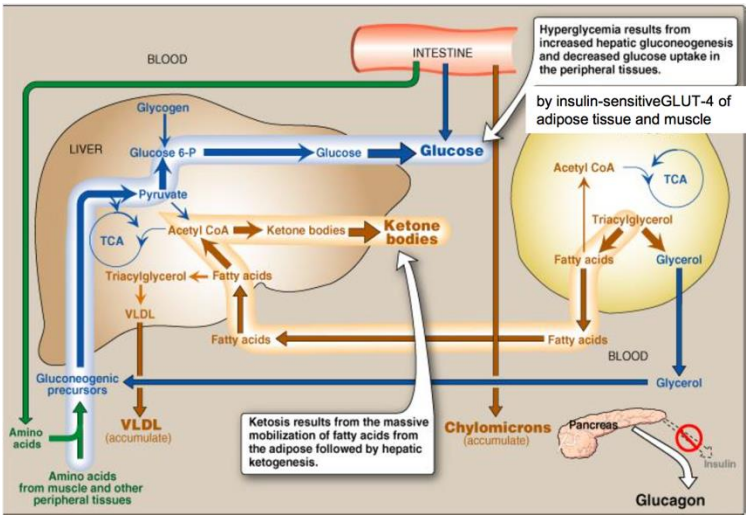
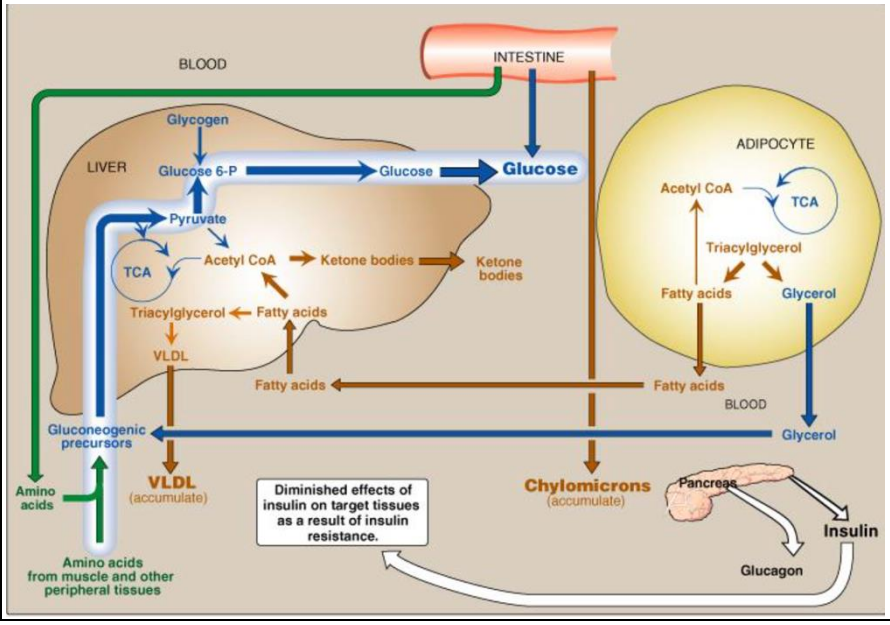
Metabolic Changes in Diabetes Mellitus		
	DM type 1	DM type 2
Age of onset	Childhood or puberty	Adult , frequently after age 35
Symptoms develop	Rapidly	Gradually
Nutritional status at the time of disease onset	Frequently undernourished	Obesity usually present
Prevalence	10%	90%
Defect & deficiency	Destroy β cells , eliminating production of insulin	No enough insulin or insulin resistance
Ketosis	Common	Rare
Plasma insulin	Low or absent	Reduce gradually (Early high –late low)
Acute complication	Ketoacidosis	Hyperosmolar coma
Genetic predisposition	Moderate	Very strong
Using of oral hypoglycemic	No response	Response
Treatment	Insulin	Diet, exercise, oral hypoglycemic, insulin
	Natural course of T1DM 1- In normal people, the activity of insulin is 100% (all of beta cells are intact)→a stimulus form the environment (e.g. **a viral infection**) triggers the process in people with **genetic determinant** that allows the β cells to be recognized as "nonself." 2- **T-cells** infiltration in the islets of Langerhans and causes **insulitis**. 3- **Over a period of years**, this autoimmune attack on the β cells leads to gradual depletion of these cells→**decrease insulin secretion**(**Subclinical**) 4- **When 80% – 90% of the β cells have been destroyed**→the pancreas fails to respond adequately to ingestion of glucose, and symptoms suddenly appear (**polyuria, polydipsia, polyphagia**) .	**Progression of T2DM** • **First 10 years** : **obese people** will develop a slight increment in glucose level with insulin resistance. **Thus, the insulin secretion will increase as a compensatory mechanism**. • **After this period of time** and due to this hypersecretion; there will be a **decline in secretion due to destruction of the β cells**, and dramatic **increase in the glucose** (126 mg/dL or higher). • the insulin level will decline but **won't be absent** (it won't go lower than 10%, which is the level of insulin that keeps the adipose tissue taking up the glucose→**prevent lipolysis and ketoacidosis)**.

Intertissue Relationship	**IN T1DM** 1- The intestine **gives glucose, chylomicron and amino acids**. In **T1DM**, there's no insulin, so the **body use gluconeogenesis** instead. 2- Amino acids enter the Kreps cycle in liver and go through gluconeogenesis to make glucose. 3- due to the lack of insulin, the adipose tissues can't use the glucose, thus they will go under **lipolysis** and release FAs and glycerol. 4- **Glycerol will be used in the gluconeogenesis**, while FAs will enter the liver and – depending on the amount of FAs released- it will produce **glucose** also. Some of the **FAs will give ketone bodies** and some will turn into triacylglycerol and then VLDL. **5-** **chylomicron and VLDL** usually get cleaved by **lipoprotein lipase**, but this enzyme needs insulin to work, so the **VLDL and chylomicron will accumulate and HDL will decrease.**  **In T2DM** Almost the same as type 1 , but Remember the 10% we mentioned before that **prevent proteolysis & lipolysis.** 

Criteria for Diagnosis of DM	**Increased risk of DM** FPG (5.6-6.9) mmol/L OGTT (7.8-11) mmol/L A1c (5.7-6.4)%	**Diagnosis of DM** FPG > 7 mmol/L OGTT > 11.1 mmol/L A1c > 6.5% Random plasma glucose > 11.1 mmol/L + **Hyperglycemia symptoms** **In the absence of unequivocal hyperglycemia , criteria 1-3 should be confirmed by repeat testing.**

HEMOGLOBIN A1C

- Hemoglobin A1C (A1C) is the result of non enzymatic covalent glycosylation of hemoglobin
- **It is used 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).

Metabolic Effects of Diabetes Mellitus

- **Absolute or relative insulin deficiency →**
  - ↓ Glucose uptake (muscle & adipose tissue)
  - ↑ Glucose production (liver)

Major Metabolic changes in DM

Absolute or relative insulin deficiency → Multiple metabolic effects

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

Mechanisms of Increase Hepatic Glucose Output

↓ Insulin → ↓ Inhibitory effect on glucagon secretion → ↑Glucagon
↑Glucagon → ↑Gluconeogenesis & glycogenolysis (liver) →↑Plasma glucose

Mechanisms of Decrease of Peripheral Glucose Uptake

Muscle	Adipose Tissue
↓ Insulin ↓ ↓Glucose & amino acid uptake ↑Protein breakdown ↓ ↑Plasma glucose ↑Plasma amino acids	↓ Insulin ↓ ↓ Glucose uptake ↓ ↑Plasma glucose

Mechanisms of Diabetic Complications

Typical Progression of T2DM	**Factors increasing the insulin resistance :**	**Factors increasing the decline of beta cells function :**
	1- genetics **2-** obesity **3-** sedentary life style **4-** aging	**1-** genetics **2-** glucose toxicity **3-** FFA toxicity

General Mechanisms for Diabetic Microvascular Complications

Chronic hyperglycemia →

1- ↑ **AGEs** of essential cellular proteins → cellular defects
2- ↑**Intracellular sorbitol** → ↑ cell osmolality → cellular swelling
3- ↑ **ROS** → oxidative stress → cell damage

Advanced Glycosylation End Products (AGEs)

- 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**

Polyol pathway

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

Sorbitol Metabolism (Polyol Pathway)

In some tissues (seminal vesicles, ovaries and liver) there's an another enzyme that act on sorbitol, it's called **sorbitol dehydrogenase**.
This enzyme's function is to convert **sorbitol into fructose** .

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 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 ↓ 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 type 1 & type 2 DM
- It correlates with the duration of DM & with glycemic control

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