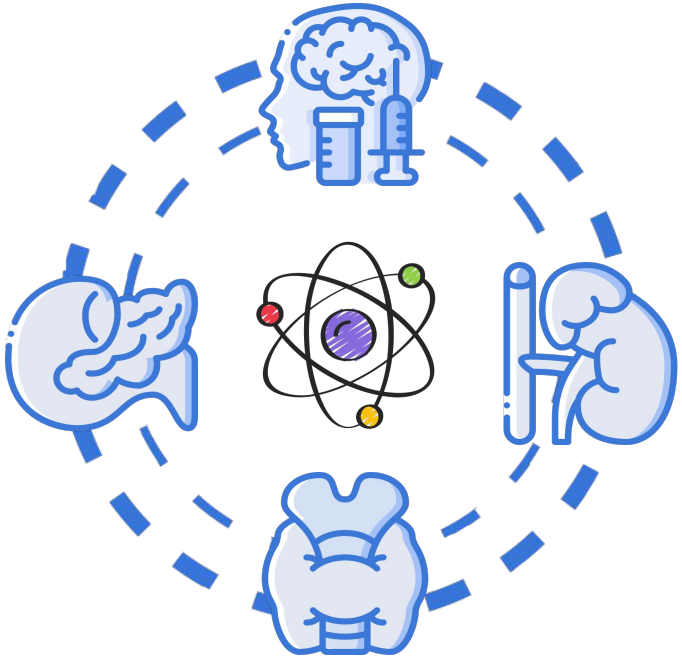
Metabolic Changes in Diabetes Mellitus



Color Index:

- Main Topic
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Editing File

Lecture outline:

- Diagnostic criteria for DM
- Metabolic changes in DM
  - Increase of hepatic glucose output
  - Decrease of glucose uptake
  - Inter-organ relationship in T1DM and T2DM
- Mechanisms of diabetic complications

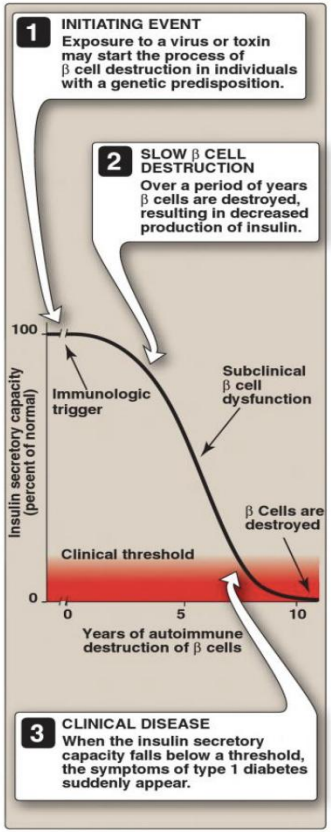
Background:

- Differences between type 1 and type 2 DM
- Natural course of T1DM
- Natural course of T2DM

	Type 1 Diabetes	Type 2 Diabetes
AGE OF ONSET	Usually during childhood or puberty; symptoms develop rapidly	Frequently after age 35; symptoms develop gradually
NUTRITIONAL STATUS AT TIME OF DISEASE ONSET	Frequently undernourished	Obesity usually present
PREVALENCE	10% of diagnosed diabetics	90% of diagnosed diabetics
GENETIC PREDISPOSITION	Moderate	Very strong
DEFECT OR DEFICIENCY	β Cells are destroyed, eliminating production of insulin	Insulin resistance combined with inability of β cells to produce appropriate quantities of insulin
FREQUENCY OF KETOSIS	Common	Rare
PLASMA INSULIN	Low to absent	High early in disease; low in disease of long duration
ACUTE COMPLICATIONS	Ketoacidosis	Hyperosmolar state
RESPONSE TO ORAL HYPOGLYCEMIC DRUGS	Unresponsive	Responsive
TREATMENT	Insulin is always necessary	Diet, exercise, oral hypoglycemic drugs; insulin may or may not be necessary. Reduction of risk factors (smoking cessation, blood pressure control, treatment of dyslipidemia) is essential to therapy.

Figure 25.1
Comparison of type 1 and type 2 diabetes.

Natural course of T1DM



Doctor's explanation:

- It starts with a genetic Predisposition to autoimmune disease + an initiating event like viral infection (immunologic trigger).
- This trigger cause T-lymphocytes infiltration of islets of Langerhans and they start destroying β cells. The process starts from the trigger and takes **7-8 years** for the symptoms to appear.
- At first the insulin level will decreases gradually but you will not see any symptoms because this level is still sufficient to maintain glucose level.
- after **80%-90%** of β cells have been destroyed clinical symptoms will appear, and when the symptoms appears the progression will be fast.
- So, if you see the clinical symptoms that means the remaining insulin secretory capacity is only **10%-20%** (the **clinical threshold**).

Progression of T2DM

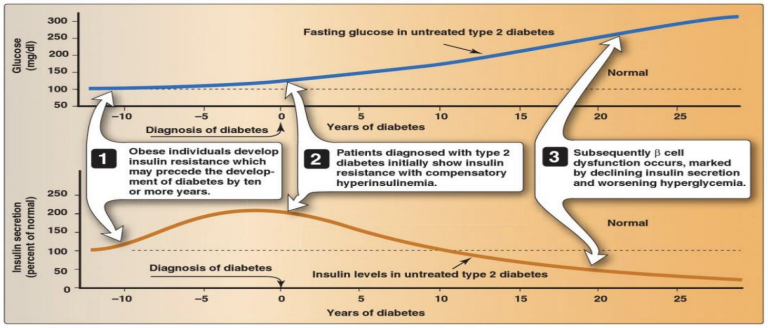


Figure 25.8
Progression of blood glucose and insulin levels in patients with type 2 diabetes.

Doctor's explanation:

- The progression of T2DM starts **10-12 years** before diagnosis.
- Before the diagnosis the person's glucose levels is normal but the insulin is increased to be able to reduce the glucose due to insulin resistance.
- At a certain point during the progression of the disease, the increase in insulin is no longer enough to lower the blood glucose and diagnosis happens.
- If not managed, as the disease progresses, glucose will cause toxic effects on β cells and cause their dysfunction (not destruction because β cells are there but not producing enough insulin) insulin levels will keep dropping, glucose levels are increased. but there will be some amount of insulin production.

*Don't skip numbers

Criteria for Diagnosis of DM*

*American Diabetes Association (ADA), 2010

Test	About test	Increased risk for diabetes (Pre-diabetic state)	Diagnosis of diabetes
In FPG	Fasting is defined as no caloric intake for at least 8h.	5.6-6.9 mmol/L (IFG) 100-125 mg/dL	7 mmol/L ≥126 mg/dL
2h PG on 75g OGTT	2-hour plasma glucose during an OGTT. test should be performed as described by the WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.	7.8-11 mmol/L (IGT) 140-199 mg/dL	11 mmol/L ≥200 mg/dL
HbA1c[1]	The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.	5.7 - 6.4%	≥6.5%
Random blood glucose			≥11.1 mmol ≥200 mg/dL +classic symptoms of hyperglycemia

1. Test results can be affected by RBC disorder(eg. thalassemia , sickle cell anemia)

HEMOGLOBIN A1C[1]

It's the result of non enzymatic covalent glycosylation of hemoglobin

Uses

- to estimate glycemic control in the last *1*-2 months
- Recently, A1C is recommended for the detection of T2DM
- A1C and fasting plasma glucose (FPG) were found to be similarly effective in diagnosing diabetes.

A1C cut-off point of >6.5 % is used to diagnose diabetes.

A1C values also correlate with the prevalence of retinopathy.

Assays for A1C has to be standardized according to the National Glycohemoglobin Standardization Program (**NGSP**).

★ ***Fructosamine* assay: glycated protein (Albumin)** with a much shorter half life than glycated hemoglobin, reflecting control over a shorter period, approximately **14 to 21 days**. May be advantageous in patient with hemoglobin variant than interfere with the accuracy of glycated hemoglobin tests.

1. T1DM
2. T2DM

Metabolic Effects of DM

Absolute[1] or relative[2] insulin deficiency

↓ Glucose uptake (muscle & adipose tissue)

↑ Glucose production (liver)

Major Metabolic changes in DM

Multiple metabolic effects:

CHO metabolism	↓ Glucose uptake by certain tissue (adipose tissue & muscles) ↑ Glycogenolysis ↑ Gluconeogenesis
Lipid metabolism	↑ Lipolysis ↑ Fatty acid oxidation ↑ Production of ketone bodies
Protein metabolism	↓ Protein synthesis ↑ Protein degradation

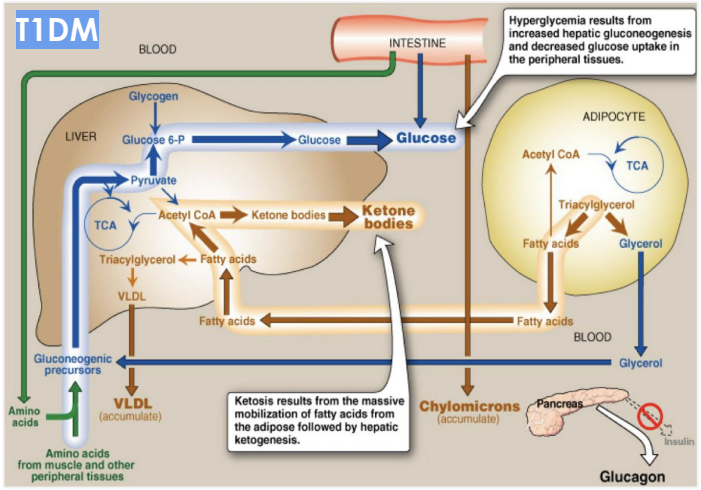
Intertissue Relationship in T1DM & T2DM

Type 1 diabetic Miletus

- ❖ the pancreas isn't secreting insulin, but it's is secreting glucagon which has 2 effects: Gluconeogenesis and Glycogenolysis.

1) **gluconeogenesis:**
   - The intestine absorbs glucose, and amino acids which are delivered to the liver along with the amino acids coming from muscle breakdown and glycerol from triacylglycerol breakdown; these substances are used for gluconeogenesis.
2) **glycogenolysis:**
   Glycogen is broken down in the liver which releases glucose.
3) **fat breakdown:**
   - the adipose tissues will undergo lipolysis and release FAs and glycerol.
   - Glycerol will be used in the gluconeogenesis, while FAs will enter the liver and give ketone bodies and some will turn into triacylglycerol and then VLDL and are released into the circulation.

➔ **So in the circulation we will have:** hyperglycemia, ketonemia, dyslipidemia (VLDL and chylomicrons). *Lipoprotein degradation catalyzed by lipoprotein lipase in the capillary beds of muscle and adipose tissue is low in diabetics (synthesis of the enzyme is decreased when insulin levels are low), the plasma chylomicron and VLDL levels are elevated, resulting in hypertriacylglycerolemia.

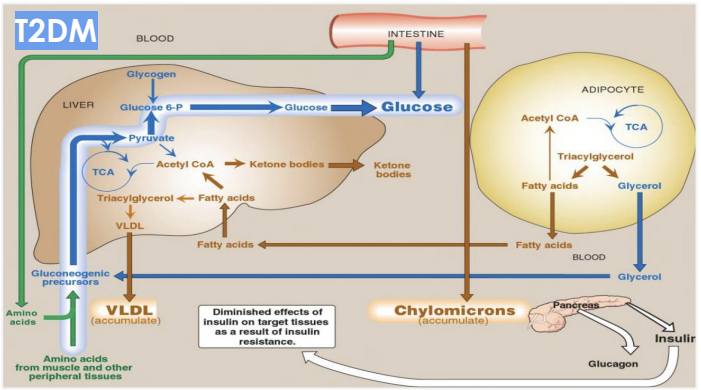


Type 2 diabetic Miletus

1) The same mechanism as type 1 BUT, Insulin is decreased and not absent.
2) That's why the amount of ketone bodies won't be as high as type 1, the little amount of insulin will inhibit it's synthesis.

- In type 1 patients the fatty acid is being used up for synthesis of ketone bodies that's why they're thin, But in type 2 they're usually obese.

➔ **So in the circulation we will have:** Dyslipidemia and hyperglycemia But no ketone bodies.



Mechanisms of:

Hepatic Glucose Output

↓ Insulin → ↓ Inhibitory effect on glucagon secretion (β destruction or dysfunction → α more active) → ↑ Glucagon → ↑ Gluconeogenesis & glycogenolysis (Liver) → ↑ Plasma glucose

Peripheral Glucose Uptake

Muscles

↓ Insulin → ↓ Glucose and amino acid uptake → ↑ Protein breakdown → ↑ Plasma glucose and amino acids

Adipose tissue

↓ Insulin → ↓ Glucose uptake → ↑ Plasma glucose

Mechanisms of Diabetic Complications

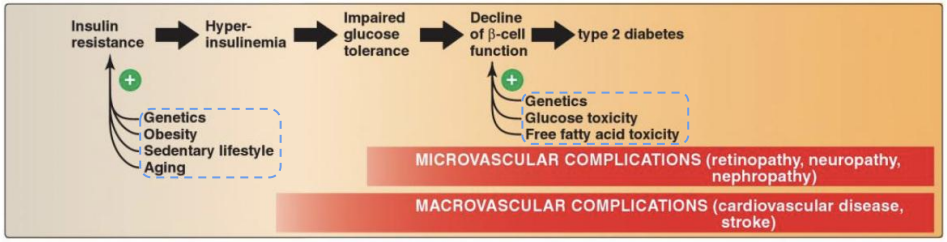


Figure 25.9
Typical progression of type 2 diabetes.

General Mechanisms for (Diabetic Microvascular Complications)

Chronic Hyperglycemia

↑ **AGEs[1] of essential cellular proteins**	↑ **Intracellular Sorbitol[2]**	↑ **ROS**
Cellular **Defects**	↑ cell osmolality	Oxidative stress
	Cellular **Swelling**	Cell **Damage**

1. (Advanced Glycation End Products): Like what happens in HbA1C ,other proteins in the blood spontaneously join to glucose (glycation) due to hyperglycemia.
2. Sorbitol is sugar alcohol made from unused glucose in the cells, and it is osmotically active.

Advanced Glycation End Products (AGEs)

- **Chronic Hyper**glycemia ➔ non-enzymatic combination between excess Glucose & Amino acids in proteins ➔ formation of **AGEs.**

A

- **AGEs** may cross link with **collagen** which leads to microvascular complications.

B

- The interaction between **AGEs** and their receptor (**RAGE**) may generate reactive oxygen species (ROS) which leads to Inflammation.

Polyol Pathway[1]

- Excess Glucose is metabolized to sorbitol within the cells by **Aldose reductase**.
- The role of sorbitol in the pathogenesis of diabetic complications is uncertain.

Hypotheses are:

01 During sorbitol production, **consumption of NADPH[2]** → oxidative stress.

02 Sorbitol accumulation will:

A. Increase the intracellular **osmotic pressure** → osmotic drag of fluid from extracellular space → cell swelling.

B. Alteration in the activity of **PKC** (protein kinase C) → altered **VEGF** (vascular endothelial growth factor) activity → altered vascular permeability.

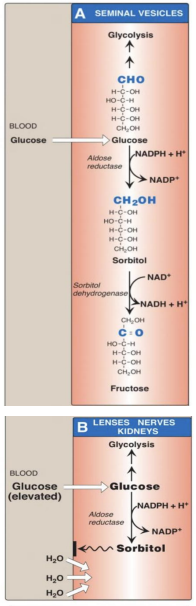
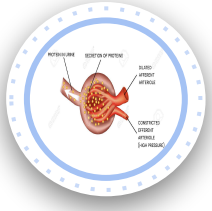


Figure 12.4
Sorbitol metabolism. NAD(H) = nicotinamide adenine dinucleotide; NADP(H) = nicotinamide adenine dinucleotide phosphate.

In **seminal vesicles & ovaries** there is enzyme called sorbitol dehydrogenase that converts sorbitol to fructose.
But, most of other tissues do not have this enzyme, causing accumulation of sorbitol and cell swelling.

1. Sorbitol formation pathway
2. Remember NADPH is important for antioxidant pathway.

Diabetic Microvascular Complications



Diabetic Nephropathy

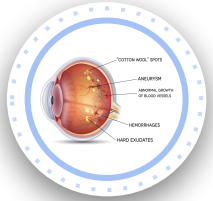
- Occurs in both type 1 & type 2 DM.
- The earliest clinical finding of diabetic nephropathy is **microalbuminuria**: The persistent excretion of small amounts of **albumin** (30-300 mg per day) into the urine.
- Microalbuminuria is an important predictor of progression to **proteinuria**: the persistent excretion of >300 mg albumin per day into the urine.
- Once proteinuria appears, there is a steady decrease in the glomerular filtration rate (GFR).
- Finally, end-stage renal disease occurs.

★ **Sequence of Events in Diabetic Nephropathy:**

Glomerular hyperfiltration → Microalbu-minuria → Proteinuria & ↓ GFR → End-stage renal disease

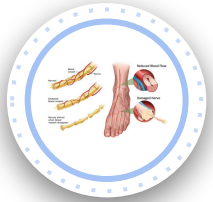
Hypothesis **Nephromegaly:** increase size of the kidney, maybe due to:

1) Ectopic lipid depositions or other mechanisms.
2) When a lot of glucose is reabsorbed through SGLT "Na dependent Glucose transporter" along with Na, that will lead to absorption of H_2O causing Hyperosmolar state. *When the blood glucose level exceeds about 160–180 mg/dL (8.9-10 mmol/L), the proximal tubule becomes overwhelmed and begins to excrete glucose in the urine.



Diabetic Retinopathy

- A progressive microvascular complication of DM, affecting the retina of the eye.
- A major cause of morbidity in DM (**blindness**).
- Its prevalence with increasing duration of disease in both type 1 & 2 DM .
- **After 20 years of the disease**:
  - Is present in **almost all** T1DM.
  - Is present in **50 – 80%** of T2DM.



Diabetic Neuropathy

- Loss of both myelinated and unmyelinated nerve fibers.
- Occurs in both type 1 & type 2 DM.
- It correlates with the duration of DM & with glycemic control.

Summary

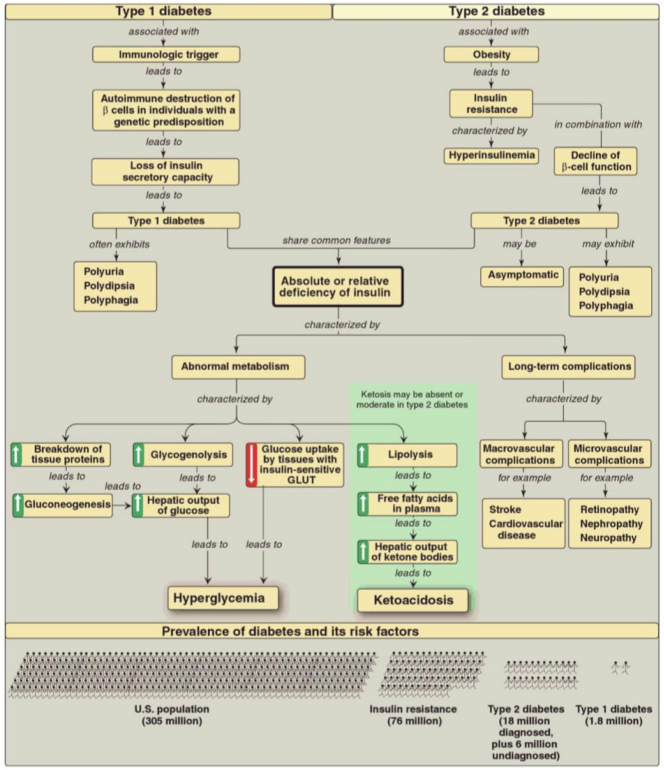


Figure 25.13
Key concept map for diabetes.

Diabetes

Diagnosis criteria

Tests:

★ **FPG**
- 7 mmol/L , ≥126 mg/dL

★ **2h PG on 75g OGTT**
- 11 mmol/L, ≥200 mg/dL

★ **HbA1c**
- ≥6.5%

★ **Random blood glucose**
- ≥11.1 mmol, ≥200 mg/dL + classic symptoms of hyperglycemia.

HbA1c

- The result of non enzymatic covalent glycosylation of hemoglobin.
- Use to estimate glycemic control in the last **1-2 months**.
- Recommended for T2DM detection (Similar to FPG in diagnosing DM)
- Assay for A1C has to be standardized according to **NGSP.**

Microvascular complications (Mechanism)

Chronic Hyperglycemia

AGEs of essential cellular proteins
" Cellular Defects"

1) **AGEs** may cross link with **collagen** which leads to **microvascular complications**.
2) Interaction between **AGEs** and their receptor (**RAGE**) may generate reactive oxygen species (**ROS**) which leads to **Inflammation**.

ROS

Oxidative stress → **"Cell Damage"**

Intracellular sorbitol

1) During sorbitol production, consumption of NADPH → **oxidative stress**.
2) Sorbitol accumulation will:
A. Increase the intracellular osmotic pressure → osmotic drag of fluid from extracellular space → **cell swelling**.
B. Alteration in the activity of PKC → altered VEGF activity → **altered vascular permeability**.

Quiz

MCQs :

Q1: which of the following used recently for detection of T2DM?

a) OGTT **b)** A1C
c) Random blood glucose **d)** 2 hours in FPG

Q2:which of the following is a Major Metabolic changes in DM effect on CHO?

a) Increase lipolysis **b)** Decrease glycogenolysis
c) Increase glycogenolysis **d)** Increase protein synthesis

Q3: patient present with ketonemia that indicate he has?

a) T2DM **b)** T1DM

Q4: which of the following considered as Microvascular complication of DM?

a) CVD **b)** Stroke
c) Neuropathy **d)** Peripheral arterial disease

Q5: Accumulation of sorbitol alters vascular permeability by:

a) Cross linkage with collagen **b)** Consumption of NADH
c) ↑ the intracellular osmotic pressure **d)** Alteration in the activity of PKC

Q6: Excess Glucose is metabolized to sorbitol within the cells by:

a) Glucose reductase **b)** Glucose oxidase
c) Aldose reductase **d)** Aldose oxidase

SAQs :

Q1: Compare between T1DM and T2DM regarding to which they are result from?

Q2: Compare between T1DM and T2DM regarding to what will you have the circulation?

Q3: What are the General mechanisms for microvascular complications in DM?

Q4: Briefly, Explain the hypotheses of sorbitol role in the pathogenesis of diabetic complications.

★ **MCQs Answer key:**

1) B 2) C 3) B 4)C 5)C&D 6) C

★ **SAQs Answer key:**

1) T1DM results from destruction of beta cells of the pancreas while T2DM is due to the development of insulin resistance.
2) Slide7
3) Slide 9
4) Slide 10

Team members

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- Amira AlDakhilallah
- Deema Almaziad
- Ghaliah Alnufaei
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- Leena Alnassar
- Lama Aldakhil
- Lamiss Alzahrani
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- Alkassem Binobaid
- Fares Aldokhayel
- Khayyal Alderaan
- Mashal Abaalkhail
- Naif Alsolais
- Omar Alyabis
- Omar Saeed
- Rayyan Almousa
- Yazen Bajeaifer

Team Leaders

Lina Alosaimi

Mohannad Alqarni

★ **Make yourself proud!!**

We hear you