DIABETES MELLITUS

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Definition

- Diabetes is a Chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys and nerves.

Highlights

2021 International Diabetes Federation IDF's estimates show that:

1 in 10

Adults (20-79 years) has diabetes
537 million people

1 in 18

Adults (20-79 years) has impaired fasting glucose
319 million people

3 in 4

People with diabetes live in low and middle-income countries

1 in 2

Adults is undiagnosed
240 million people

1 in 6

Live births (21 million) affected by hyperglycaemia in pregnancy, 80% have mothers with GDM

11.5%

Of global health expenditure spent on diabetes (USD 966 billion)

1 in 9

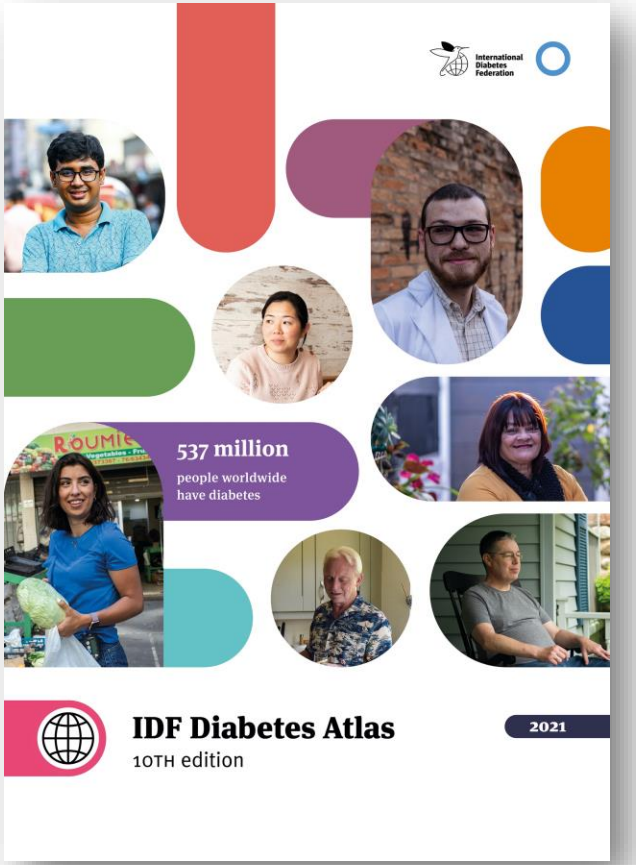
Adults (20-79 years) has impaired glucose tolerance
541 million people

1.2 million

Children and adolescents below 20 years have type 1 diabetes

6.7 million

Deaths attributed to diabetes



- In 2021, the IDF 10 Edition of the Atlas estimates that 1/10 people aged 20-79 have diabetes.
- This equates to **537 million** people in the world
- By 2045, this number will increase to **784 million**
- Prevalence of Diabetes in Jordan **14.8 %.**

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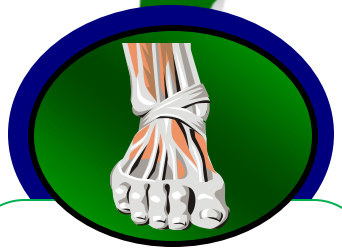
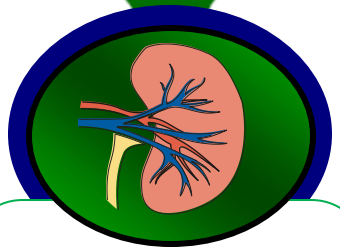
Impact of Diabetes Mellitus

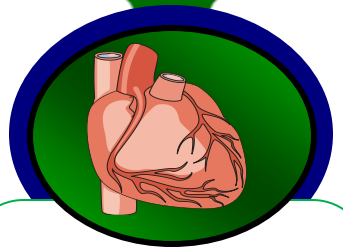
Diabetes



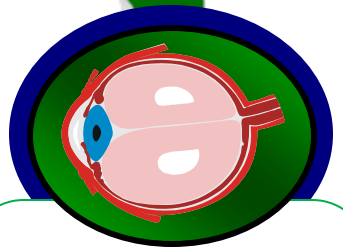
The leading cause of nontraumatic lower extremity amputations



The leading cause of new cases of end stage renal disease

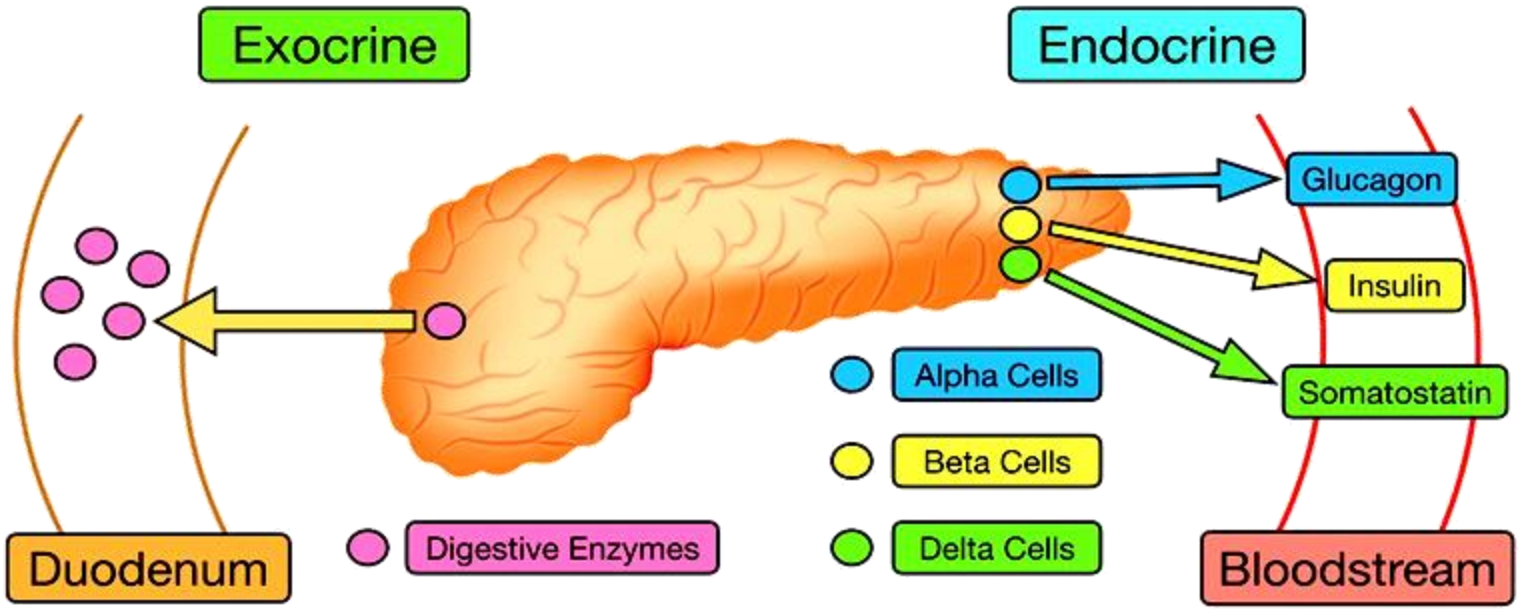


A 2- to 4-fold increase in cardio-vascular mortality



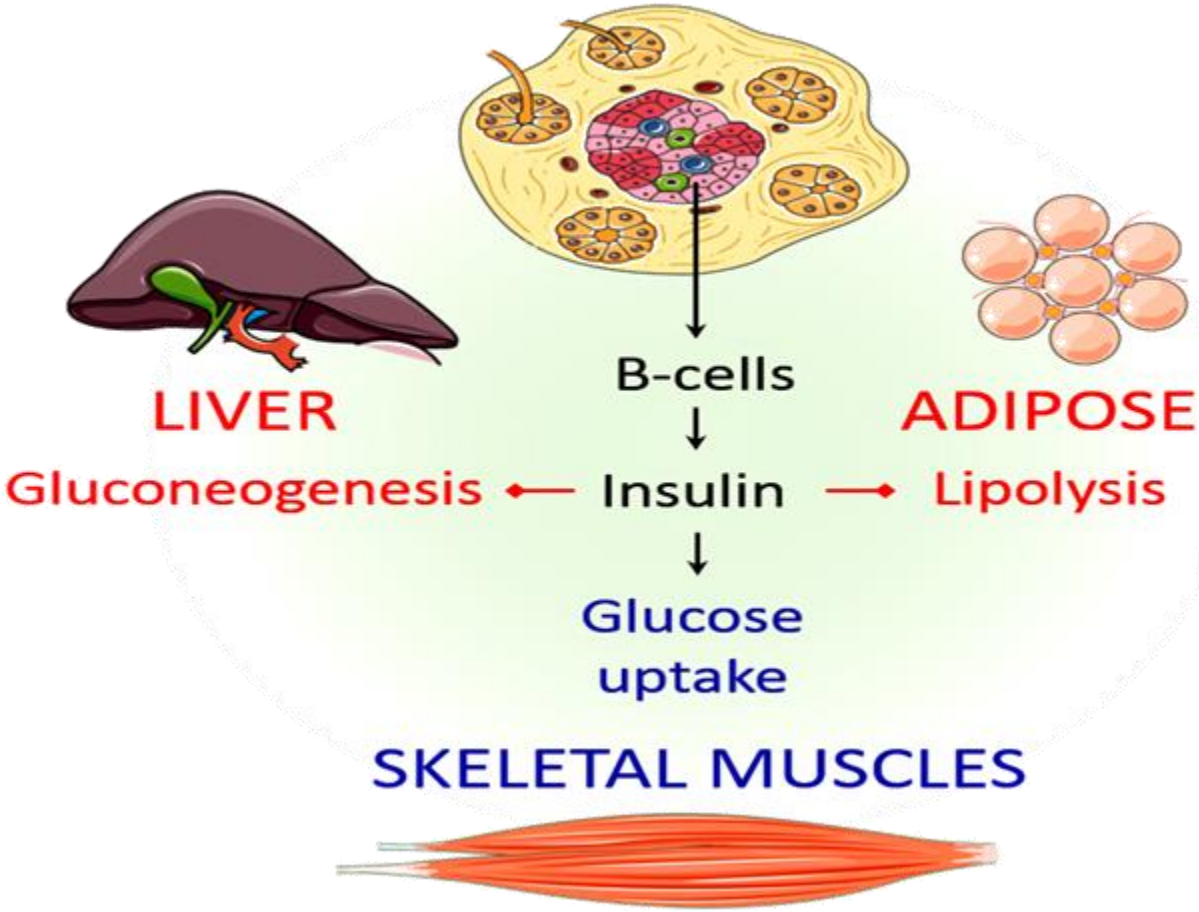
The leading cause of new cases of blindness in working-aged adults

Function of the Pancreas

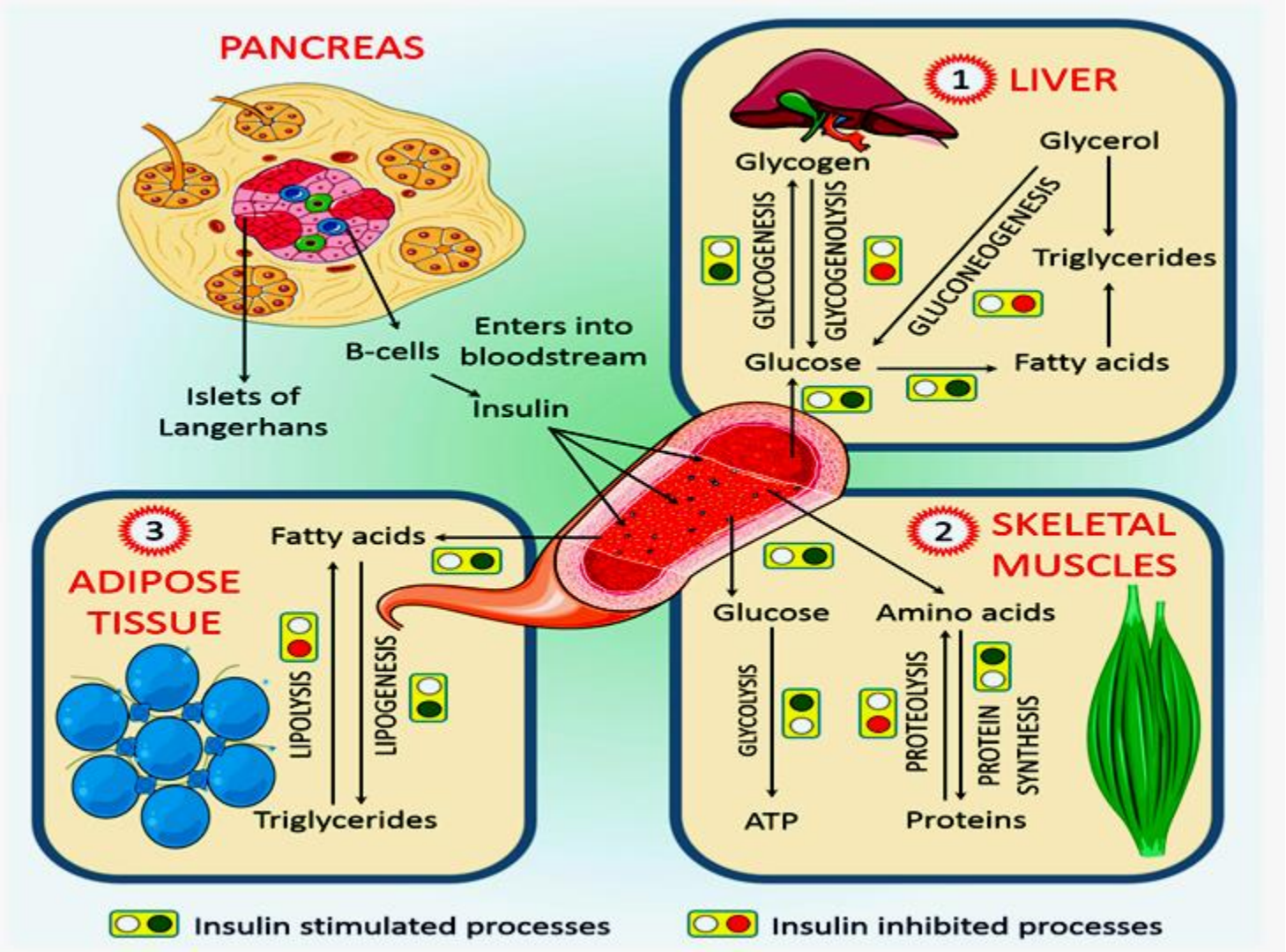


Digestive (exocrine) and hormone (endocrine) functions of the pancreas including glucagon (alpha cells), insulin (beta cells), and somatostatin (delta cells) release

Normal Insulin Physiology



Graphical illustration



Major physiological roles of insulin in the liver, adipose tissue, and skeletal muscles.

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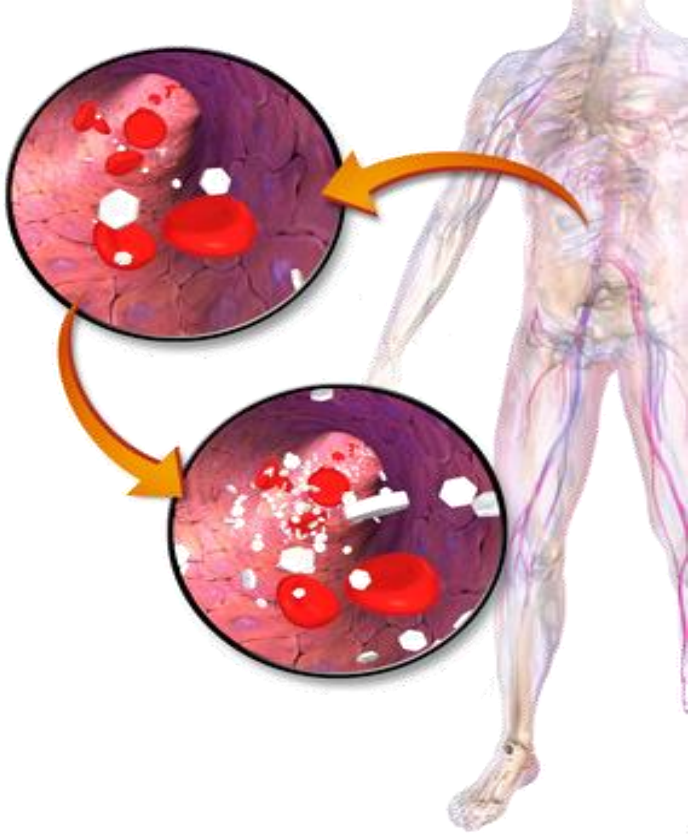
The classical symptoms of hyperglycemia

- Polyuria
- Polydipsia
- Nocturia
- Fatigue
- Blurred vision
- non intentional weight loss
- DKA may be the initial presentation in approximately 25 percent of adults with newly diagnosed type 1 diabetes



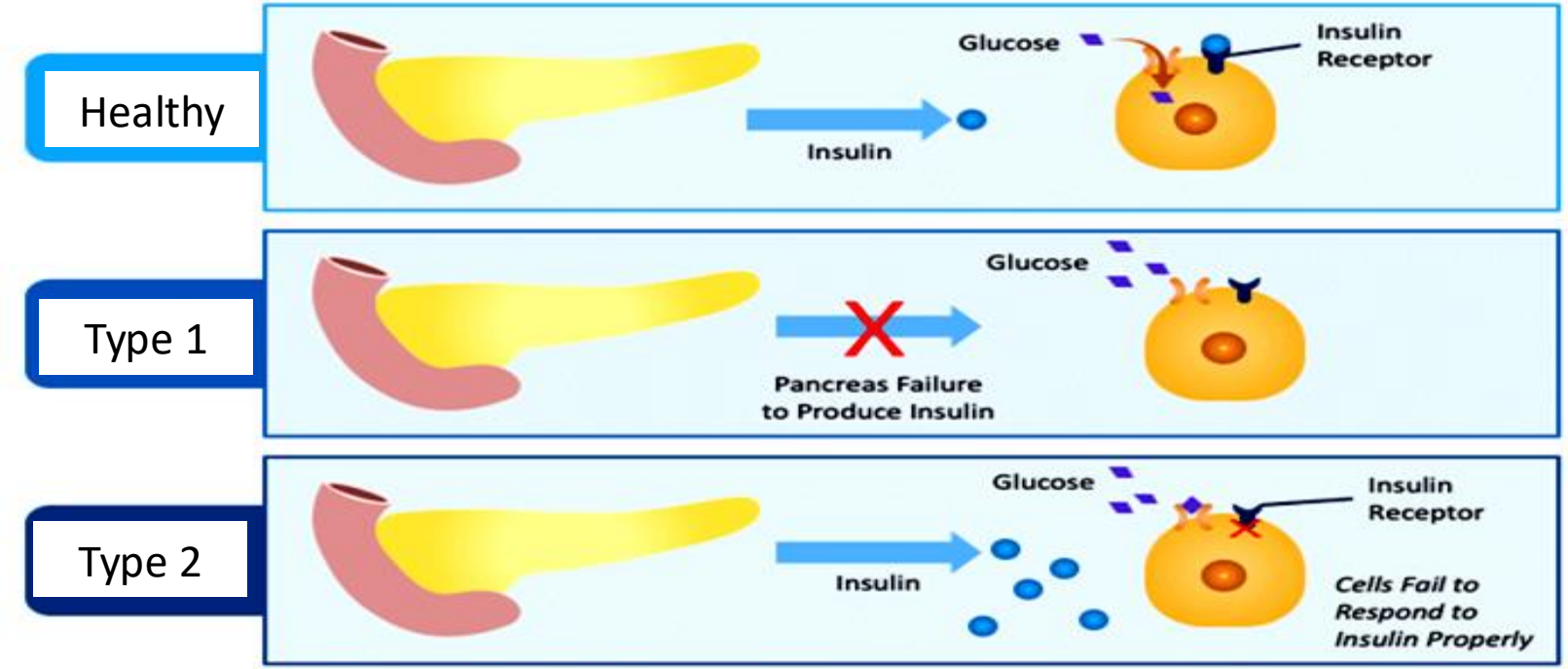
White hexagons in the image represent glucose molecules, which are increased in the lower image.

Classification of Diabetes

Diabetes can be classified into the following general categories:

1. **Type 1 diabetes** (due to autoimmune ß-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
2. **Type 2 diabetes** (due to a non-autoimmune progressive loss of adequate ß-cell insulin secretion frequently on the background of insulin resistance and metabolic syndrome)
3. **Specific types of diabetes due to other causes**, e.g., **monogenic diabetes syndromes** (such as neonatal diabetes and maturity-onset diabetes of the young), **diseases of the pancreas** (such as cystic fibrosis and pancreatitis), and **drug- or chemical-induced diabetes** (such as with glucocorticoid use)
4. **Gestational diabetes mellitus** (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

DIABETES MELLITUS



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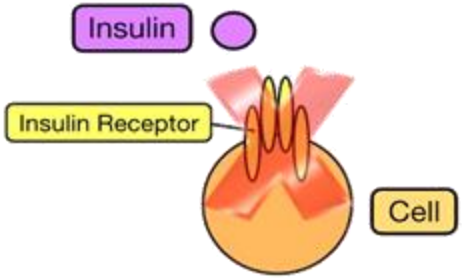
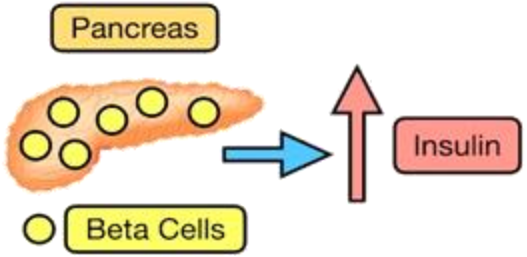
Type 2 Diabetes Mellitus

Pathophysiology

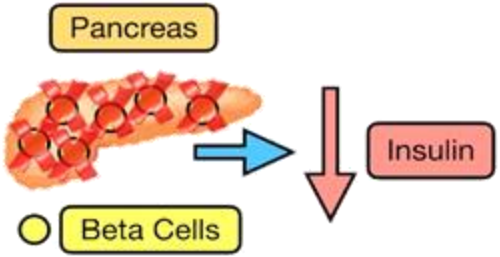
1. Insulin receptors on cell surfaces become resistant to insulin



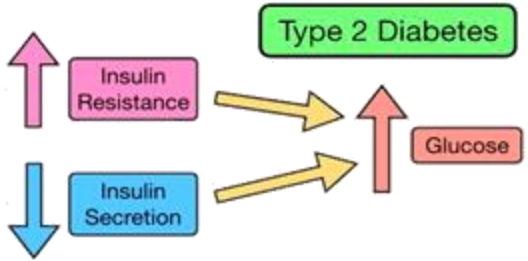
2. There is a compensatory increase in insulin production and secretion



3. This leads to accelerated beta cell changes, damage, and decreased insulin secretion



4. The insulin resistance and inadequate insulin secretion leads to type 2 diabetes



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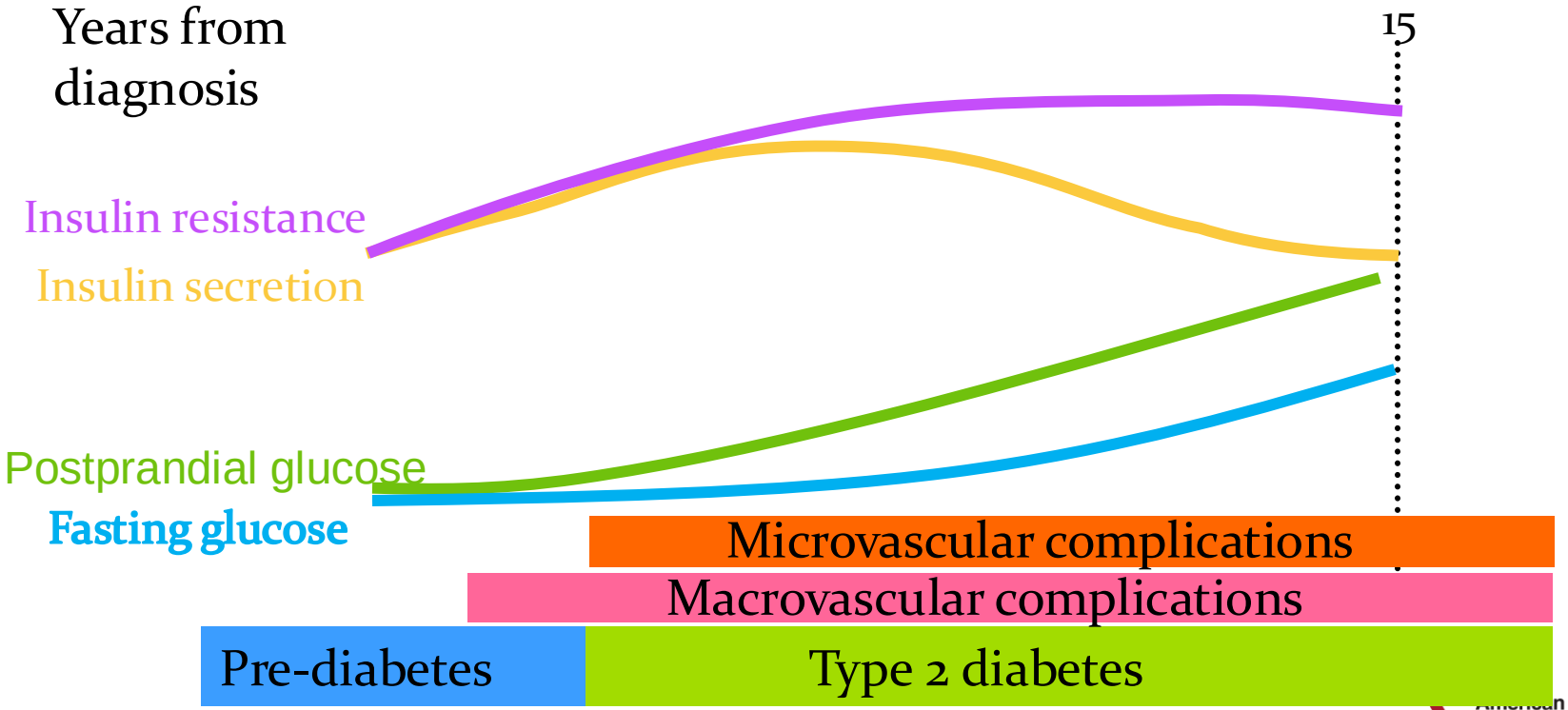
Natural History of DM 2



Comparison of type 1 and 2 diabetes		
Feature	**Type 1 diabetes**	**Type 2 diabetes**
Onset	Sudden	Gradual
Age at onset	Any age (mostly young)	Mostly in adults
Body habitus	Thin or normal	Often obese
Ketoacidosis	Common	Rare
Autoantibodies	Usually present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased
Concordance in identical twins	50%	90%
Prevalence	Less prevalent	More prevalent - 90 to 95% of U.S. diabetics

Autoimmune Diseases

People with type 1 diabetes should be screened for autoimmune thyroid disease soon after diagnosis and periodically thereafter.

Adults with type 1 diabetes should be screened for celiac disease in the presence of gastrointestinal symptoms, signs, laboratory manifestations, or clinical suspicion suggestive of celiac disease.

Monogenic Diabetes Syndromes

Table 2.6—Most common causes of monogenic diabetes (171)

	Gene	Inheritance	Clinical features
MODY	*HNF1A*	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
	GCK	AD	GCK-MODY: higher glucose threshold (set point) for glucose-stimulated insulin secretion, causing stable, nonprogressive elevated fasting blood glucose; typically, does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
Neonatal diabetes	*KCNJ11*	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (*PLAGL1, HYMA1*)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication, or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	EIF2B1	AD	Permanent diabetes: can be associated with fluctuating liver function (172)
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test; UPD6, uniparental disomy of chromosome 6; 2-h PG, 2-h plasma glucose.

The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:

- Diabetes diagnosed within the first 6 months of life
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, no obesity, lacking other metabolic features, especially with strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), stable A1C between 5.6% and 7.6% (between 38 and 60 mmol/mol), especially if no obesity

Diagnosis of Diabetes:

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Gestational Diabetes Mellitus

Table 2.7—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Prediabetes

Table 2.5—Criteria defining prediabetes*
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Prediabetes and Type 2 Diabetes screening

*Testing for prediabetes and/or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI ≥25 kg/m2) who have one or more risk factors .

*For all people, screening should begin at age 35 years.

A1C (continued)

In conditions associated with an altered relationship between A1C and glycemia, only plasma blood glucose criteria should be used to diagnose diabetes.

CASE 1

- MUSTAFA 45 yrs old male , presented with serum glucose reading of 220 mg/dl 1 hour after eating mansaf and konafah , he reports no symptoms , how would you advise this gentleman ??
- A. he has diabetes
- B. he has impaired glucose tolerance
- C he needs more testing before making a diagnosis of diabetes
- D. his reading is normal after big meal

Case 1

- Two weeks later mustafa came to clinic ,labs results : fasting glucose 120 , hba1c 5.9 what would you tell him regarding his concerns about diabetes ??
- A he has diabetes and should start metformin
- B his results within normal range
- C he should do further labs to make diagnosis
- D he has prediabetes and should start life style modification

CASE 2

- 22 old male pt , previously healthy , presented with new onset unintentional weigh loss , polyurea , he had random serum glucose of 350 mg/dl , on P/E he had stable vital sings , BMI 20 , otherwise unreamrkable physical examination , what is the best next step ???
- A, advise he has type 2 diabetes , start metformin and solfonylurea
- B.Admit pt and start insulin drip
- C.Check serum c peptide , anti GAD , anti insulin and anti isle cell antibodies
- D.Pancreas ct

CASE 3

- A 33-year-old w male attends his GP with a eight month history of , lethargy and polydipsia., his mother has diabetes that is diagnosed at age of 45 , 290,his bmi 38 , What is the most likely diagnosis?

A.Type 2 diabetes mellitus

B.Type 1 diabetes mellitus

C.Latent Autoimmune Diabetes of Adulthood

D.Maturity Onset Diabetes of the Young

CASE 4

- An 18-year-old man presents to the clinic as he incidently found that his fasting blood sugar around 140 on repeated occasions . His father and grandfather were diagnosed with type 1 diabetes at the beginning of their 20 s and take a basal-bolus insulin regimen. He is slim with a body mass index of 20 kg/m2 , he reports no symptoms
- **Which of the following is the most likely diagnosis?**

A.Latent autoimmune diabetes of adults (LADA)

B.Maturity onset diabetes of the young (MODY)

C.Type 1 diabetes

D.Type 2 diabetes

Estimated Average Glucose

Table 6.1—Estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (13,14). Adapted from Nathan et al. (13).

Glycemic Goals

An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate

Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits.

Glycemic targets

Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*#
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. #CGM may be used to assess glycemic target as noted in Recommendation 6.5b and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per **Fig. 6.2**). †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in people with diabetes.

Pharmacologic Therapy for Adults With Type 1 Diabetes

individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion

Pharmacologic Therapy for Adults With Type 2 Diabetes

Healthy lifestyle behaviors, diabetes self-management education and support
Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals.

A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences

Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300mg/dL [16.7mmol/L]) .

Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment

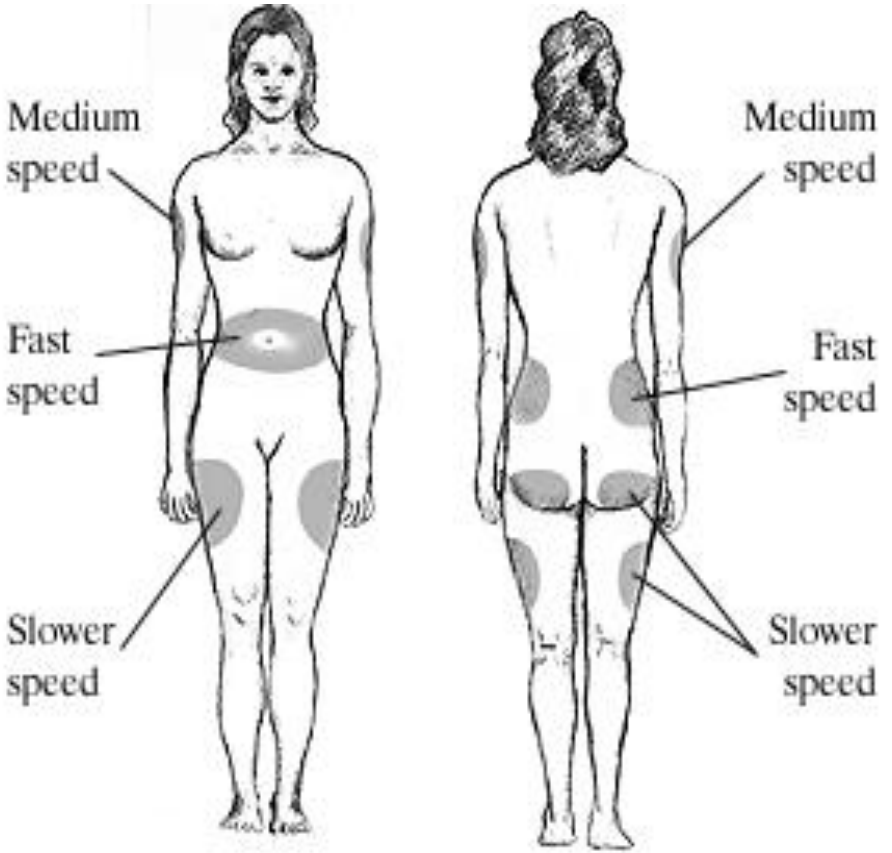
Diabetes Medications

- Oral diabetes medications are routinely used before insulin for the treatment of type 2 diabetes.
- Examples of oral diabetes medications include:
- **Biguanides** (metformin)
- **Thiazolidinediones** (pioglitazone, rosiglitazone)
- **Sulfonylureas** (glimepiride, glyburide, glipizide)
- **SGLT-2 Inhibitors** (dapagliflozin, canagliflozin, empagliflozin)
- **DPP-4 Inhibitors** (alogliptin, linagliptin, saxagliptin, sitagliptin)
- **GLP-1 Mimetics/Agonists** (exenatide, liraglutide)
- **Meglitinides/Glinides** (nateglinide, repaglinide)
    - Similar to sulfonylureas but act more quickly
- **Alpha-Glucosidase Inhibitors** (acarbose, miglitol)

Metformin	• Good glucose-lowering effect • Oral route • Low cost • No hypoglycemia	• Risk of lactic acidosis in patients with impaired kidney function, heart failure, hypoxemia, alcoholism, cirrhosis, contrast exposure, sepsis, and shock • Gastrointestinal side effects
Insulin secretagogues: • Sulfonylureas: glyburide, glibenclamide, glipizide, gliclazide, and glimepiride • Glinides: repaglinide and nateglinide	• Good glucose-lowering effect • Low cost • Oral route	• Risk of hypoglycemia • Significant drug-to-drug interactions • Risk of cardiovascular events
Thiazolidinediones: pioglitazone	• Good glucose-lowering effect • Oral route • No hypoglycemia	• Slow onset of action • Contraindicated in patients with heart failure, hemodynamic instability, and hepatic dysfunction
Sodium glucose co-transporter 2 inhibitors: canaglifozin and dapaglifozin	• Modest glucose-lowering effect • Oral route • No hypoglycemia	• Increased risk of urinary and genital tract infections • Risk of dehydration
α-Glucosidase inhibitors: acarbose and miglitol	• Mild glucose-lowering effect • Oral route • No hypoglycemia	• Gastrointestinal side effects • Contraindicated in patients with inflammatory bowel disease, partial bowel obstruction, or severe renal or hepatic disease
Glucagon-like peptide-1 receptor agonists: exenatide and liraglutide	• Good glucose-lowering effect • No hypoglycemia • Reduction of insulin requirement	• Subcutaneous injections • Gastrointestinal side effects • Decreased appetite and weight loss • Concern regarding acute pancreatitis
Dipeptidyl peptidase-4 inhibitors: sitagliptin, saxaglitpin, linagliptin, and alogliptin	• Moderate glucose-lowering effect • Oral route • No hypoglycemia	• Concern regarding acute pancreatitis

Pharmacologic Therapy

- **Insulin Therapy and Insulin Preparations**
- **Insulin preparations vary according to three main characteristics:**
  - Time course of action
  - Species (source)
  - Manufacturer



Main types of insulin preparations

Type	Onset	Peak	Duration	Comments
Rapid-acting insulin analogue	5-15 min	30-60 min	2-5 hr	Can be injected at the start of a meal
Short-acting (soluble/regular insulin)	30 min	1-3 hr	4-8 hr	Usually injected 15-30 minutes before a meal. Clear solution
Intermediate or long-acting insulin (isophane or zinc insulin)	1-2 hr (NPH, Lente) 2-3 hr (Ultralente)	4-8 hr 4-8 hr	8-12 hr (NPH) 8-24 hr (Ultralente)	Used to control glucose levels between meals. May be combined with short-acting insulin
Long-acting insulin analogue	30-60 min	No peak	16-24 hr	Usually taken once daily

CASE 5

- a 49-year-old HGV driver, uses metformin, glimperide and linagliptin for his type 2 diabetes., he experiences frequent symptoms of hypoglycaemia.
- **Would you make any changes to his medication?**

CASE 6

- 45 YRS old male pt , known to have DM Type 2 , HF with of 45% , came to clinic as regular follow up visit ,Hba1c 7.6, protien creatinie by spot urine 380 mg/day , BMI 25 , He is on metformin 850 1*3 , concor 5 1*1 , angiotic 1*1 , atorvastatin 20 1*1

What medication should be added next ???

- A.GLIMPERIDE (SOLFONYLUREA)
- B.PIOGLITASONE
- C.EMPAGLIFLOZIN (SGLT2 INHIBITOR)
- D. MEGLITINIDES

Acute Complications of Diabetes

There are three major acute complications of diabetes related to short-term imbalances in blood glucose levels:

Hypoglycemia

Diabetic ketoacidosis (DKA)

Hyperglycemic hyperosmolar nonketotic syndrome (HHNS)

DKA vs HHS

Diabetic ketoacidosis		Hyperosmolar hyperglycaemic state
More common in type 1 diabetes mellitus	**Association**	More common in type 2 diabetes mellitus
Relatively lower	**Mortality rate**	Relatively higher
Abdominal pain, polyuria, polydipsia, dehydration, Kussmaul breathing, acetone-smelling (sweet) breath	**Presentation**	Fatigue, altered level of consciousness, hyperviscosity (increases risk for MI and stroke), hypotension
Hours	**Onset**	Days
1. Glucose >11.1mmol/L 2. pH <7.3 or bicarbonate <15mmol/L 3. Ketone >3mmol/L or urine ketone ++ on dipstick	**Diagnostic criteria**	1. Hypovolaemia 2. Marked hyperglycaemia (>30mmol/L) without significant ketonuria or acidosis 3. Significantly raised serum osmolality (>320mosmol/kg)
• Fluid replacement • IV insulin (0.1unit/kg/h) • Potassium replacement	**Management**	• Normalised the osmolality gradually • Replace fluid and electrolyte • No insulin unless significant ketonuria or acidosis
Thromboembolism, gastric stasis, arrythmias secondary to hyper/hypokalaemia, ARDS, AKI Iatrogenic (due to incorrect fluid therapy): cerebral oedema, hypokalemia, hypoglycaemia	**Complication**	MI, stroke, peripheral arterial thrombosis, Rare: seizure, cerebral oedema, central pontine myelinolysis

CASE 7

13 yrs old male pt , known to have type 1 diabetes

Presented to ER for the third time this month c/o epigastric pain , vomotting , polyurea , and polydypsia ,you find that he has acetone breath , BG 450 , on the previous two visits he was admitted to critical care unit

History ????

Labs ???

Case 7

- This pt was suspected to have DKA ,lab results was delayed , ER doctor started insulin infusion and normal saline , two hours later pt started to have muscle cramps , and irregular heart beats , shortly after the pt starts to deteriorate ???????

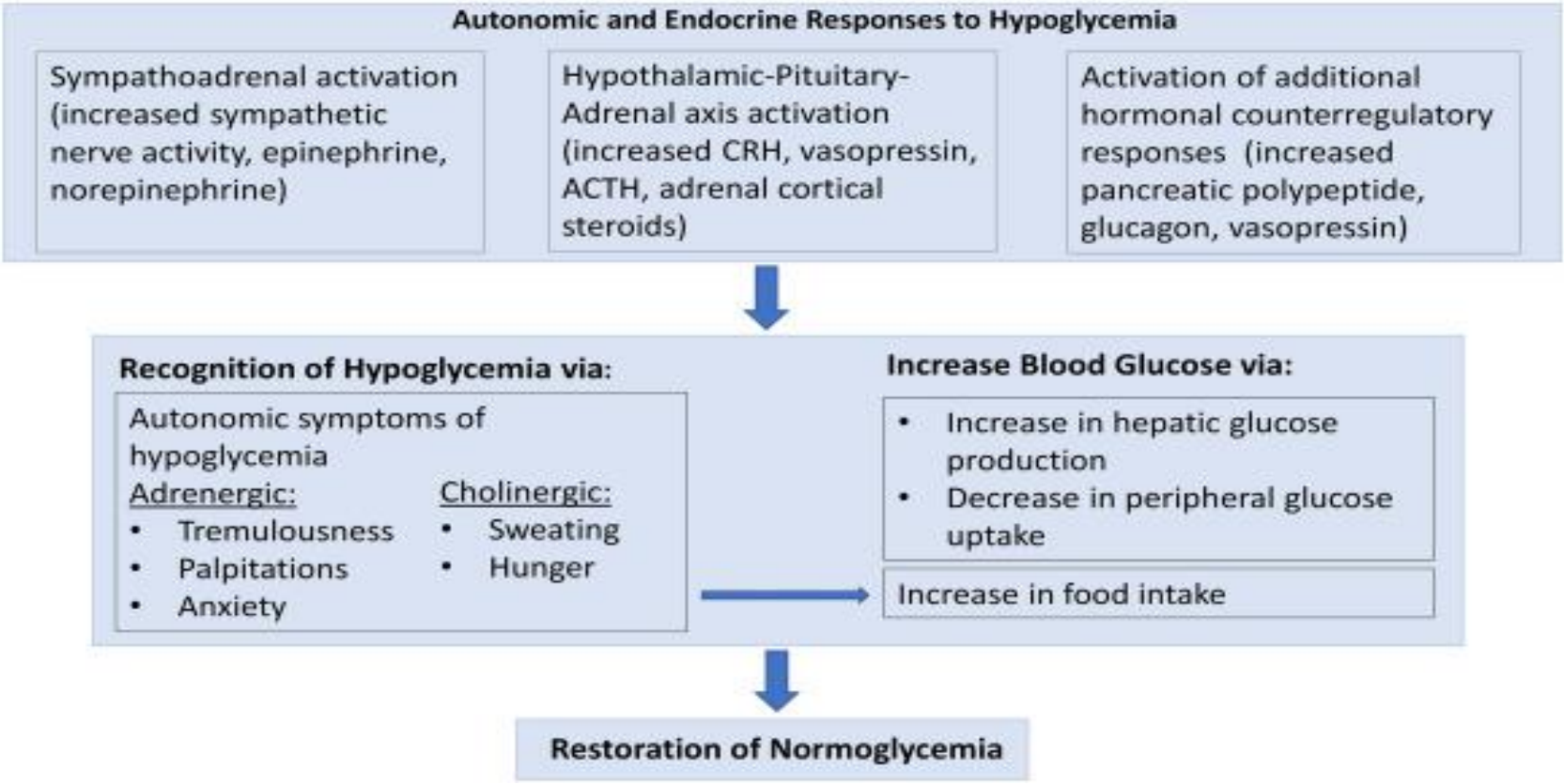
Hypoglycemia

Table 6.4—Classification of hypoglycemia

	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia

Reprinted from Agiostratidou et al. (74).

ADAPTIVE RESPONSES TO HYPOGLYCEMIC STRESS



Hypoglycemia Unawareness

- The defense mechanisms may be impaired by repeated hypoglycemia events, physical exercise, and sleep thus contributing to the development of hypoglycemia.

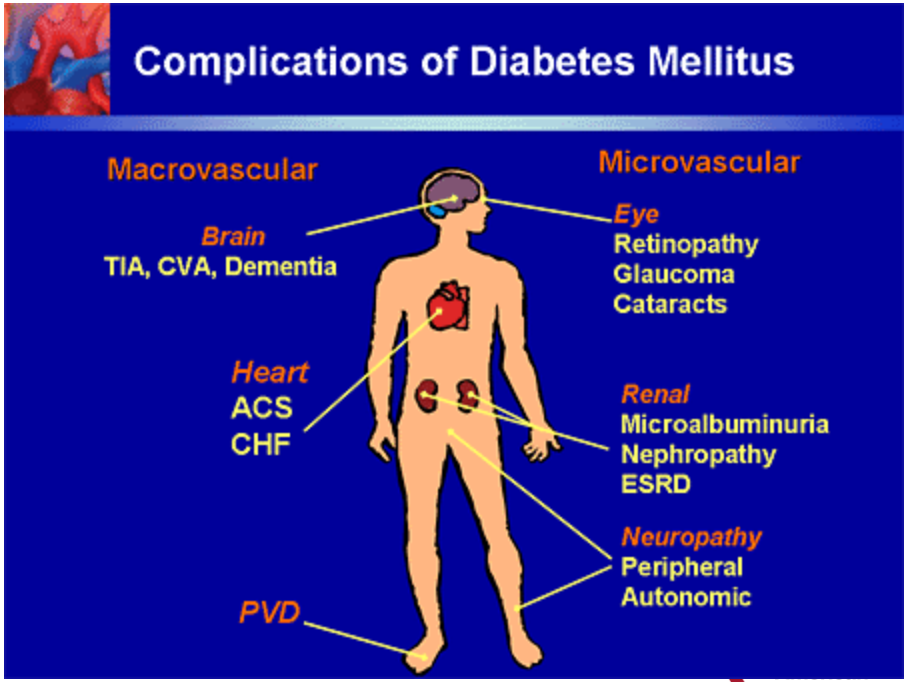
- Patients with symptomatic hypoglycemia should ingest 15 to 20 grams of fast-acting carbohydrate
- Patients should be instructed to retest after 15 minutes. If the glucose remains ≤70 mg/dL (3.9 mmol/L), repeat treatment may be necessary. This can be followed by long-acting carbohydrate (a meal or a snack) to prevent recurrent symptoms.

- **Severe** — Severe hypoglycemia requires the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
- **With IV access** — Patients already in the hospital can usually be treated quickly by giving 25 g of 50 percent glucose (dextrose) intravenously (IV).
- **Without IV access:Glucagon** (subcutaneous, intramuscular, or nasal)

Long-Term Complications of Diabetes

➢The general categories of long-term diabetic complications are:

- Macro vascular
- Micro vascular
- Neuropathy



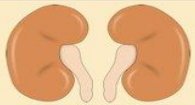
Type 2 Diabetes Mellitus

Complications

Microvascular Complications

High glucose can damage small blood vessels leading to:

Diabetic Retinopathy



Diabetic Nephropathy

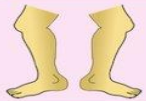
Diabetic Neuropathy

Macrovascular Complications

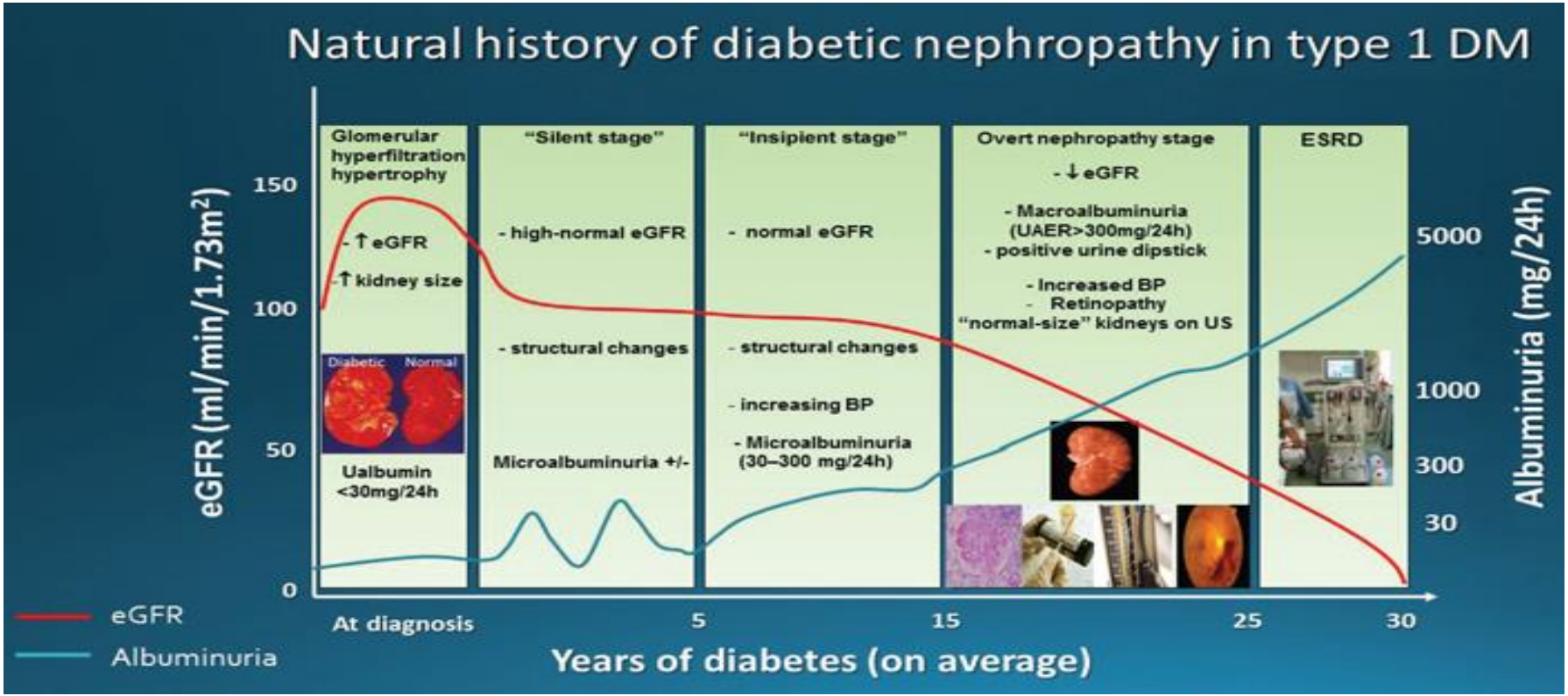
High glucose can cause plaque formation leading to:

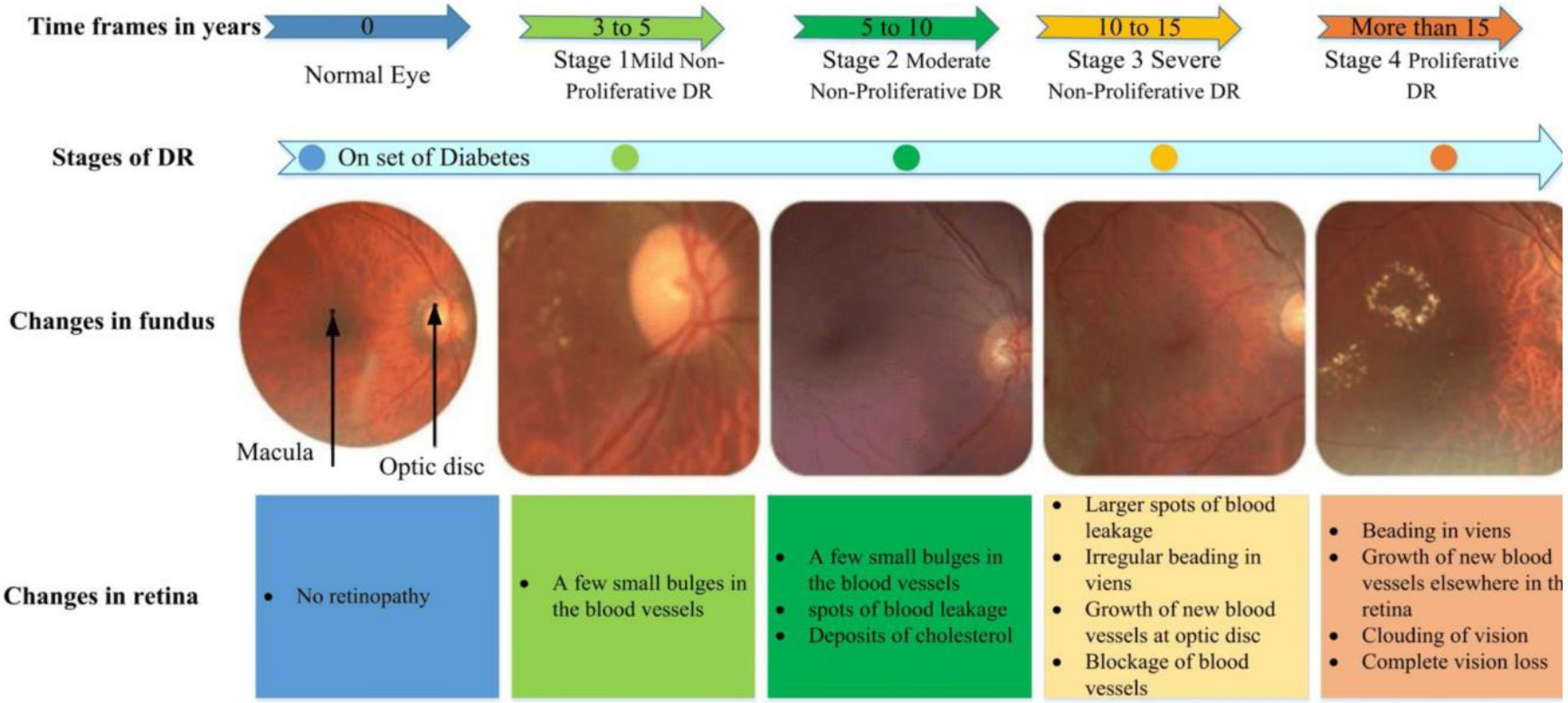
Cardiovascular Disease

Heart Attack & Stroke



Peripheral Vascular Disease





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