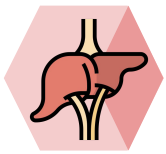
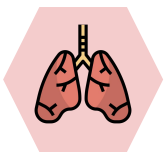
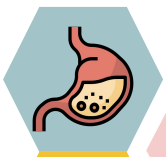
Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Diabetes Mellitus


Objectives :

- Epidemiology DM , T1DM & T2DM.
- Molecular mechanisms of Insulin signaling.
- Molecular Mechanism in Diabetes.
- Main pathology of Type 1 DM & Histopathology. Main pathology of T2DM.
- Predisposing factors for T1DM & T2DM.
- The course of disease development T1DM & T2DM.
- Clinical Presentation of T1DM & T2DM.
- Diagnosis of Diabetes.

Worked on this lecture:

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Resources :

Doctors Slides & notes: Dr Shadin Al Katari
Books: Kumar, Step up, Davidson
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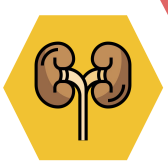
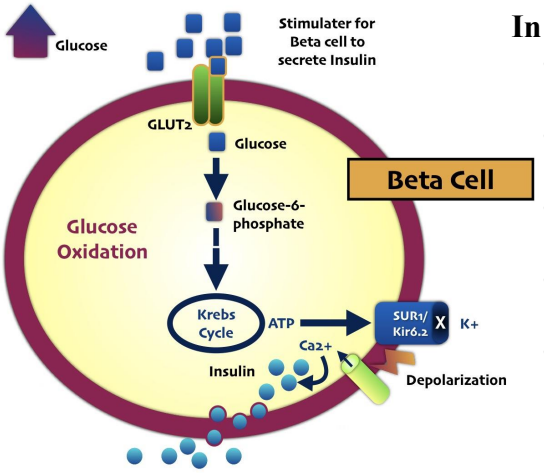



Basic mechanism of glucose control:

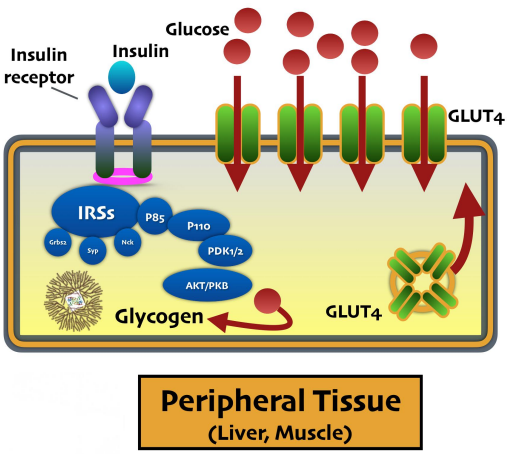
Doctor said you need to understand the normal physiology

- Blood glucose is tightly regulated and maintained within a narrow range by **insulin & glucagon**. This is essential for ensuring a continuous supply of glucose to the central nervous system.
- **Insulin**: the primary regulator of glucose metabolism and storage is secreted from **pancreatic β cells** into the portal circulation in response to a rise in blood glucose.
- After ingestion of a meal containing carbohydrate, normal blood glucose levels are maintained by:
  - Suppression of hepatic glucose production.
  - Stimulation of hepatic glucose uptake.
  - Stimulation of glucose uptake by peripheral tissues.
- **Incretins** are amino acids and hormones such as **glucagon-like peptide 1 (GLP-1)** and **gastrointestinal peptide (GIP),** released from the small intestines following food intake and can augment (increase) insulin release. As a result, insulin release is greater when glucose is administered by mouth than when the same rise in plasma glucose is achieved by intravenous glucose infusion, a phenomenon termed the **(incretin effect).**



In Beta cells:

- Glucose enters Beta cell (1) through facilitated diffusion mediated by **GLUT2**
- Glucose get phosphorylated by glucokinase and enters Krebs cycle (**Glycolysis**) to produce **ATP**
- ATP **closes Potassium channels** that normally secrets K out
- Potassium increases intracellularly which will cause **Depolarization**
- **Ca channel opens** (Voltage gated channel), Calcium enters the cell leading to the **release of insulin** from its vesicles by exocytosis

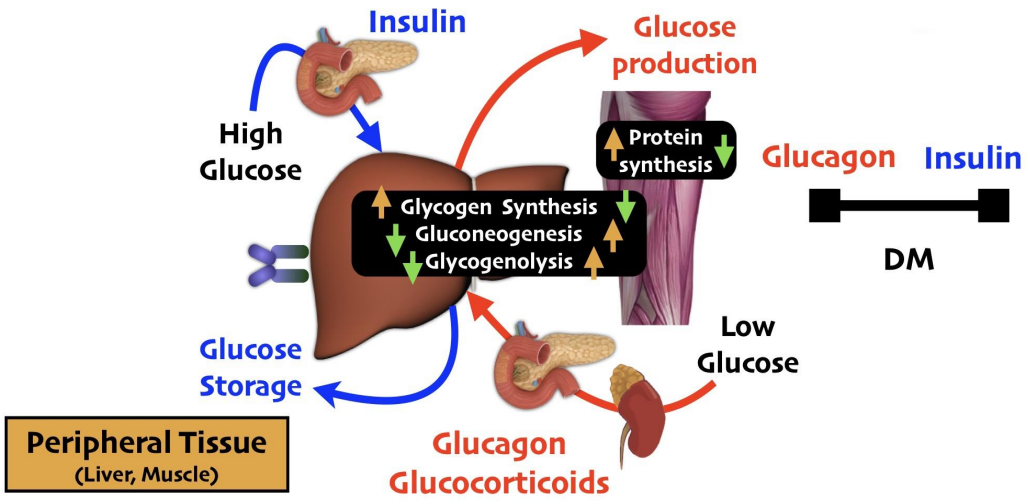


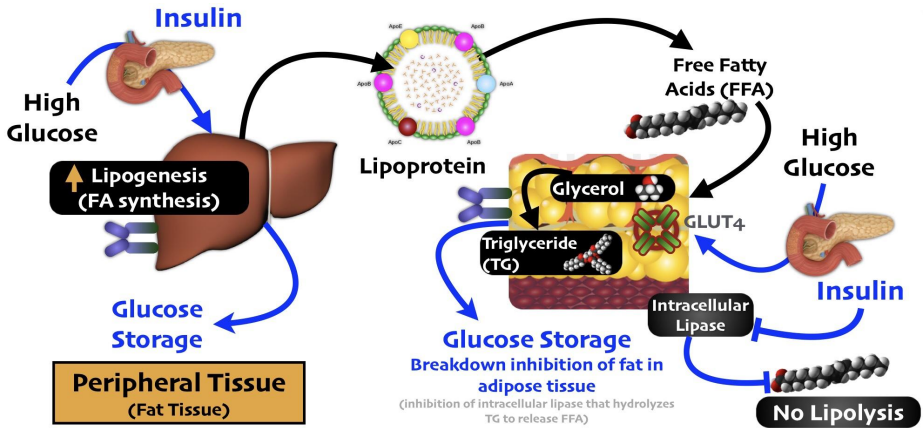
In peripheral cells:

- Insulin & insulin-like growth factor binds to receptor and according to cell needs it activate either one of two pathways :
  - <u>Growth signal</u>
    - Cell proliferation,
    - Tissue development & differentiation
  - <u>Metabolic signal:</u>
    - Regulation of energy metabolism (Glucose)
    - It helps expressing GLUT4 to the cell membrane which facilitate Glucose entrance.
    - Glucose get converted to **glycogen** for storage

Basic mechanism of glucose control Cont.

Understand don't memorize





High glucose:

- ➔ Insulin release from Beta cells
- ➔ Insulin effect on the **liver**
  - ◆ ↑ Glycogen synthesis
  - ◆ ↓ Gluconeogenesis
  - ◆ ↓ Glycogenolysis
  - ◆ ↑ lipogenesis (FA synthesis)
  - ◆ ↑ Lipoprotein synthesis
- ➔ Insulin effect on the muscles
  - ◆ ↑ protein synthesis
- ➔ Insulin effect on the Adipose tissue
  - ◆ Inhibition of intracellular lipase > No lipolysis
  - ◆ ↑ TGs deposition

Low glucose:

- ➔ Release of Glucagon (Counter regulatory hormone that oppose the action Insulin)
- ➔ Their effect on the liver:
  - ◆ ↓ Glycogen synthesis
  - ◆ ↑ Gluconeogenesis
  - ◆ ↑ Glycogenolysis
- ➔ Effect on muscles
  - ◆ ↓ protein synthesis
- ➔ Effect on the Adipose tissue
  - ◆ No inhibition of intracellular lipase > ↑ lipolysis > ↑ FFA

- Other Counter regulatory hormones:
  - Glucocorticoids
  - Growth hormone
  - Epinephrine

Diabetes mellitus

General characteristic:

Type I:

- Autoimmune destruction of pancreatic Beta cells. In **genetically susceptible individuals** and triggered by some **environmental factors.** T cell-mediated autoimmune disease
- Characterized by a severe deficiency of insulin.
- Not related to obesity
- Onset is typically in youth, before the age of 20. but can occur in any age (last week the doctor diagnosed a 54 y/o patient)

Type II

- 90% or more of all diabetic patients.
- **Characterized by resistance to the action of insulin** and an **inability to produce sufficient insulin** to overcome this 'insulin resistance'.
- Insulin levels are usually normal to high at first but may diminish over many years of having diabetes.
- **Obesity** plays a major role in insulin resistance. (BMI >30)
- Often goes undiagnosed for many years.
- Risk factors:
    - Obesity, sedentary lifestyle
    - Impaired glucose tolerance/ Impaired fasting glucose
    - Hypertension, Hyperlipidemia
    - Polycystic ovarian syndrome, Metabolic syndrome

Table 20.2 The spectrum of diabetes: a comparison of type 1 and type 2 diabetes mellitus

	Type 1	Type 2
Age	Younger (usually <30)	Older (usually >30)
Weight	Lean	Overweight
Symptom duration	Weeks	Months/years
Higher risk ethnicity	Northern European	Asian, African, Polynesian and American-Indian
Seasonal onset	Yes	No
Heredity	HLA-DR3 or DR4 in >90%	No HLA links
Pathogenesis	Autoimmune disease	No immune disturbance
Ketonuria	Yes	No
Clinical	Insulin deficiency ± ketoacidosis Always need insulin	Partial insulin deficiency initially ± hyperosmolar state Need insulin when beta cells fail over time
Biochemical	C-peptide disappears	C-peptide persists

Pre diabetic

- Impaired glucose tolerance.
- One to five percent annual increase in risk of developing type II diabetes.
- Increased risk for cardiovascular disease.

Difference between a genetic disease and a familial disease

- **Genetic Disease:**
    - A single gene responsible for a pathology.
        - **e.g**. Diabetes Mellitus 1 (HLA-DR3 or DR4)
- **Familial Disease:**
    - A collection of genes (Polygenic) from a previous generation passed to another generation (Hereditary)
        - **e.g**. Diabetes Mellitus 2

DM1 results from genetic + environmental + immune
if you were asked which type is more familial? it will be Type 2 not 1, However both can be familial.

Pathogenesis:

Type I:

Autoimmune: T cell mediated destruction of Beta cells causing insulin deficiency.

- Autoantibodies: are the best predictors of progression to DM type 1.
  - **GADA** (Glutamic acid decarboxylase antibodies). Most sensitive
  - IA2A (Insulinoma-2 Antigen Antibody), ZnT8A (Zinc Transporter 8 Antibody) More specific

Environmental: Factors that act as a trigger for the autoimmune response.

- E.g infection with **mumps** virus, **coxsackie B** virus **Rotavirus** or **EBV.**

Overt Type 1 DM does not appear until about **90% of β-cells are destroyed.**

Type II:

1. **Insulin resistance:**

Obesity plays a major role Especially central obesity

- Increased plasma levels of free fatty acids make muscles more insulin resistant.
- Adipokines
  - ↑Leptin:
    - Normally it suppresses appetite but in obesity it becomes resistance and the body compensate by increasing its levels
  - ↓Adiponectin:
    - Decreased in obesity which causes more insulin resistance
- Hypertrophic adipose tissue
  - ↑ circulating peptides including the cytokines TNF-α and IL-6

2. **Decreased insulin secretion**

- B-cells dysfunction, it becomes desensitized to glucose, leading to decreased insulin secretion.

Clinical Presentation:

- **Polyuria:** Osmotic effect of glucose in renal tubules causing diuresis.
- **Polydipsia:** Physiological response to diuresis to maintain plasma volume.
- **Weight loss** Mainly in type I**:** Due to the loss of anabolic effect of insulin
- **Blurred vision:** Swelling of lens due to osmosis caused by hyperglycemia.
- **Fungal infections.**
- **Numbness, tingling of hands and feet**: Neuropathy.

Type I

- Symptoms develop more quickly over days to weeks.
- Sometimes symptoms appear after an illness. Eg. Respiratory Infection
- Patients often present with acute **diabetic ketoacidosis (DKA)**
  - Polyuria, Polydipsia
  - Abdominal pain ± Nausea, vomiting
  - Dehydration
  - **Fruity breath**
  - Kussmaul breathing “air hunger”
  - Mental changes (**confusion**, coma)

Diagnosis:

Tests:

- **Random Blood Sugar**
  - Sensitive test → good for screening → when negative, rule out the disease.
- **Fasting blood sugar**
  - Specific test → good for diagnosis → when positive, the disease is present.
- **OGTT (oral glucose tolerance test)** Gold standard
  - Sensitive & specific so it is the best confirmatory test. (but it is expensive & time consuming).

Sensitivity & specificity:
A sensitive test for screening, when it is **positive** that means you might have the disease. When it is negative that means for sure you are normal.
A specific test is for diagnosis, when it is **positive** that means the disease is present. When it is negative that means you might be normal.

Screening

- All adults between ages 40 and 70 every 3 years.
- Early screening for those with risk factors.
  - Obesity, family history, history of gestational diabetes.
- Anyone with signs or symptoms of diabetes.

Diagnosis

- **Person with typical hyperglycaemic symptoms:**
  - One abnormal laboratory value is diagnostic
- **Asymptomatic person:**
  - Two values on seperate days are required for diagnosis.

diabetes tests				
Test	SENSITIVITY	SPECIFICITY	Impaired Glucose Tolerance	Diabetes Mellitus
Fasting blood sugar	-	+	110-125 mg/dL (5.5- 6.9 mmol/l)	>= 126 mg/dL (7 mmol/L)
Random Blood Sugar With symptoms	+	-	-	>= 200 mg/dl (11.1 mmol/l)
OGTT	+	+	140-199 mg/dL (8-11 mmol/l)	>= 200 mg/dl (11.1 mmol/l)
Hb1Ac	+	-	5.7 - 6.4%	>=6.5%

Management:

1. Diet & lifestyle modifications:

All patients with diabetes require healthy diet therapy.
Reducing alcohol consumption and stopping smoking.
Weight management and regular exercise is encouraged to reduce cardiovascular risk.

2. Insulin

Insulin is the main treatment and cornerstone of type 1 management.
Type 1 diabetics start out deficient of insulin (the disease actually isn't evident until 90% of functional beta cells are lost) that's why we **start them immediately on insulin.** (unlike type 2)

Method of administration:

- Self-administered by SC injection in abdomen, buttocks, arm,leg.
- Given intravenously or IM for emergency ketoacidosis.

Why not orally?

- The human insulin is a dimer of an A-chain and B-chain,which are linked together by disulfide bonds. if you take orally stomach acid will break it down and inactivate it.

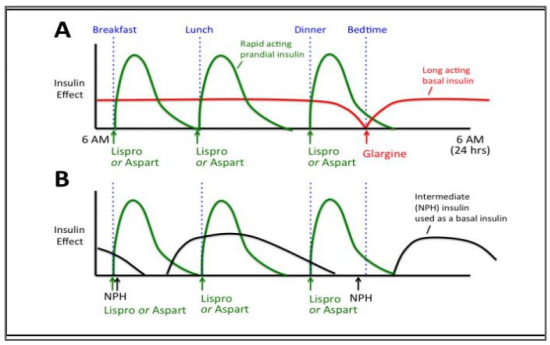
Who needs insulin?

- DM1
- **DM2 if severe persistent hyperglycemia.**
- Atypical presentation.
  - MODY → Mature Onset DM of Young
    - It has 6 types differ in severity
  - LADA → Latent Autoimmune Diabetes in Adult
    - Type 1 in adult
    - Adult presenting with DKA
  - Pancreatic insufficiency or after endocrine disease (Cushing's)

Insulin side effect:

- Hypoglycemia
- Hypersensitivity reactions
- Lipodystrophy at injection site "Alternate site frequently to avoid this issue"
- **Weight gain** (due to anabolic effects of insulin)
- Insulin resistance.
- Hypokalemia "cause insulin causes the K uptake into the cells"

Insulin preparations			
Ultra short acting insulin	Short acting insulin	Intermediate acting insulin	Long acting insulin
-Lispro -Aspart	**-Regular** -Humulin	-NPH -Lente	-Glargine -Detemir



Management Cont.

3. Oral Hypoglycemic drugs:

- **Metformin (**Biguanide**)**
  - Blocks hepatic gluconeogenesis
  - Increases insulin sensitivity
  - Helps in weight loss
  - Not associated with hypoglycemia
  - Contraindicated in those with renal dysfunction because it can accumulate and cause lactic Acidosis
  - Safe in pregnancy. (other oral anti-diabetics are not)

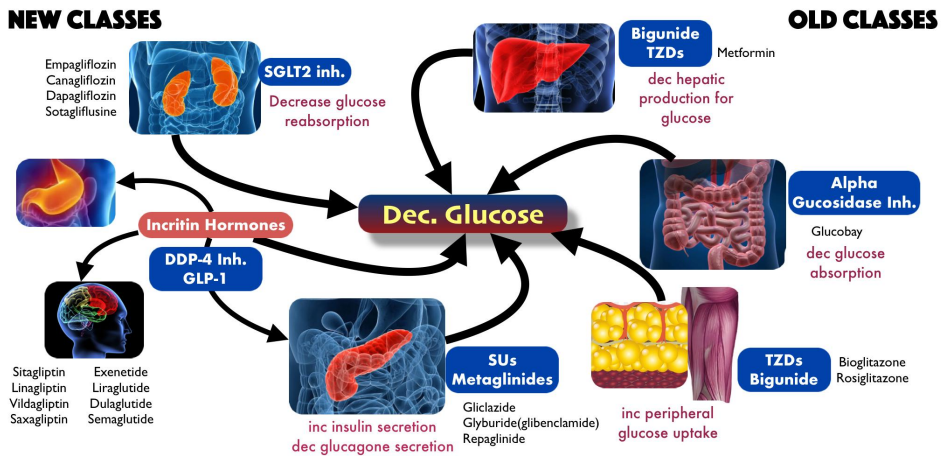
- **Sulfonylureas** (insulin secretagogues)
  - Work in pancreas by increasing insulin secretion.

- **alpha glucosidase Inhibitor.**
  - Decrease glucose absorption from intestine by binding to alpha glucosidase inhibitor.

- **Thiazolidinediones (**TZDs)
  - Bind to and activate peroxisome proliferator-activated receptor-gamma (PPAR-γ)
  - Increase peripheral glucose uptake.
  - Reduce hepatic gluconeogenesis
  - Contraindicated in CHF because they increase fluid overload.

- **Incretin hormones** (DPP-4 inhibitors - GLP-1)
  - DDP4 is enzyme degrade the incretin.
  - MOA for both:
    - Indirectly **increases insulin** production and **decrease glucagon** production.
    - Delay gastric emptying.
    - Decrease appetite.
  - Enhances weight reduction
  - **GLP-1** has a cardiovascular benefit

- **SGLT2 Inhibitor**
  - Decrease glucose reabsorption in proximal convoluted tubules.
  - Improves weight loss and has a cardiovascular benefit
  - Polyuria and frequent UTI is a side effect.



Management Cont.

Type I:

All type I diabetic patients require Insulin

- (0.5-1.0 unit/kg per day) to achieve to acceptable glycemic control.
- Start with a conservative dose (0.2 units/kg), adjusted according to the patient's glucose levels.
- Many different regimens exist, and every patient has unique needs
- Intensive insulin therapy:
    - Mimic normal insulin physiology
        - Basal insulin:
            - Long-acting insulin is given once daily in the evening.
        - Bolus insulin:
            - Regular insulin is given 30 to 45 minutes before each meal, and should be adjusted according to preprandial home glucose measurements.

Type II Management guidelines:

Diet and exercise should ideally be the only interventions in most type II diabetic patients, and are especially effective in obese and sedentary patients. most patients, however, do not control glucose levels through diet and exercise alone, and will require **pharmacologic treatment:**

- **HgA1C <9%**
    - Lifestyle modification
    - Monotherapy (Metformin is usually the first line treatment)
    - Follow up 3-6 m
- **HgA1C > 9%** or If not controlled by monotherapy
    - Lifestyle modification
    - Dual therapy (metformin + additional agent)
    - Follow up 3-6 m
- **HgA1C > 10%** or If not controlled by dual therapy
    - Consider Insulin
    - Basal insulin with the oral medications.

The drug choice:

- First line treatment drug is Metformin
- Additional agent according to the patient condition:
    - ASCVD
        - GLP1 or SGLT2i
    - HF or CKD
        - SGLT2i
- No health condition from the above, choose according to your goal or concern:
    - Minimize hypoglycemia
        - DDP4i or GLP1RA or SGLT2i or TZD. If A1C above the target add another one from these drugs.
    - 2- Weight loss
        - GLP1 or SGLT2i
    - Cost is an issue
        - SU or TZD

Summary

Diabetes Mellitus Type 1

★ It is a clinical syndrome characterised by an increase in plasma blood glucose (hyperglycemia).
★ It has an **immune** pathogenesis and is characterized by severe insulin deficiency.
★ It is a **genetic** disease not a familial disease.
★ In KSA we have two peaks of incidence, at age **9** and age **13**.

Pathogenesis

1. Autoimmune: Islet cell antibodies (ICA) will go through the blood circulation to → pancreas where they attack and cause an inflammation (Insulitis) & destruction of Beta cells thus causing insulin deficiency (**hypoinsulinemia**).
2. Environmental: An infection with **mumps** virus, **coxsackie B** virus or **EBV** will trigger B lymphocytes to produce antibodies, so as the mRNA starts transcripting antibodies against the virus it will also activate segment DR3 and 4 which will produce the Islet cell antibodies (ICA).

Clinical Presentation

Acute presentation:
★ Polyphagia, polydipsia, polyuria and weight loss
★ Ketonuria.

Subacute presentation:
★ Lack of energy, visual blurring.
★ Pruritus vulvae or balanitis.

Presentation as **complications**:
★ Staphylococcal skin infections.
★ Retinopathy.
★ Polyneuropathy.
★ Erectile dysfunction.
★ Arterial disease.
★ Peripheral gangrene.

Diagnosis

WHO criteria for the diagnosis of diabetes are:
★ **Fasting** plasma glucose >7.0 mmol/L (**126** mg/dL).
★ **Random** plasma glucose >11.1 mmol/L (**200** mg/dL).
★ **HbA_{1c} >6.5** (48 mmol/mol)

1 abnormal laboratory value is diagnostic in symptomatic individuals; **2** values are needed in asymptomatic people.

Management

Insulin
Ultra short acting insulins:
Lispro, Aspart.
Short acting Insulins:
Regular, Humulin.
Intermediate acting insulin:
NPH, Lente.
Long acting insulin:
Glargine, Detemir.

Diet & lifestyle modifications

Beta cells transplantation

Summary

Diabetes mellitus (DM) is defined as persistently high fasting glucose levels greater than 125 on at least 2 separate occasions.

Diagnosis of Diabetes Mellitus (DM)

Normal blood glucose levels 70 to 120 mg/dL, maintained in a very narrow range. According to the American Diabetes Association (ADA) and the World Health Organization (WHO), diagnostic criteria for diabetes include the following:

Tests	Blood Glucose level
1-Random plasma glucose	Greater or equal to 200 mg/dL, with classical signs and symptoms (increasing weight, Polydipsia , polyuria) patient doesn't have to fast
2-Fasting plasma glucose	126 mg/dL or more ,on more than one occasion(It is done on more than one occasion to avoid false dx).
3- 2-hour plasma glucose	Greater than or equal to 200 mg/dL during an oral glucose tolerance test with a loading dose of 75 gm.
4-Glycated hemoglobin (HbA1C) level	Greater than or equal to 6.5%

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Clinical	Insulin deficiency ± ketoacidosis Always need insulin	Partial insulin deficiency initially ± hyperosmolar state Need insulin when beta cells fail over time
Biochemical	C-peptide disappears	C-peptide persists

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

Questions

Q1) The risk factors for type 1 diabetes include all of the following except:
A-Diet
B-Genetic
C-Autoimmune
D-Environmental

Q2) Risk factors for type 2 diabetes include all of the following except:
A-Advanced age
B-Obesity
C-Smoking
D-Physical inactivity

Q3) Type 2 diabetes accounts for approximately what percentage of all cases of diabetes in adults?
A-55%-60%
B-35%-40%
C-90-95%
D-25-30%

Q4) Among female children and adolescents, the first sign of type 1 diabetes may be:
A-Rapid weight gain
B-Constipation
C-Genital candidiasis
D-Insomnia

Q5) Which ONE of the following histopathologic features is most likely to be seen in a pancreatic biopsy taken from type II diabetic patient?
A-Lymphocytes infiltrating the Langerhans
B-Amyloid depositions
C-Scattered reactive inflammatory cells as neutrophils
D-Diffuse destruction of beta cells

Q6) Which of the following diabetes drugs acts by decreasing the amount of glucose produced by the liver?
A-Sulfonylureas
B-Meglitinides
C-Biguanides
D-Alpha-glucosidase inhibitors

Q7) What is the most common adverse event of insulin in type 1 diabetes?
A-Hypoglycemia
B-Lipohypertrophy
C-Skin allergy
D-Anxiety or depression

Q8) Which of the following regimens offers the best blood glucose control for persons with type 1 diabetes?

A-A single anti-diabetes drugs
B-Once daily insulin injections
C-A combination of oral anti-diabetic medications
D-Three or four injections per day of different types of insulin.

Q9) A 57-year-old man is admitted to the intensive care unit with altered mental status, hyperventilation, and a markedly elevated glucose level.
Which of the following is the most accurate measure of the severity of his condition?
A-Glucose level.
B-Serum bicarbonate.
C-Urine ketones.
D-Blood ketones.

Q10) A 41-year-old man has been recently diagnosed with type 2 diabetes and has been following a plan of lifestyle measures to improve his diet and increase his level of exercise. On returning to clinic, his BMI is 23, fasting plasma glucose 9.0 mmol/L, blood pressure 133/84 mmHg and HbA1c of 7.1 per cent. The most appropriate treatment option is:
A-Metformin
B-Sulphonylurea
C-Insulin
D-Further diet and exercise

Questions and some Explanations

Q11) 55-year-old man is seen in the clinic for follow-up of type 2 diabetes mellitus. He feels well, has been exercising regularly, and has had good control of his blood glucose on oral metformin, with HgA1c of 6.4%. He has a history of mild hypertension and hyperlipidemia. Which of the following statements is correct regarding routine testing for diabetic patients?
A-Dilated eye examination twice yearly
B-24-hour urine protein annually
C-Home fasting blood glucose measurement at least once per week
D-Urine microalbumin annually
E-Referral to neurologist for peripheral neuropathy evaluation

Q12) A 49-year-old man has recently been diagnosed with type 2 diabetes and is being carefully monitored. He has been advised to maintain a healthier diet and lifestyle, he attends a follow-up clinic and claims to have been following the diet stringently since his last appointment three months ago. The most appropriate investigation is:
A-Random plasma glucose
B-Fasting plasma glucose
C-Urine dipstick
D-Glycated haemoglobin
E-Weight measurement

Q13) 50-year-old woman is 5 ft 7 in tall and weighs 185 lb. There is a family history of diabetes mellitus. Fasting blood glucose (FBG) is 160 mg/dL and 155 mg/dL on two occasions. HgA1c is 7.8%. You educate the patient on medical nutrition therapy. She returns for reevaluation in 8 weeks. She states she has followed diet and exercise recommendations, but her FBG remains between 130 and 140 and HgA1C is 7.3%. She is asymptomatic, and physical examination shows no abnormalities. Which of the following is the treatment of choice?
A-Thiazolidinediones such as pioglitazone
B-Encourage compliance with medical nutrition therapy
C-Insulin glargine at bedtime
D-Metformin

Some Explanations:

1-Type 1 diabetes is a primary failure of pancreatic beta cells to produce insulin. It primarily affects children and young adults and is unrelated to diet.

2-Additional risk factors for type 2 diabetes are a family history of diabetes, impaired glucose metabolism, history of gestational diabetes, and race/ethnicity.

4-The signs and symptoms that suggest type 1 diabetes include excessive thirst, hunger, urination, weight loss, fatigue, irritability, blurred vision, and infection with candida albicans (also known as yeast infections).

6-Biguanides, such as metformin, lower blood glucose by reducing the amount of glucose produced by the liver. Sulfonylureas and Meglitinides stimulate the beta cells of the pancreas to produce more insulin. Alpha-glucosidase inhibitors block the breakdown of starches and some sugars, which helps to reduce blood glucose levels

8-Because persons with type 1 diabetes do not produce insulin, they require insulin and cannot be treated with oral anti-diabetic drugs. Several injections of insulin per day, calibrated to respond to measured blood glucose levels, offer the best blood glucose control and may prevent or postpone the retinal, renal, and neurological complications of diabetes.

9-Hyperglycemia is not the best measure of the severity of DKA. The glucose level can be markedly elevated without the presence of ketoacidosis. Urine ketones mean very little. Although blood ketones are important, they are not all detected. If the serum bicarbonate is very low, the patient is at risk of death. If the serum bicarbonate is high, it does not matter how high the glucose level is, in terms of severity. Serum bicarbonate level is a way of saying “anion gap.” If the bicarbonate level is low, the anion gap is increased.

Answers: 1-A 2-C 3-C 4-C 5-B 6-C 7-A 8-D 9-B 10-B 11-E 12-D 13-D