetes Mellitus

"A group of metabolic diseases characterized by **hyperglycemia** resulting from defects in insulin secretion, insulin action, or both"

→ Persistent hyperglycemia is associated with many metabolic complications.

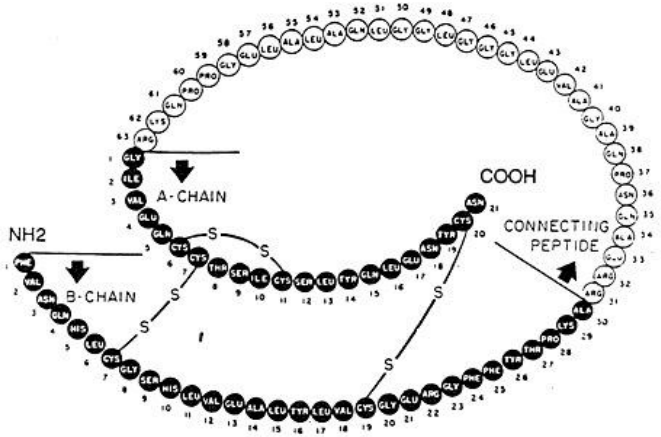
American Diabetes association (ADA)

A closer look at …

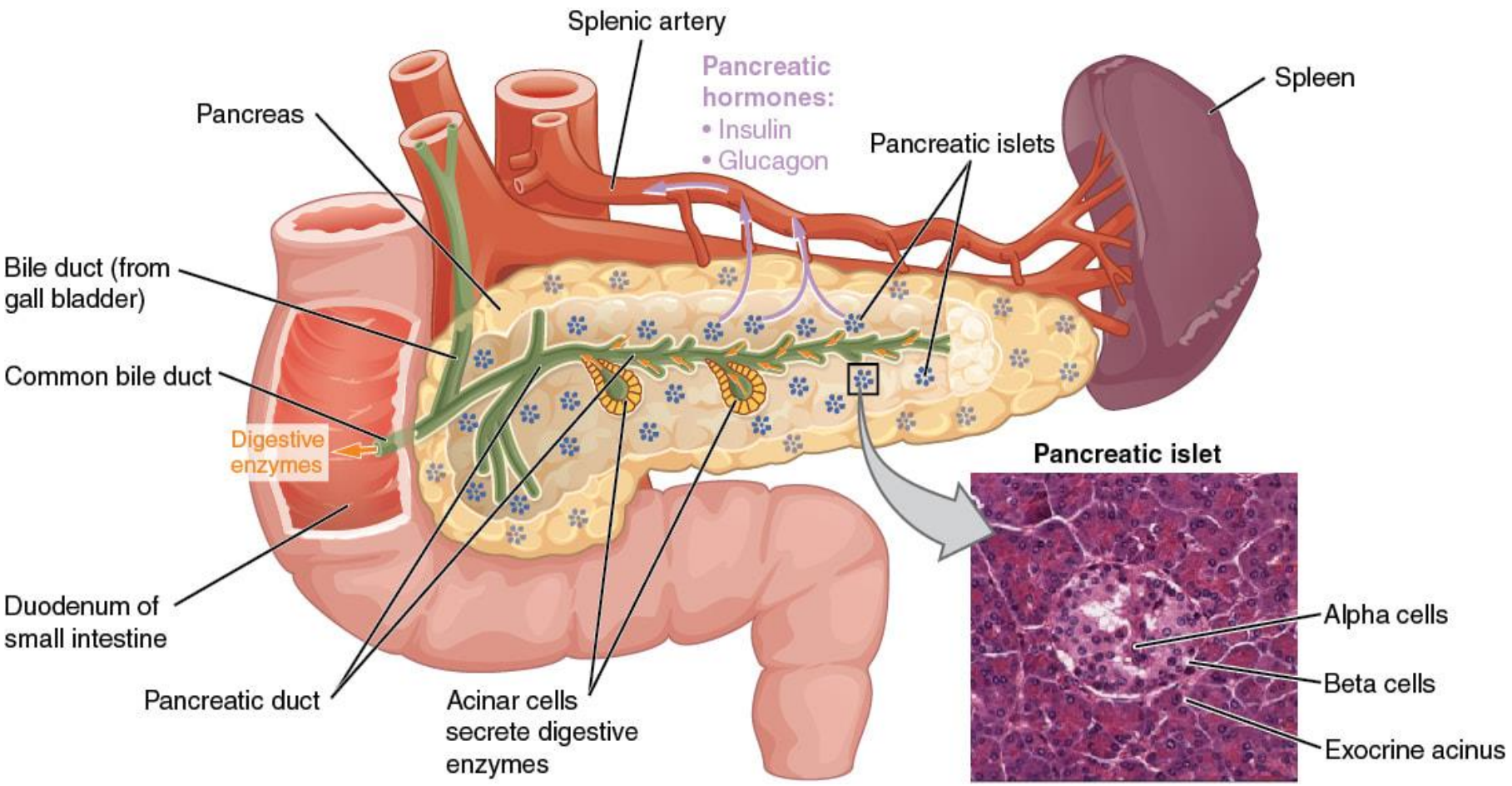
Insulin & the Pancreas

- Insulin is an **anabolic hormone** secreted by special cells in the pancreas called B-cells in response to increased blood glucose concentration.

- Insulin , like other hormones, is a protein comprising of 2 polypeptide chains A (with 21 amino acid residues) and B (with 30 amino acid residues) held by disulfide bridges.



The pancreas



→ **(In healthy individuals)**

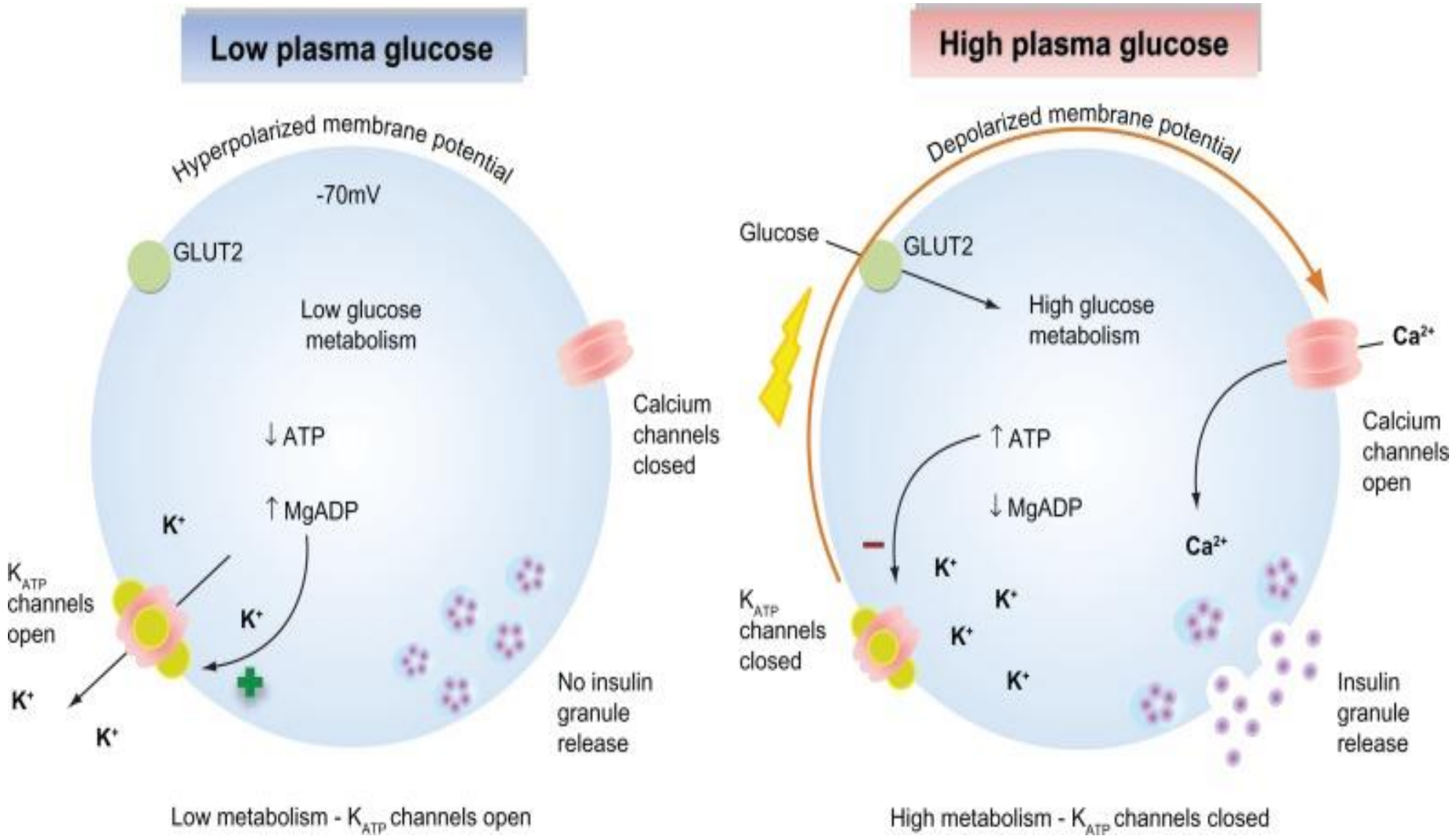
Insulin secretion

- The major trigger of insulin secretion is **Glucose.**

- Insulin is also secreted in response to **other various stimuli** including; Arginine, sulphonylureas and other neural, endocrine and pharmacological agents.

- Insulin secretion in B-cells is mediated by glucose uptake through **GLUT-2** receptors.

B-cell insulin secretion



Insulin action in the body

- Stimulates the uptake of glucose, K+ and AA in insulin sensitive cells.

In the muscles :

- Stimulation of protein synthesis.
- Inhibition of protein degradation.

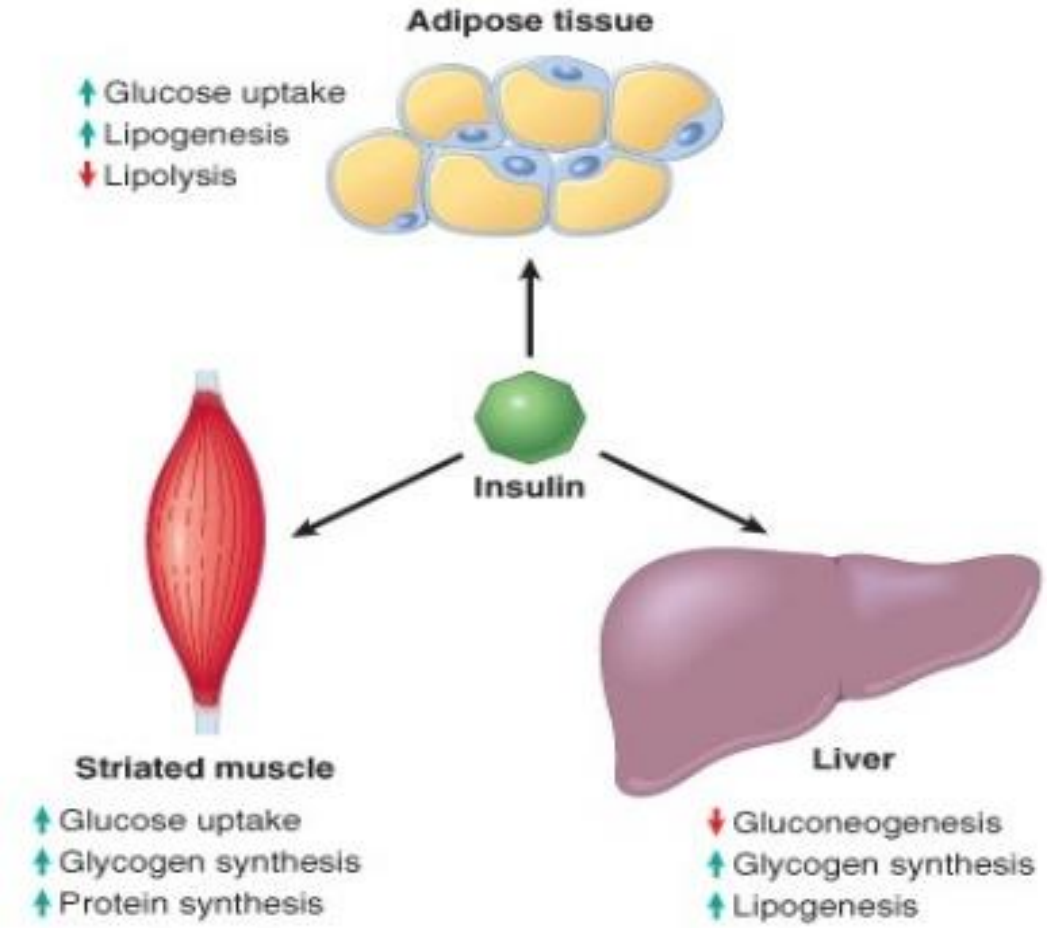
In the liver:

- Stimulation of glycogen synthesis.
- Inhibition of **gluconeogenesis.**

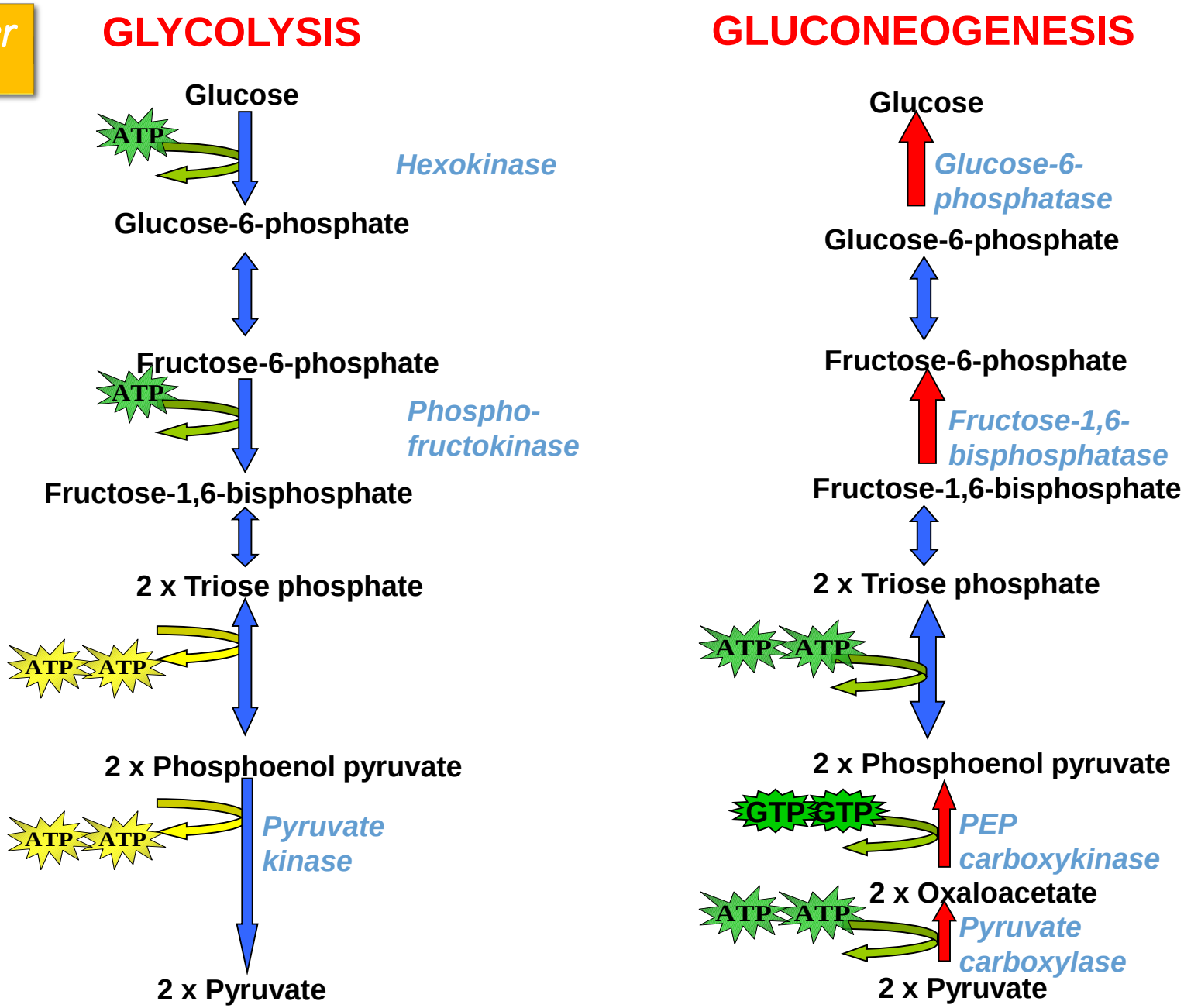
In the adipose tissue:

- Activation of lipogenesis.

Effects of insulin on target tissues.



A reminder


GLYCOLYSIS
Glucose
ATP
Hexokinase
Glucose-6-phosphate
Fructose-6-phosphate
ATP
Phospho-fructokinase
Fructose-1,6-bisphosphate
2 x Triose phosphate
ATP ATP
2 x Phosphoenol pyruvate
ATP ATP
Pyruvate kinase
2 x Pyruvate
GLUCONEOGENESIS
Glucose
Glucose-6-phosphatase
Glucose-6-phosphate
Fructose-6-phosphate
Fructose-1,6-bisphosphatase
Fructose-1,6-bisphosphate
2 x Triose phosphate
ATP ATP
2 x Phosphoenol pyruvate
GTP GTP
PEP carboxykinase
2 x Oxaloacetate
ATP ATP
Pyruvate carboxylase
2 x Pyruvate

Gluconeogensis

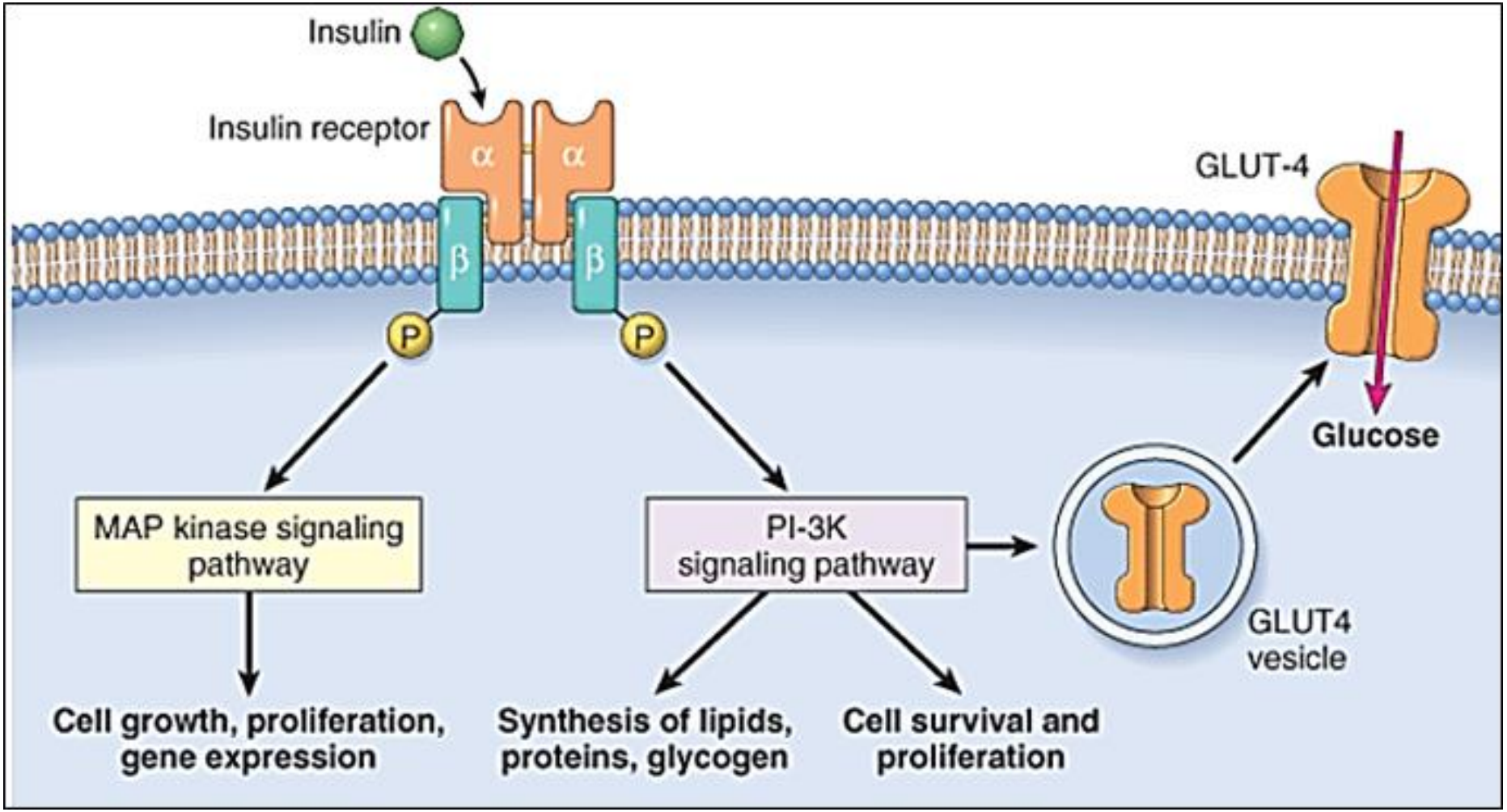
Gluconeogenesis is the pathway that synthesises glucose from pyruvate

It takes place in the liver and the kidney cortex (not in the brain)

The substrates are
Pyruvate
Lactate
Glycerol
Amino acids

Gluconeogenesis shares most of its intermediates and many reactions with glycolysis BUT it is NOT simply the reverse of glycolysis.

Insulin mechanism of action at cellular level



Insulin mechanism of action at cellular level

- The **insulin receptor** is a combination of 4 subunits held together by disulfide linkages: two α-subunits lying outside the cell membrane and two β-subunits protruding into the cell cytoplasm.

- When insulin binds to the α-subunit in target tissues, the β-subunits in turn become activated.

- Activation of the β-subunits triggers a series of reactions that draw the **glucose transporter** to the cell membrane.

Insulin mechanism of action (Cont.)

- Cells (liver, muscle, adipose, *but not* brain) are now able to increase their uptake of glucose.

- Insulin sensitive glucose uptake occurs in the muscles and adipose tissue through **GLUT-4.**

- Insulin has an important role in lipid and protein metabolism ..not only glucose.

Glucose transporters

Name (amino acids)	Tissue distribution	Approx. K_m	Important features
GLUT1 (492)	Erythrocytes, foetal tissue, placenta, brain	5-7 mmol/L	Non-insulin mediated glucose uptake
GLUT2 (524)	**Liver, kidney, intestine, pancreatic β-cell**	High (7-20 mmol/L)	Allows glucose to 'equilibrate' across the membrane. **Responsible for most intestinal glucose uptake**
GLUT3 (496)	**Brain**	Low (1.6 mmol/L)	Allows relatively **constant rate of glucose uptake** independent of extracellular concentration over the normal range
GLUT4 (509)	**Muscle, adipose tissue**	5 mmol/L	**The insulin-sensitive tissue glucose transporter**
GLUT5 (501)	Jejunum	5 mmol/L for fructose	Probably responsible for fructose uptake from intestine
SGLT1 (664)	Duodenum, jejunum, renal tubules		The sodium–glucose co-transporter of the small intestine (not part of the same family as GLUTI-5)

Insulin regulates the uptake of nutrients into the cells, the storage of nutrients not being used, and the conversion of one nutrient type to another.

Other physiological effects of insulin

- Insulin also plays an important role in the heart tissue; by signaling cardiac contractibility and vascular tone.

- It is also found in high concentrations in the brain; where it modulates neural development, body weight and eating behaviors , in addition to some cognitive processes.

(Rodelo et al., 2017)

Glucose as a fuel

- Glucose is the preferred source of energy by our body organs.
- Excess glucose is stored in the body as ***glycogen*** and ***fat***.

- **Plasma glucose** is the fist source of energy in the body.
- When depleted ; the body starts using glucose stored as glycogen (in the liver and muscles) or fat (in adipose tissue).

- Liver stores 2-3% glycogen → The main role of glycogen in the liver - regulation of blood glucose concentration and glucose homeostasis
- Muscles stores 1-3% glycogen and it is used only by the muscles for contraction.

Glucose sources & Interconversion of fuels

Proteins cannot be made from either carbohydrates or triacylglycerols, but can be made into both

Fatty acids can be made from carbohydrates and proteins, but cannot be converted back into either.

Carbohydrates can be made from proteins and can be used to make triacylglycerols

Why can't Fatty acids produce glucose?

Why Fat cannot be converted into glucose?

" Once glucose is converted to acetyl- coA there is no method of getting back to glucose."

→ The pyruvate dehydrogenase reaction that converts pyruvate to acetyl CoA is not reversible .

→ Further, the two carbons in the acetyl CoA molecule are lost upon entering the citric acid cycle. Thus, the acetyl CoA is used for energy.

Sources of energy in the body

- After glycogen depleted, gluconeogenesis from amino acids
- Fatty acid oxidation and ketogenesis to conserve protein as much as possible
- Energy expenditure decreased

Hierarchy of fuels oxidized in consumer organs

Fuel	Brain	Muscle
Fatty acids	Not used	First priority if available
Ketones	First priority if available	Not used if fatty acids available
Glucose	Used exclusively, most of the time	Used only if fatty acids and ketones not available
Alcohol	First priority if available	First priority if available

Glucose homeostasis

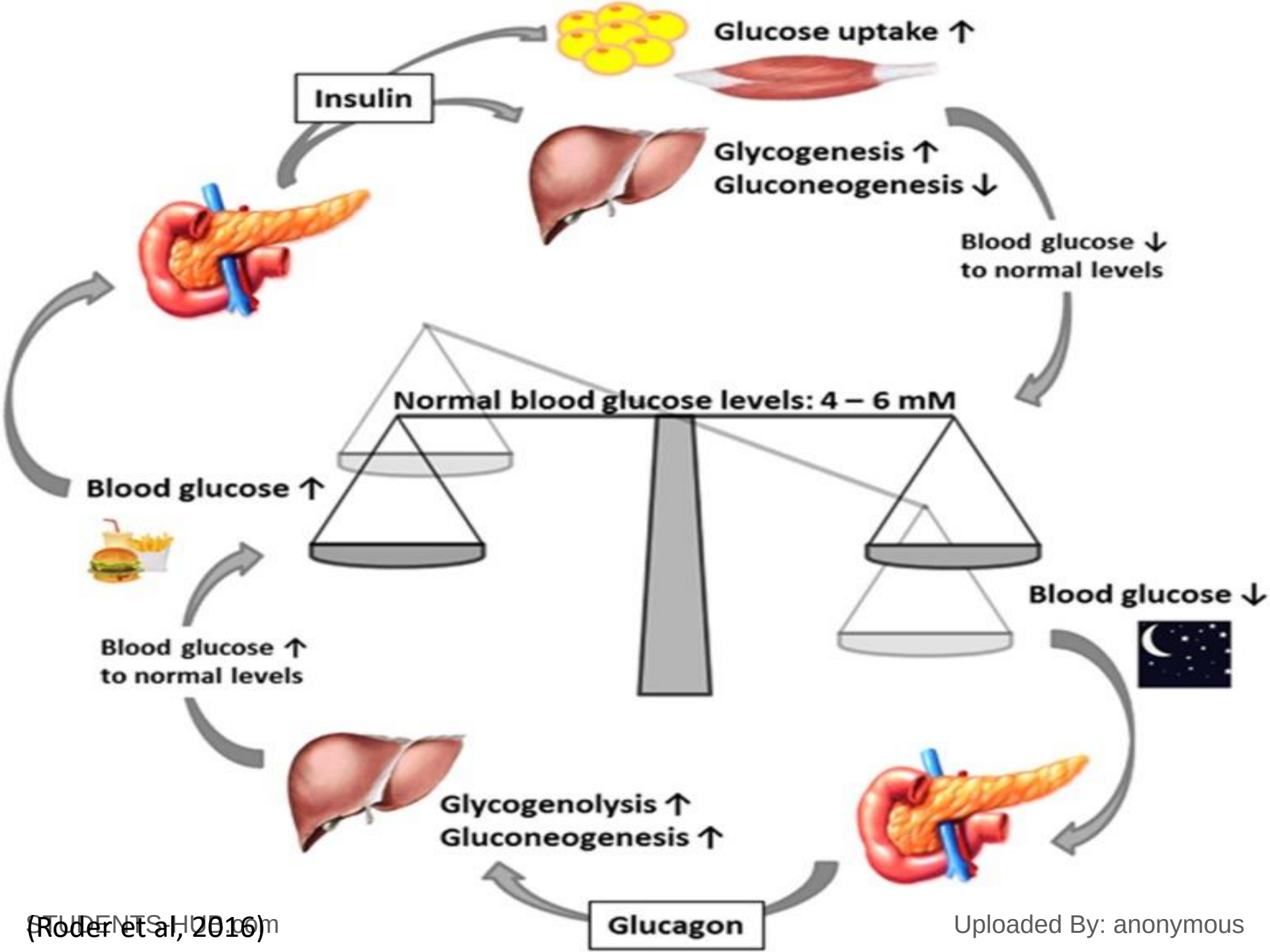
- **Homeostasis** means the maintenance of constant internal conditions by the body's control systems.
- Glucose homeostasis is regulated primarily by ***insulin*** and ***glucagon***.
- Both hormones have opposite actions in the body in order to maintain glucose within normal range.
- Glucagon : produced in the fasting state.
- Insulin: secreted in the fed state.

(Roder et al, 2016)

Glucagon Vs. Insulin

GLUCAGON Stimulates:

- GLYCOGENOLYSIS: Breakdown of glycogen into glucose
- GLUCONEOGENESIS: Increase of synthesis of glucose from amino acids and the glycerol portion of fat
- LIPOLYSIS: Activation of *adipose cell lipase* making fatty acids available for use as energy source



(Roder et al, 2016)

Role of the liver in regulation of blood glucose

Why does blood glucose concentration need to be maintained within limits?

Glucose is toxic and will react with the basic side-chains of protein amino acids
It is also a preferential fuel for the brain and kidney cortex

TOO HIGH: diabetes/complications
TOO LOW: coma

The LIVER is the most important organ for regulation of blood glucose. It contains the body's most readily accessible store of glycogen for breakdown to glucose if levels fall too low.

Summary : metabolic effects of insulin

- Increases rate of glucose transport into target cell
- Increases rate of glucose utilization and ATP formation
- Increases conversion of glucose to glycogen (liver, skeletal muscle)
- Increases amino acid absorption and protein synthesis
- Increases triglyceride synthesis (adipose tissue)

DECREASES HIGH BLOOD GLUCOSE LEVELS

What happens in diabetes ?

- **Decreased insulin secretion** from pancreatic B-cells

Or/And

- Impaired insulin action in target tissues **(insulin resistance)**

→ Leading to what is known as **“Hyperglycemia”**.

Without insulin

***G*lucose transport into the cells will be insufficient.**

- ✓ **Lacking glucose, cells will have to rely on protein and fat catabolism for fuel.**

Also, when there is not enough insulin, excess glucose cannot be stored in the liver and muscle tissue.

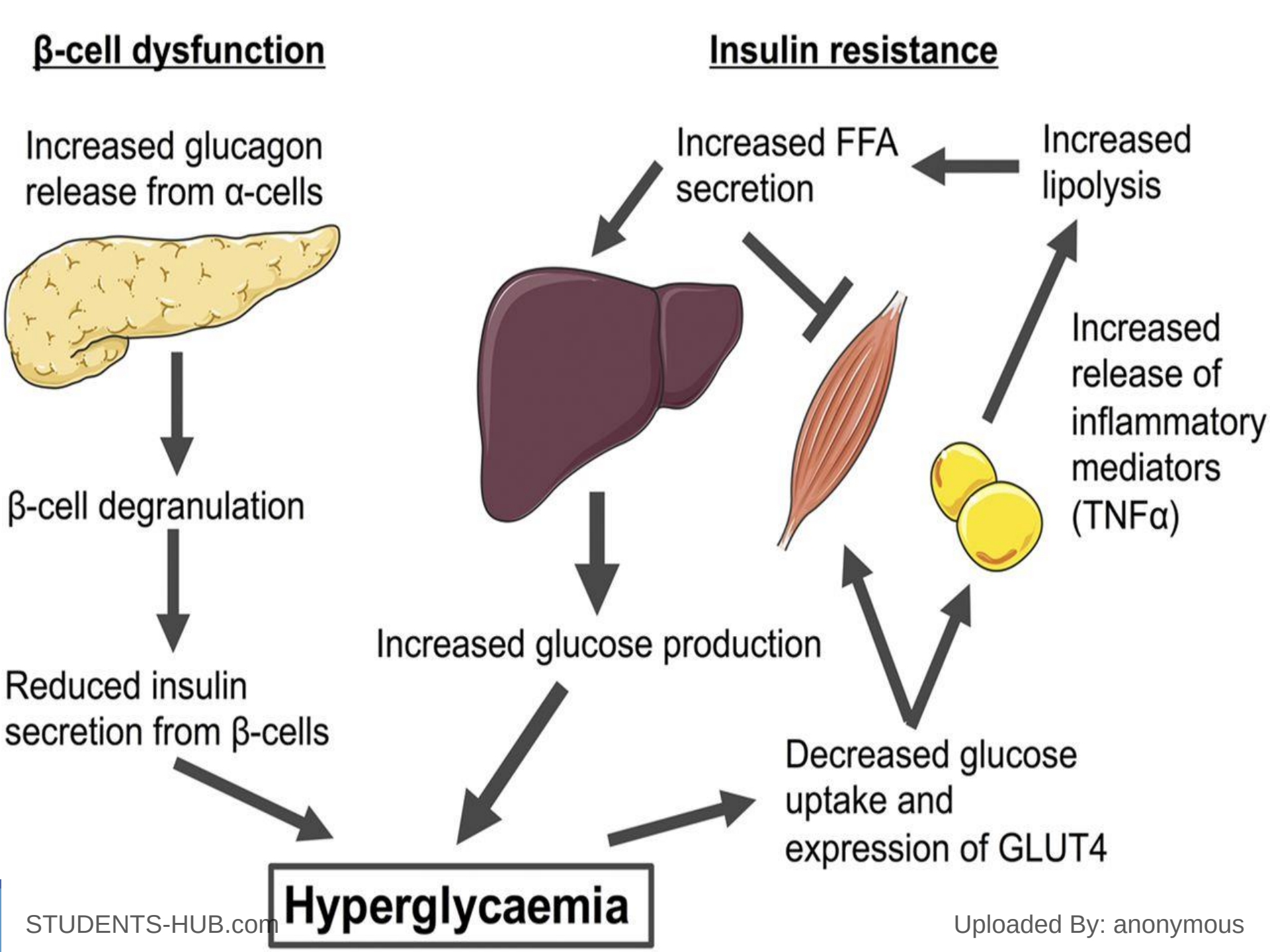
- ✓ **Instead, glucose accumulates in the blood-- above normal levels.**

Some important definitions

- **Insulin resistance**: reduced sensitivity to insulin in muscle, adipose tissue and liver cells.

- **Hyperglycemia**: elevated plasma glucose concentrations.

- **Glucose intolerance** : another term that describes hyperglycemia and DM pathophysiology.



Insulin resistance

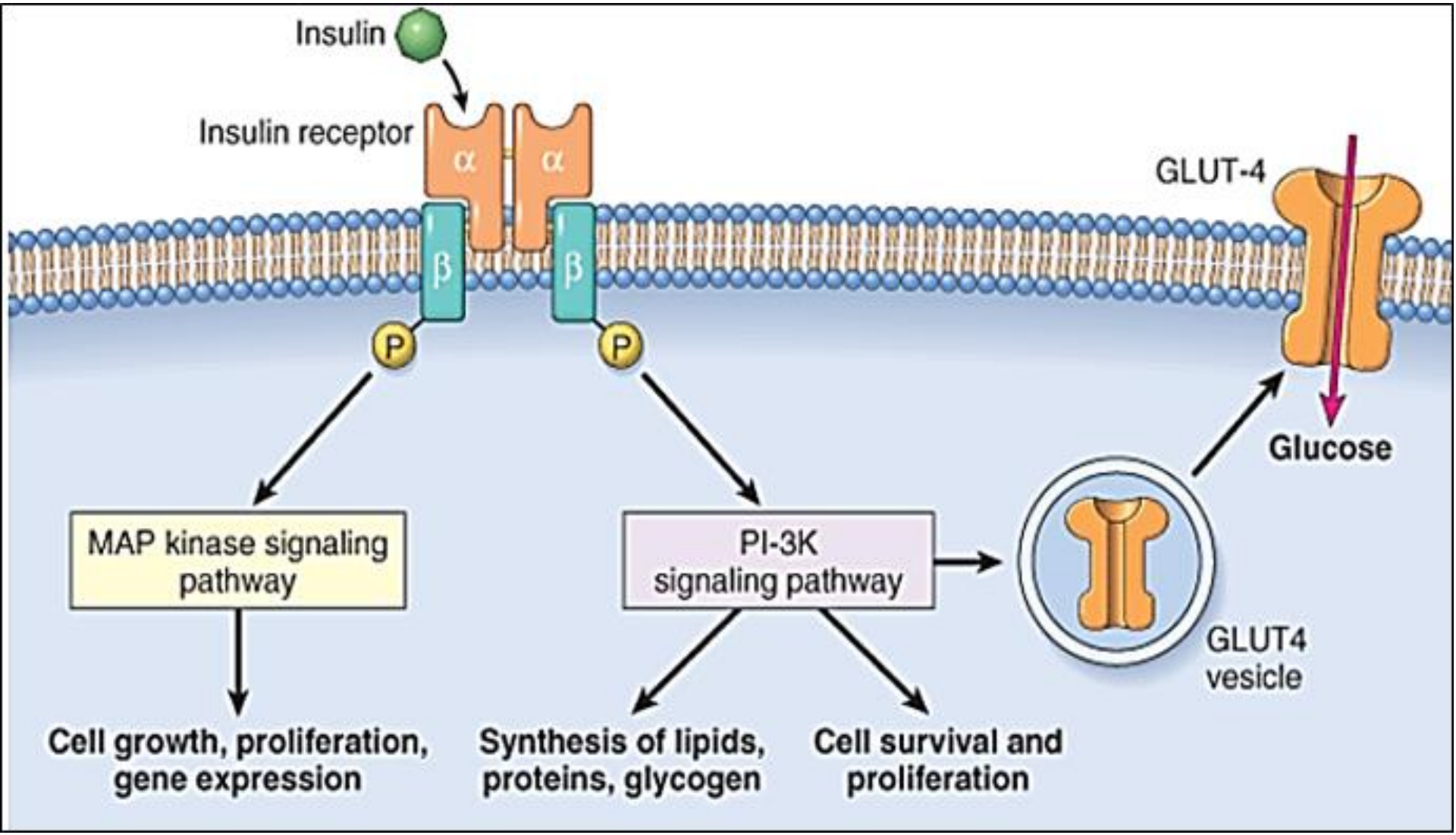
At the molecular level Insulin resistance is caused by →

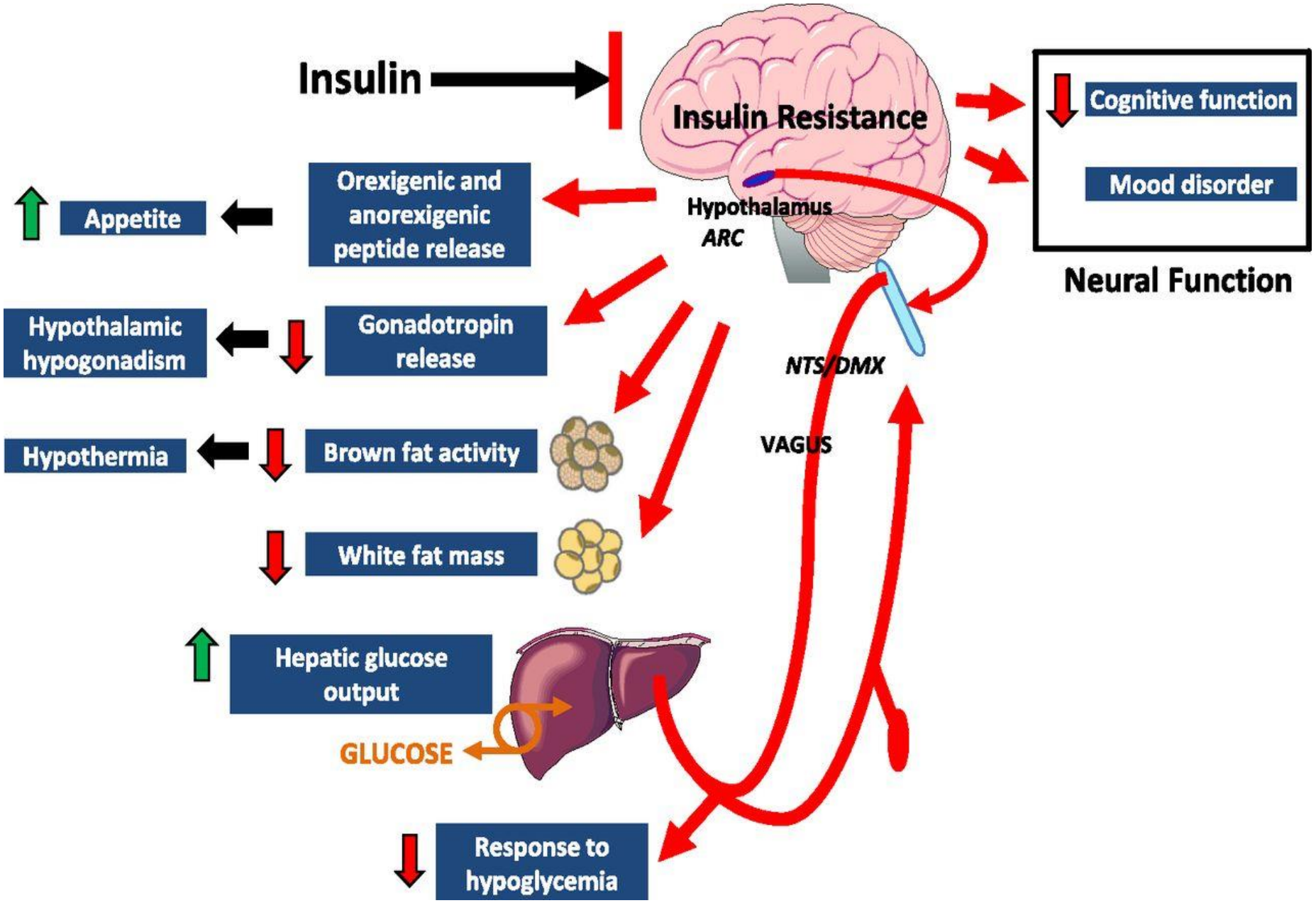
- Mutations in the insulin receptors.

- Impaired expression of glucose transporters (GLUT-4) on the cellular membranes of target tissues.

→ these defects reduce glucose uptake in muscle and adipose tissue.

(Rodelo et al, 2017)

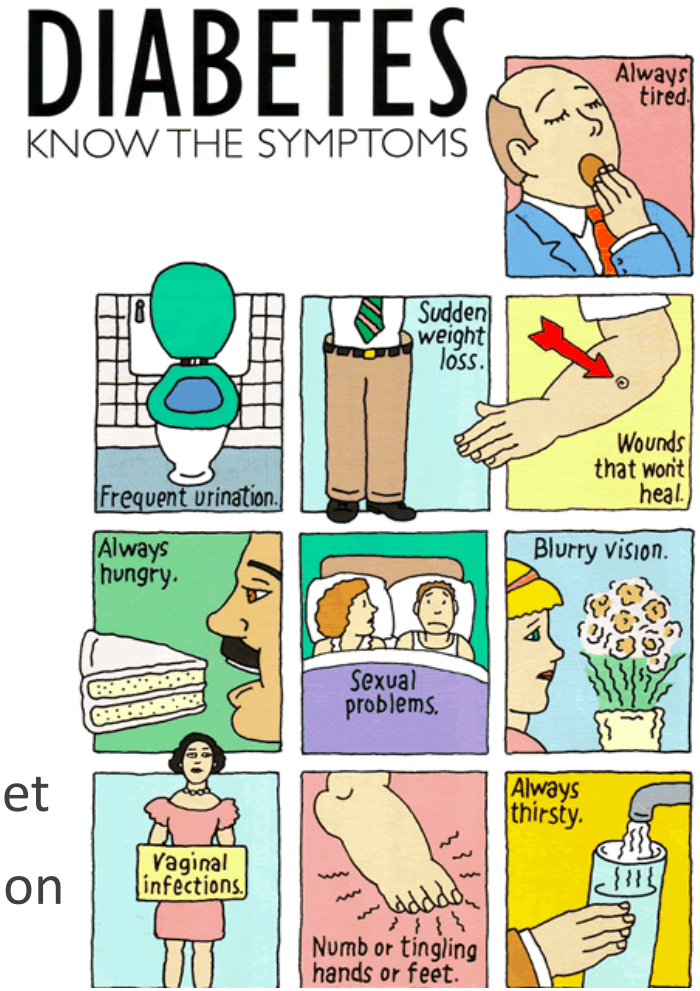

Insulin
Insulin receptor
α
α
β
β
P
P
GLUT-4
Glucose
MAP kinase signaling pathway
PI-3K signaling pathway
GLUT4 vesicle
Cell growth, proliferation, gene expression
Synthesis of lipids, proteins, glycogen
Cell survival and proliferation


Insulin
Insulin Resistance
Cognitive function
Mood disorder
Neural Function
Hypothalamus
ARC
Orexigenic and anorexigenic peptide release
Appetite
Hypothalamic hypogonadism
Gonadotropin release
NTS/DMX
VAGUS
Hypothermia
Brown fat activity
White fat mass
Hepatic glucose output
GLUCOSE
Response to hypoglycemia

Pathophysiology of DM

Symptoms

- Polydipsia (increased thirst).
- Polyuria (Frequent urination).
- Weight change (gain or loss)
- Extreme fatigue or lack of energy
- Blurred Vision
- Frequent or recurring infection
- Cuts and bruises that are slow to heal
- Tingling or numbness in the hands or feet
- Trouble getting or maintaining an erection



Classification of DM

- Type I diabetes (DM I).
- Type II diabetes (DMII).
- Gestational Diabetes Mellitus (GDM).
- Other specific types of diabetes:
  - Monogenic diabetes syndromes
  - Diseases of the exocrine pancreas, e.g., cystic fibrosis
  - Drug- or chemical-induced diabetes

American Diabetes Association Standards of Medical Care in Diabetes, 2018.

Diagnosis of DM

FPG, 2-h PG during 75-g OGTT, and A1C are equally appropriate for diagnostic testing.

- FPG: fasting plasma glucose, after a fast of at least 8 hours.
- 2-h PG: plasma glucose levels two hours after consuming a load of 75 g glucose.
- A1C or HbA1c: also called Glycosylated Hb, estimates 'average glucose'
- RBS: random blood sugar level taken at anytime during the day regardless of food intake.

Diagnostic criteria of DM

Fasting plasma glucose (FPG)
≥126 mg/dL

OR

2-h plasma glucose ≥200 mg/dL
during an OGTT

OR

A1C ≥6.5%

OR

Classic diabetes symptoms + random plasma glucose
≥200 mg/dL

(American Diabetes Association Standards of Medical Care in Diabetes, 2018.)

CONFIRMATION of DIAGNOSIS

Diagnosis can be confirmed:

If display diabetes symptoms **and**

- Random venous plasma glucose ≥ 11.1.mmol/l (≥200 mg/dl) **or**
- Fasting plasma glucose **≥** 7.0 mmol/l (≥ 126 mg/dl) **or**
- OGTT 2hr plasma glucose ≥ 11.1.mmol/l (≥200 mg/dl)

If asymptomatic, minimum of two values in the above ranges on separate days

What about prediabetes ?
-Screening criteria-

Prediabetes is referred to individuals who are asymptomatic but at high risk for developing diabetes.

- Screening for Prediabetes should begin at age 45 for all people regardless of weight.

- Test for prediabetes in **asymptomatic adults of any age** with **BMI ≥25 kg/m2 or** ≥23 kg/m2 (in Asian Americans) who have 1 or more additional **risk factors** for diabetes.
- Those individuals are at high risk for developing cardiovascular diseases (CVD).
- If tests are normal, repeat at a minimum of **3-year intervals.**

Who else should be screened ?

- First degree family history of DM.
- Sedentary lifestyle.
- Individuals with ischaemic heart disease, cerebrovascular disease, peripheral vascular disease or treated hypertension.
- Women who have had gestational diabetes.
- Obese women with polycystic ovary disease with BMI $\geq$ 30
- Individuals with severe mental health problems
- Individuals with hypertriglyceridemia not due to alcohol excess or renal disease

THE MORE RISK FACTORS A PERSON HAS, THE GREATER THE LIKELIHOOD OF DEVELOPING DIABETES

ARE YOU AT RISK FOR TYPE 2 DIABETES?

American Diabetes Association.

Diabetes Risk Test

1. **How old are you?**
   Less than 40 years (0 points)
   40—49 years (1 point)
   50—59 years (2 points)
   60 years or older (3 points)

2. **Are you a man or a woman?**
   Man (1 point) Woman (0 points)

3. **If you are a woman, have you ever been diagnosed with gestational diabetes?**
   Yes (1 point) No (0 points)

4. **Do you have a mother, father, sister, or brother with diabetes?**
   Yes (1 point) No (0 points)

5. **Have you ever been diagnosed with high blood pressure?**
   Yes (1 point) No (0 points)

6. **Are you physically active?**
   Yes (0 points) No (1 point)

7. **What is your weight status?** *(see chart at right)*

Write your score in the box.

Add up your score.

If you scored 5 or higher:
You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes (a condition that precedes type 2 diabetes in which blood glucose levels are higher than normal). Talk to your doctor to see if additional testing is needed.

Height	Weight (lbs.)		
4′ 10″	119-142	143-190	191+
4′ 11″	124-147	148-197	198+
5′ 0″	128-152	153-203	204+
5′ 1″	132-157	158-210	211+
5′ 2″	136-163	164-217	218+
5′ 3″	141-168	169-224	225+
5′ 4″	145-173	174-231	232+
5′ 5″	150-179	180-239	240+
5′ 6″	155-185	186-246	247+
5′ 7″	159-190	191-254	255+
5′ 8″	164-196	197-261	262+
5′ 9″	169-202	203-269	270+
5′ 10″	174-208	209-277	278+
5′ 11″	179-214	215-285	286+
6′ 0″	184-220	221-293	294+
6′ 1″	189-226	227-301	302+
6′ 2″	194-232	233-310	311+
6′ 3″	200-239	240-318	319+
6′ 4″	205-245	246-327	328+
	(1 Point)	(2 Points)	(3 Points)

You weigh less than the amount in the left column (0 points)

Adapted from Bang et al., Ann Intern Med 151:775-783, 2009.
Original algorithm was validated without gestational diabetes as part of the model.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, American Indians, and Asian Americans and Pacific Islanders.

Higher body weights increase diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weights than the rest of the general public (about 15 pounds lower).

For more information, visit us at diabetes.org or call 1-800-DIABETES (1-800-342-2383)

Lower Your Risk

The good news is that you can manage your risk for type 2 diabetes. Small steps make a big difference and can help you live a longer, healthier life.

If you are at high risk, your first step is to see your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (1-800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Visit us on Facebook
Facebook.com/AmericanDiabetesAssociation

Figure 2.1—ADA risk test.

Prediabetes diagnostic criteria

FPG 100–125 mg/dL

(Impaired Fasting Glucose: IFG)

OR

2-h plasma glucose 140–199 mg/dL

(Impaired Glucose Tolerance: IGT)

OR

A1C 5.7–6.4%

Prediabetes – recommendations

- FPG, 2-h PG after 75-g OGTT, and A1C, are **equally appropriate** for prediabetes testing.
- In patients with prediabetes, identify and, if appropriate**, treat other CVD risk factors**.
- Consider prediabetes testing in **overweight/obese children** and adolescents with 2 or more additional diabetes risk factors.

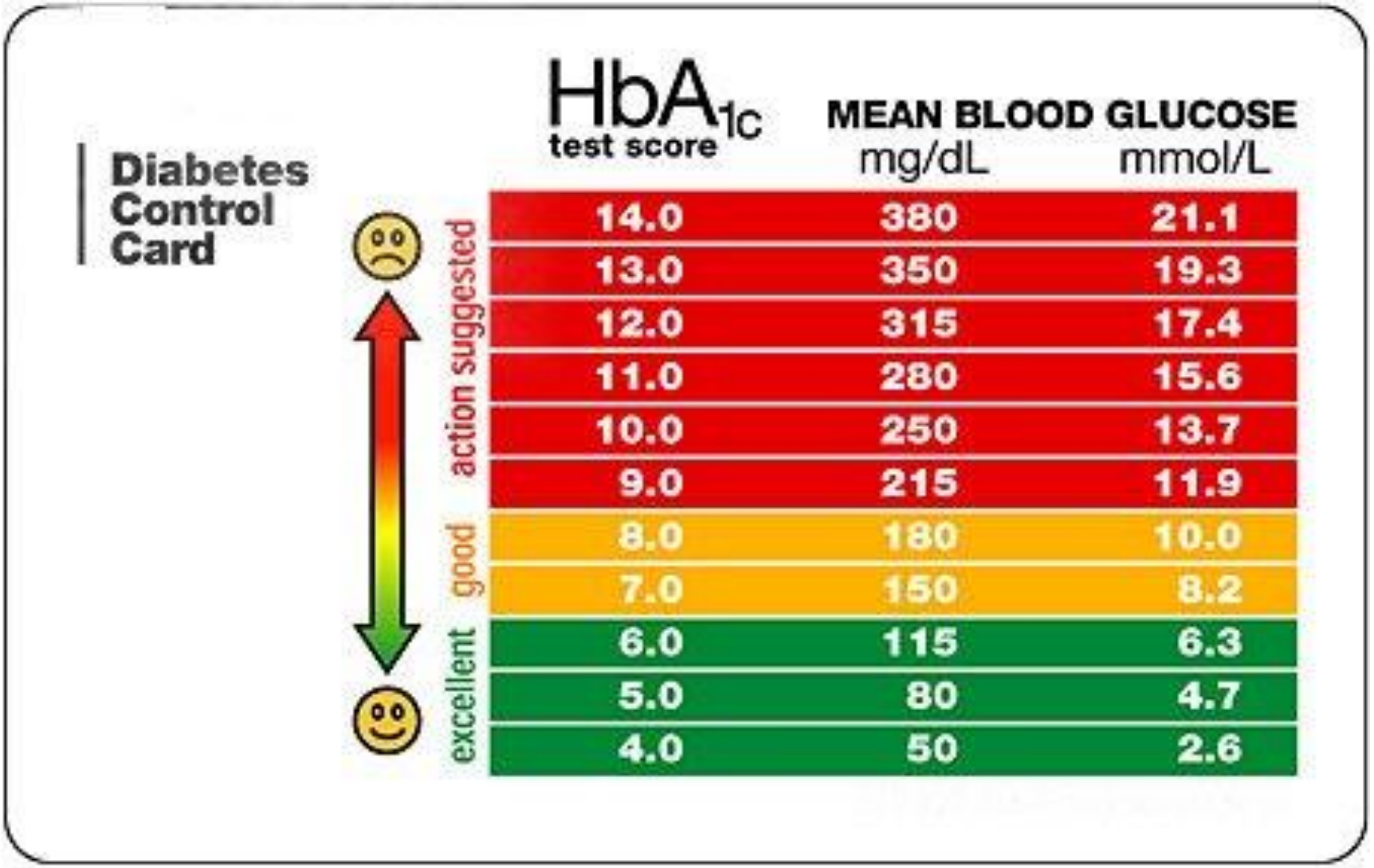
A close look at: Haemoglobin A_{1c} (HbA_{1c}) (1)

- The attachment of glucose non-enzymatically to haemoglobin forms HbA1C.
- Life span of red blood cell (RBC) = 120 days
- Levels of HbA_{1c} reflects **average glycaemic control** over the previous 6 - 8 weeks
- Gold-standard measurement of chronic glycaemia.
- Used as a tool for monitoring the control of DM.

HbA_{1c} (2)

- Test at diagnosis for baseline then every 3 months whilst stabilising.
- When stabilised test 6 monthly (ideally), and at least annually.
- Formerly reported as % of total blood haemoglobin
- Reference range: 4.5 - 6.2 %

Hb A_{1c} (3)


Diabetes Control Card
HbA1c test score
MEAN BLOOD GLUCOSE
mg/dL
mmol/L
action suggested
good
excellent
14.0 380 21.1
13.0 350 19.3
12.0 315 17.4
11.0 280 15.6
10.0 250 13.7
9.0 215 11.9
8.0 180 10.0
7.0 150 8.2
6.0 115 6.3
5.0 80 4.7
4.0 50 2.6

Hb A_{1c} (4)

Not appropriate for diagnosis of diabetes in:

- ALL children and young people
- Any age suspected of having **Type 1 DM**
- Patients with diabetes symptoms < 2 months
- Patients at high risk who are critically ill
- Patients on medication that may cause rapid glucose rise e.g. steroids, antipsychotics

Hb A_{1c} (4) Cont.

Not appropriate for diagnosis of diabetes in:

- Acute pancreatic damage / surgery.
- In pregnancy
- Presence of genetic, haematologic and illness-related factors that influence HbA1c and its measurement

Thank you