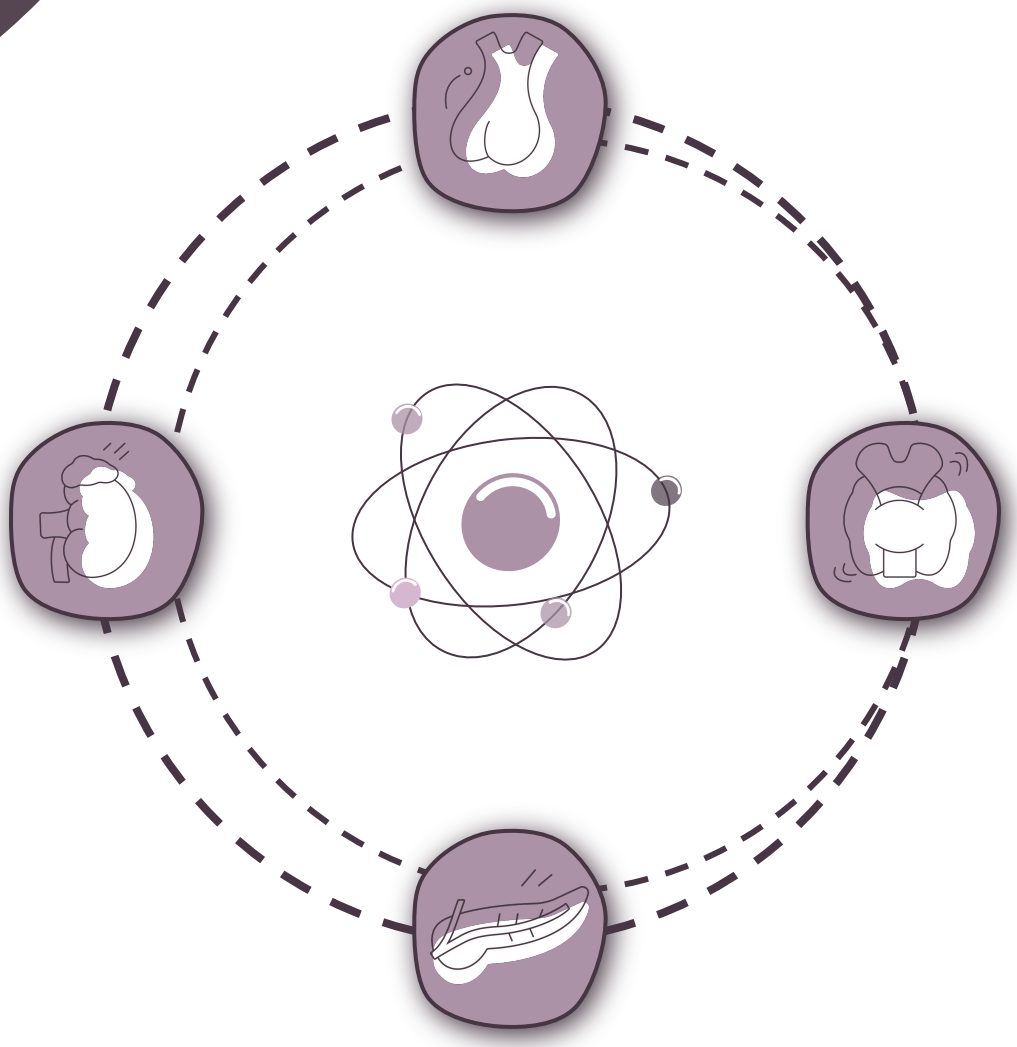
Biochemistry
Team 443



# L8: Metabolic changes in diabetes mellitus

Presented by:
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# Objectives

1. **Background**
   - Differences between type 1 and type 2 DM
   - Natural course of T1DM
   - Natural course of T2DM
2. **Diagnostic criteria for DM**
3. **Metabolic changes in DM**
   - Increase of hepatic glucose output
   - Decrease of glucose uptake
   - Inter-organ relationship in T1DM and T2DM
4. **Mechanisms of diabetic complications**

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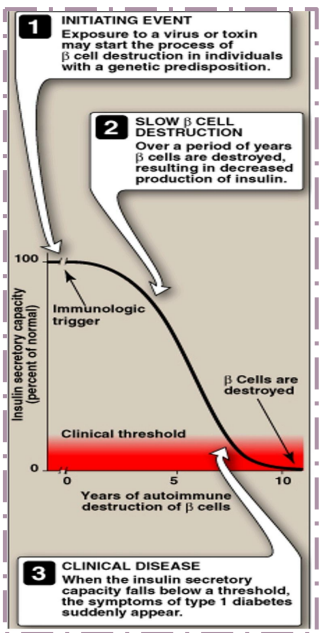
# 1 Comparison of type 1 & type 2 DM

| | Type 1 DM | Type 2 DM |
|---|---|---|
| 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 | 90,000=<10% of diagnosed diabetics | 10 millions=> 90% of diagnosed diabetics |
| Genetic predisposition | moderate (Dr sumbul :not as much as T2 but still there is genetic predisposition) | Very strong |
| Defect or deficiency | Beta cells are destroyed, eliminating production of insulin | Insulin resistance combined with inability of beta cells to produce appropriate quantities of insulin |
| Frequency of ketosis | Common | Rare (bc: it has insulin that prevent it) |
| Plasma insulin | Low to absent | High early in disease; Low to absent in disease of long duration |
| Acute complications imp | ketoacidosis | Hyperosmolar hyperglycemic coma |
| Treatment with oral hypoglycemic drugs | Unresponsive | Responsive |
| Treatment | Insulin is always necessary | diet , exercise, oral hypoglycemic drug OHG, +/- insulin (may or may not be necessary) reduction of risk factors (weight reduction, smoking cessation, BP control, treatment of dyslipidemia) is essential to therapy) |

## Natural course of T1 DM

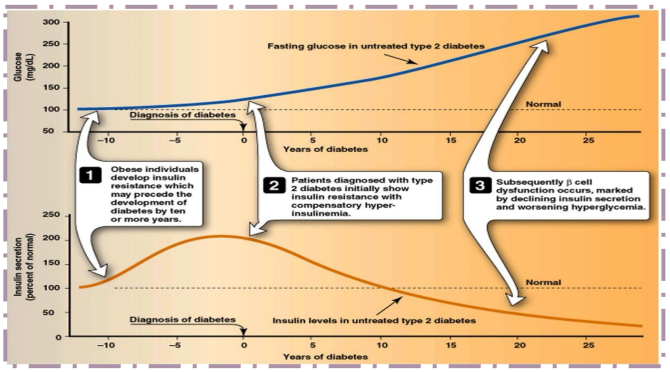



2 main symptoms: polydipsia, polyurea

❖ 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 $\beta$ cells. The process starts from the trigger and takes 7-8 years for the symptoms to appear.
❖ At rst 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 $\beta$ 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).

الزبدة :
Genetic(not strong) + environmental factors (virus) →inflammation →T-cell infiltration →insulitis → destruction of Beta cells

## Progression of T2 DM




❖ 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 $\beta$ cells and cause their dysfunction (not-destruction because $\beta$ 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.

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# Criteria for Diagnosis of DM

## Categories of increased risk of DM

- **IFG ( impaired fasting glucose ):** FPG ( fasting plasma glucose ) 100-125 mg/dl ( 5.6-6.9mmol/L)
- **IGT ( impaired glucose tolerance):** 2h-PG (post glucose) in the 75-g OGTT 140-199 mg/dL ( 7.8-11.0 mmol/L)
- **A1C ( glycated hemoglobin):** 5.7-6.4% (39-46mmol/mol)

For all three test, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

## Criteria for diagnosis of DM

1- **A1C ≥ 6.5 %.** The test should be performed in a laboratory using a method that is NGSP (national glycohemoglobin standardization program) certified and standardized to the DCCT (diabetes control and complications trial)
**OR**

2- **FPG** (fasting plasma glucose ) **≥ 126 mg/dL (7.0 mmol/L).**
Fasting is defined as no caloric intake for at least 8 h.
**OR**

3- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, **a random plasma glucose greater than or equal to 200 mg/dL (11.1 mmol/L)**
**OR**

4- **Two-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L)** during an OGTT (oral glucose tolerance test).
The test should be performed as described by the world health organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

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# Hemoglobin A1C

-Hemoglobin A1C is the result of non enzymatic covalent glycosylation of hemoglobin.
-It is used to estimate glycemic control in the last 1-2 months..

Because RBC lifespan is 120 days

Recently, A1C is recommended for the detection of T2 DM.

Why T2? Because it is discovered in a regular check (slow)

They're equally good

-A1C and fasting plasma glucose (FPG) were found to be similarly effective in diagnosing diabetes.
-A1C cut-off point of greater than or equal 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).

Extra: HbA1c levels are affected by red blood cell turnover (hemolytic anemia) which could cause falsely low HbA1c levels

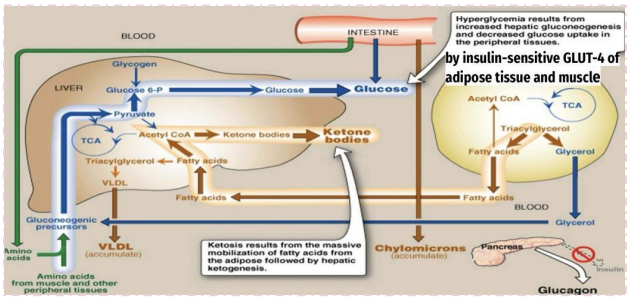
## Metabolic Effects of Diabetes Mellitus

**Absolute or relative insulin deficiency:**

Absolute = T1DM , Relative = T2DM

- Increase glucose production (liver )
- Decrease glucose uptake (muscle and adipose tissue)

### Intertissue Relationship in T1 DM

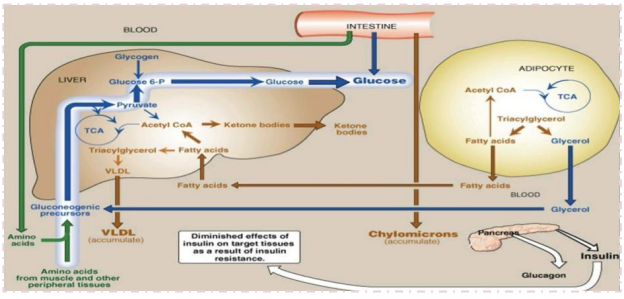



the pancreas isn't secreting insulin, but it's is secreting glucagon which has 2 effects: Gluconeogenesis and Glycogenolysis.

1- gluconeogenesis: 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).

### Intertissue Relationship in T2 DM




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.

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# Major Metabolic changes in DM

**Absolute or relative insulin deficiency**

**Multiple metabolic effects**

### CHO metabolism

- Decrease uptake by certain tissues (adipose tissue and muscle)
- Increase glycogenolysis
- Increase gluconeogenesis

### Lipids metabolism

- Increase lipolysis
- Increase fatty acid oxidation
- Increase production of ketone bodies

Dr sumbul : excessive in T1 because there is absolute deficiency of insulin

### Protein metabolism

- Decrease protein synthesis
- Increase protein degradation

Can be utilized in gluconeogenesis .

# Mechanisms

## Mechanisms of Increase Hepatic Glucose Output

| |
|---|
| ↓ insulin |
| ↓ inhibitory effect on glucagon secretion |
| ↑ glucagon |
| ↑ Gluconeogenesis & glycogenolysis (liver) |
| ↑ plasma glucose |

## Mechanisms of Decrease of Peripheral Glucose Uptake

| Muscle | Adipose Tissue |
|---|---|
| ↓ insulin | ↓ insulin |
| • ↓ glucose and AA uptake<br>• ↑ protein breakdown | ↓ glucose uptake |
| • ↑ plasma glucose<br>• ↑ plasma amino acid | ↑ plasma glucose |

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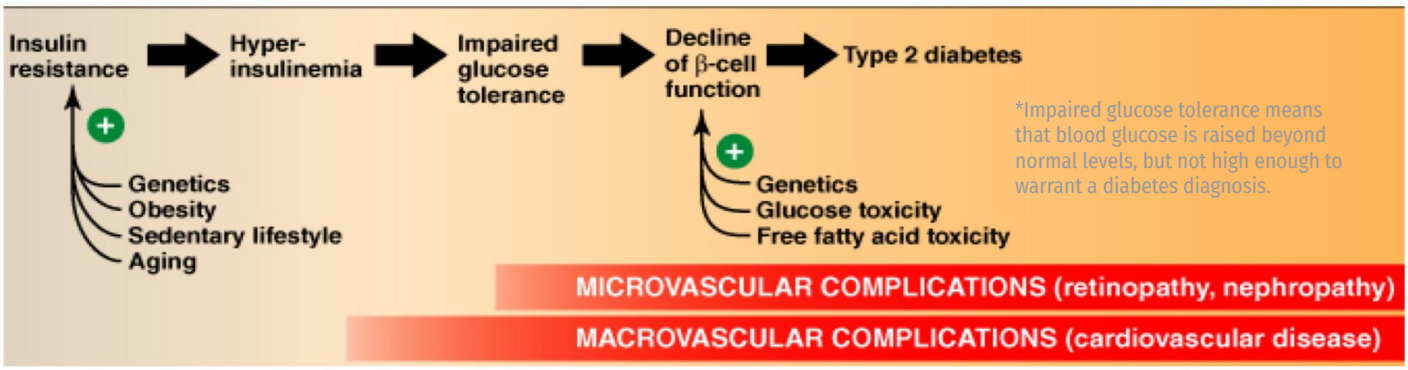
# Mechanisms of Diabetic Complications




Microvascular Complications start before Macrovascular Complications

## General Mechanisms for (DM Microvascular Complications)

**Chronic Hyperglycemia**

- ↑ AGEs of essential cellular proteins → Cellular Defects
- ↑ Intracellular sorbitol → ↑ cell osmolality → Cellular Swelling
- ↑ ROS → Oxidative stress → Cellular damage

### Advanced Glycation End Products (AGEs)

(Advanced Glycation End product): like what happens in HbA1C , other proteins in blood spontaneously join to glucose (glycation) due to hyperglycemia

- Chronic Hyperglycemia ➔ non-enzymatic combination between excess Glucose & Amino acids in proteins ➔ formation of AGEs.
- AGEs may cross link with collagen ➔ microvascular complications
- The interaction between AGEs and their receptor (RAGE) may generate reactive oxygen species (ROS) ➔ inflammation

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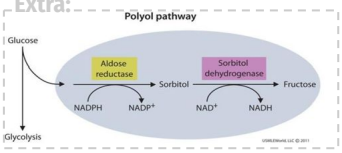
# Polyol Pathway

Extra:




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

Sorbitol is sugar alcohol made from unused glucose in the cells, and it is osmotically active

alcoholic form of glucose :الزيدة هو

During sorbitol production, consumption of NADPH2 ➔ oxidative stress

Sorbitol accumulation will:

Increase the intracellular osmotic pressure➔ osmotic drag fluid from extracellular space➔ cell swelling

Alteration in the activity of PKC (protein kinase C) ➔ altered VEGF (vascular endothelial growth Factors ) activity➔ altered vascular permeability

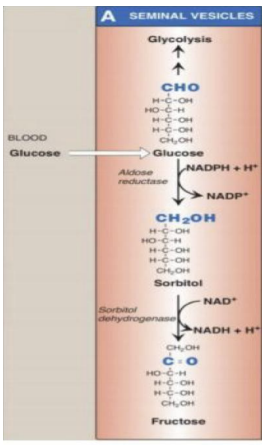



Figure 12.4
Sorbitol metabolism. NAD(H) = nicotinamide adenine dinucleotide; NADP(H) = nicotinamide adenine

# DM Microvascular Complications

## Diabetic Retinopathy

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

## Diabetic Nephropathy

- Occurs in both type 1 & type 2 DM.
- The **earliest** clinical finding of diabetic nephropathy is **microalbuminuria** (لأن حجم albumin أصغر )
  (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
↓
Microalbuminuria
↓
Proteinuria ↓GFR
↓
End-stage renal disease

## Diabetic neuropathy

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

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# Summary

<table>
<tr><td rowspan="2">Comparison between<br>To the slide</td><td>Type 1 Diabetes</td><td colspan="2">1-Usually during childhood or puberty; symptoms develop rapidly .<br>2-Nutritional status at time of disease onset: Frequently undernourished.<br>3-Genetic predisposition : Moderate .<br>4-Defect or deficiency : Beta cells are destroyed, eliminating production of insulin.<br>5-Acute complications : ketoacidosis.</td></tr>
<tr><td>Type 2 Diabetes</td><td colspan="2">1-Frequently after age 35; symptoms develop gradually .<br>2-Nutritional status at time of disease onset : Obesity usually present.<br>3-Genetic predisposition : Very strong .<br>4-Defect or deficiency : Insulin resistance combined with inability of beta cells to produce appropriate quantities of insulin.<br>5-Acute complications: Hyperosmolar coma.</td></tr>
<tr><td colspan="2">Metabolic Effects of Diabetes Mellitus</td><td colspan="2">Absolute or relative insulin deficiency :<br>1- Decrease glucose uptake (muscle and adipose tissue).<br>2-Increase glucose production (liver ).</td></tr>
<tr><td rowspan="3">Major Metabolic changes in DM</td><td rowspan="3">Absolute or relative insulin deficiency<br>↓<br>Multiple metabolic effects:</td><td>CHO metabolism:<br>• Decrease uptake by certain tissues (adipose tissue and muscle).<br>• Increase glycogenolysis.<br>• Increase gluconeogenesis .</td></tr>
<tr><td>Lipids metabolism:<br>• Increase lipolysis .<br>• Increase fatty acid oxidation .<br>• Increase production of ketone bodies.</td></tr>
<tr><td>Protein metabolism:<br>• Decrease protein synthesis .<br>• Increase protein degradation.</td></tr>
</table>

# Test Yourself!

## MCQs

**Answers:** B-B-A-B

**Q1: which type of diabetes is responsive to treatment with hypoglycemic drugs ?**
**A.** Type 1 diabetes
**B.** Type 2 diabetes
**C.** Both A and B
**D.** None of the above

**Q2: Which ONE of the following is a diagnostic feature for a 45 year old diabetic?**
**A.** Fasting plasma glucose > 6 nmolL
**B.** HbA1c > 6.5
**C.** Random sample of plasma glucose > 10 nmol/L
**D.** Post Oral Glucose tolerance test > 9 nmol\L

**Q3: : which of the following is an acute complication of T2 DM?**
**A.** hyperosmolar coma
**B.** ketoacidosis
**C.** renal failure
**D.** blindness

**Q4: Q1: Absolute or relative insulin deficiency causes which of the following :**
**A.** decrease lipolysis
**B.** increase lipolysis
**C.** decrease protein degradation
**D.** increase protein synthesis

## SAQs

**Q1: Mention the effect of DM on the metabolism of proteins, carbs & lipids?**
Answer:
- Proteins: Reduces protein synthesis and increases its degradation.
- Carbs: Decreased uptake of glucose by tissues & increases both glycogenolysis & gluconeogenesis.
- Lipids: Increases lipolysis and FFA oxidation and ketone bodies production (in liver)

**Q2: List the mechanisms of decrease of peripheral glucose uptake on the muscle and adipose tissue?**
Answer:
Muscle: ↓ Insulin, ↓ glucose and amino acid uptake, ↑ protein breakdown, ↑ plasma glucose and amino acid.
Adipose tissue: ↓ Insulin, ↓ glucose uptake, ↑ plasma glucose.

# Meet The Team!

## Team Leaders

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**Deena Almahawas**

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- Mohammed AlSalamah
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- Hamad AlZomaia
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- Faisal AlZuhairy
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