Biochemistry Team 435

جامعة الملك سعود
King Saud University 1957

METABOLIC CHANGES IN DIABETES MELLITUS

* Please check out this link to know if there are any changes or additions.

We advice to study **"physiology of pancreas and insulin" & "Diabetes (pathology)"** lectures before you start studying this lecture.

Revised by
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Color index: Important | Doctors notes | Further explanation.

OBJECTIVES:

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

COMPARISON BETWEEN TYPE 1 AND TYPE 2 DM

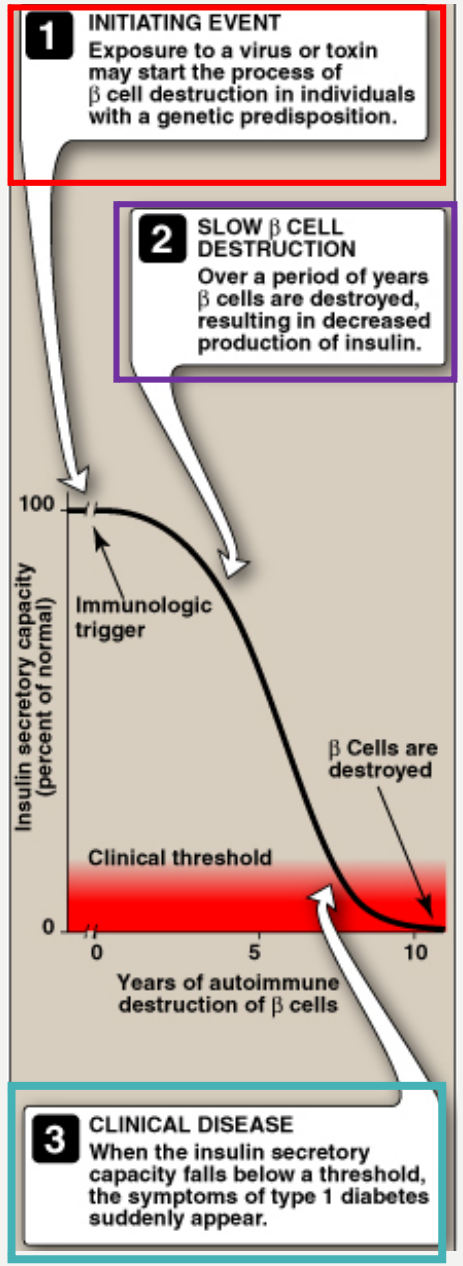
	Type I Diabetes:	Type II diabetes:
Age of onset:	➢ Usually during **childhood** or **puberty**. ➢ Symptoms develop **rapidly**.	➢ Frequently **after age 35**. ➢ Symptoms develop **gradually**.
Nutritional status at time of disease onset:	Frequently **undernourished**.	**Obesity** usually present. In the past, obesity was one of the risk factors but now it's considered as a cause.
Prevalence:	**< 10 %**	**> 90 %**
Genetic predisposition:	**Moderate**	**Very strong.** If one of an identical twins has type II diabetes then the other one is definitely gonna to develop it (eventually)
Defect or deficiency:	**Beta cells are destroyed** (After being exposed to toxins), eliminating production of insulin.	**Insulin resistance** combined with **inability** of beta cells to produce **appropriate quantities of insulin**.
Frequently of ketosis:	**Common**	**Rare** (insulin is still there --> inhibition of ketosis)
Plasma insulin:	**Low** to **absent**	**High** early in disease; **low** to absent in disease of long duration
Acute Complications:	**Ketoacidosis**	**Hyperosmolar coma** (caused by high glucose levels)
Treatment with oral hypoglycemic drugs:	**UN**responsive.	**Responsive**.
Treatment:	**Insulin** is always necessary.	**Diet**, **exercise**, **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 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." (يعني يعتبرها الجهاز المناعي مب من الجسم فلذلك يهاجمها) → **T-cells** infiltration in the islets of Langerhans and causes **insulitis**.

2- Over a period of years, this autoimmune attack on the β cells leads to gradual depletion of these cells → decrease insulin secretion(**Subclinical**)

3- 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**).

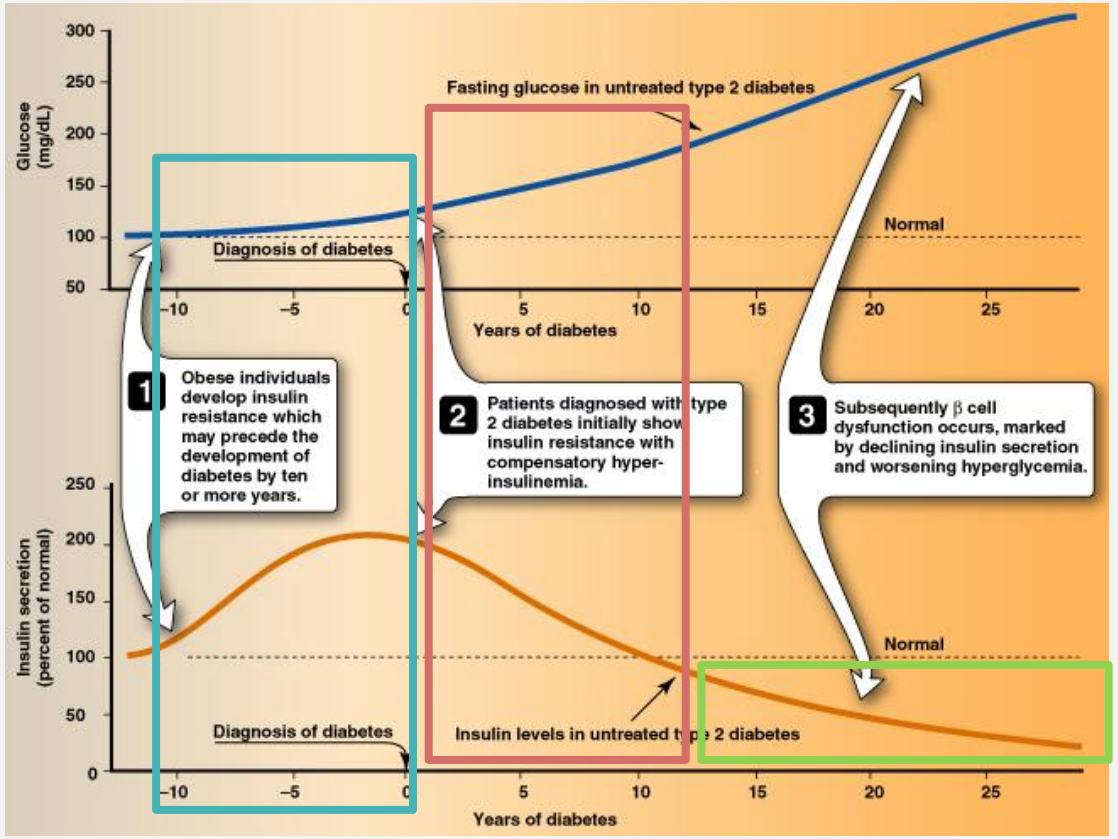


PROGRESSION OF T2DM

- **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).



CRITERIA FOR DIAGNOSIS OF DM

Test:	About test:	Increased risk for diabetes: (pre diabetic state)	Diagnosis of diabetes هنا نكون متأكدين أن المريض عنده سكر إذا ظهرت لنا أحد هذي النتائج
2h in FPG:	Fasting is defined as **no caloric intake for at least 8 h**.*	**5.6 - 6.9 mmol\L (IGF)**	**7 mmol\L**
OGTT on 75g:	**2-hour** plasma glucose during an OGTT. Test should be performed as described by the WHO, using a glucose load containing the equivalent of **75 g** anhydrous glucose **dissolved in water.*** يعطون الشخص 75 قرام جلوكوز ويقيسونه بعد ساعتين بالحالة النورمال الجلوكوز بيرتفع بعدين بيرجع نورمال ليش؟ لأن فيه هوميوستيسس.. اذا الشخص يعاني من مشاكل الجلوكوز ماراح يرجع نورمال	**7.8 – 11 mmol\L (IGT)**	**11 mmol\L**
A1c:	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% mmol\L**	**>= 6.5% mmol\L**
Random blood glucose	هنا نقيس مستوى الجلوكوز (عشوائيا) بدون تهيئة ظروف معينة "مانعطيهم جلوكوز من نفسه مرتفع" هالتست يستخدم لمن الشخص يجي ومعاه اعراض الهايبر جلايسيما الكلاسيكال	-	**>= 11.1 mmol**

To convert from mmol\L to mg\dl use this equation: (mmol\L * 18 = mg\L)
القيم اللي حطيناها فقط بالميلي مول لتسهيل الحفظ! **أغلب** هذي الأرقام والمعلومات ماخذينها في الفيزيو، يعني المفروض انكم حافظينها خلاص :)

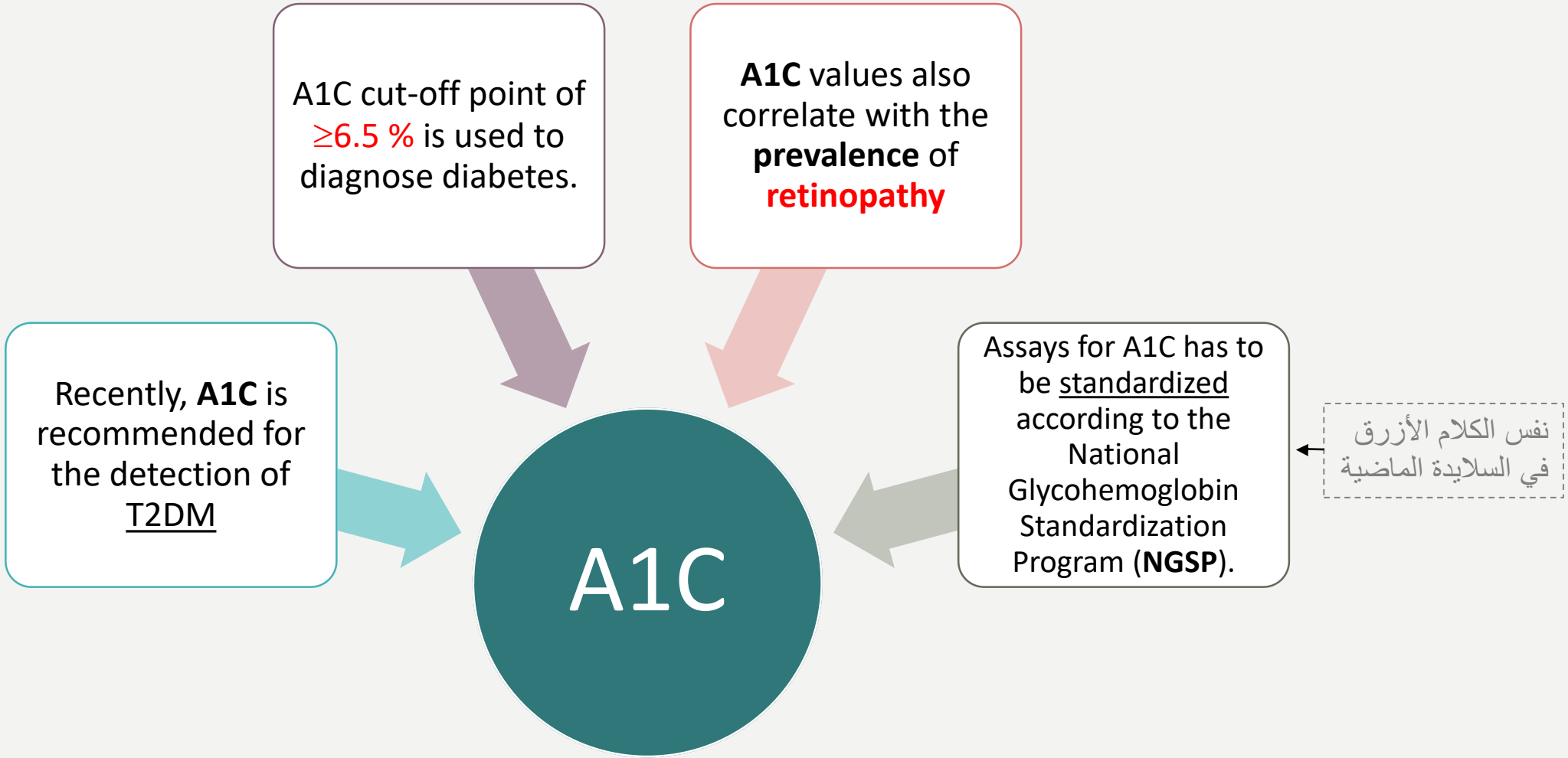
DCCT is used to standardize the HbA1C to confirm if it really gives us the indication of the past 2-3 months or not.

*In the absence of unequivocal hyperglycemia, they should be **conformed by repeat testing**.

FPG: Fasting plasma glucose || **IFG:** Impaired fasting glucose. || **PG**: post glucose. || **OGTT**: Oral glucose tolerance test. || **IGT**: Impaired glucose tolerance.
A1C: Glycated hemoglobin. (HbA1C) || **DCCT**: diabetes control and complications test. ||**NGSP**: National Glycohemoglobin Standardization Program.

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 3 months.
- **A1C** and **fasting plasma glucose (FPG)** were found to be similarly effective in diagnosing diabetes.

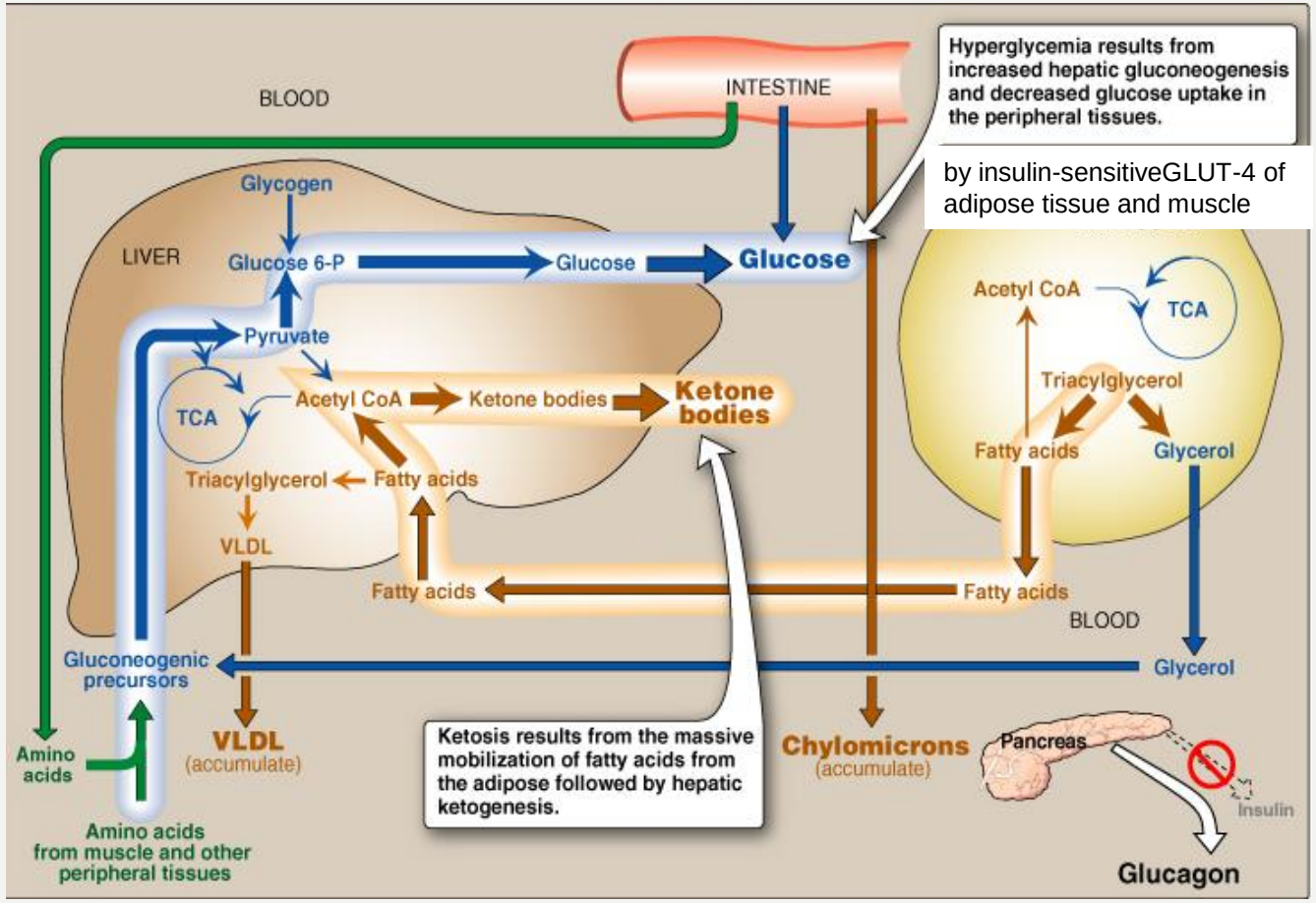


INTERTISSUE RELATIONSHIP IN T1DM

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.

we can test cholesterol along with A1C and other tests to confirm the T1DM diagnosis).

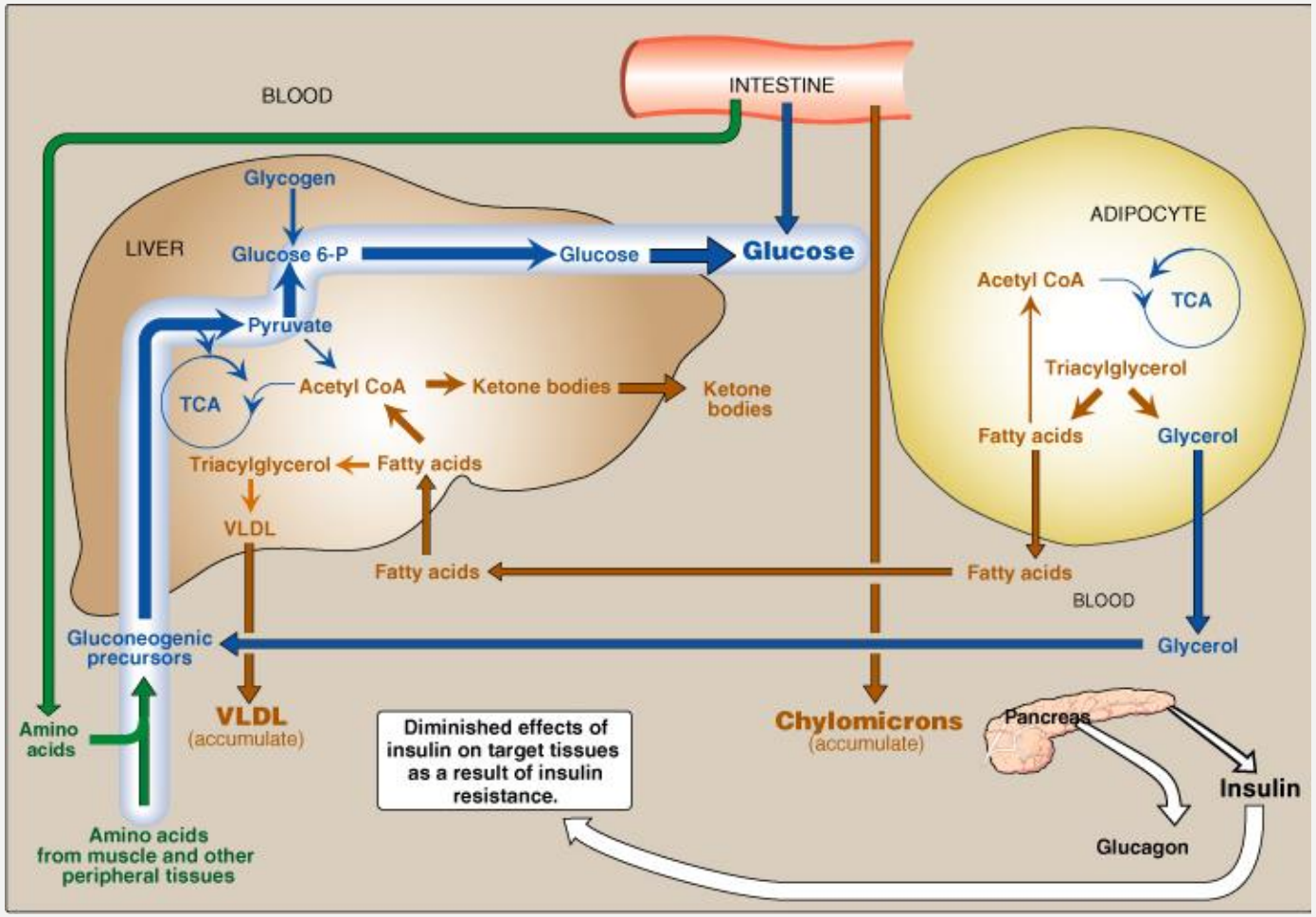


Why we don't store all the glucose going to the liver?
Insulin deficiency causes a drops in glucokinase and hexokinase levels → so they can't trap glucose inside the liver.

INTERTISSUE RELATIONSHIP IN T2DM

نفس السلايد الماضي تقريبا، بس الفرق هنا عن تايب 1 أن هنا فيه انسولين (كمية قليلة) وبالتالي تمنع تكسر البروتينات والدهون.

Remember the 10% we mentioned before that prevent proteolysis & lipolysis.



MAJOR METABOLIC CHANGES IN DM

هذا السلايد زي الملخص للتغيرات في الدايابيتس، مافيه شي جديد كلها متكررة.

Absolute or relative insulin deficiency

↓

Multiple metabolic effects

↓

CHO metabolism

- ↓ Glucose uptake by certain tissues (adipose tissue & sk. muscle)
- ↑ Glycogenolysis
- ↑ Gluconeogenesis

Lipid metabolism

- ↑ Lipolysis
- ↑ Fatty acid oxidation
- ↑ Production of Ketone bodies (in liver)

Protein metabolism

- ↓ Protein synthesis
- ↑ Protein degradation

METABOLIC EFFECTS OF DM

Absolute* or relative** insulin deficiency leads to:

↓ Glucose uptake

↓ Glucose uptake by muscle & adipose tissue:

❖ **Mechanisms of Decrease of Peripheral Glucose Uptake:**

➢ **In muscles:**

❑ ↓ Insulin → ↓ Glucose & amino acid uptake → ↑Protein breakdown → ↑Plasma glucose & amino acids.

➢ **Adipose Tissue**

❑ ↓ Insulin → ↓ Glucose uptake → ↑Plasma glucose.

↑ Glucose production

↑ Glucose production (from liver):

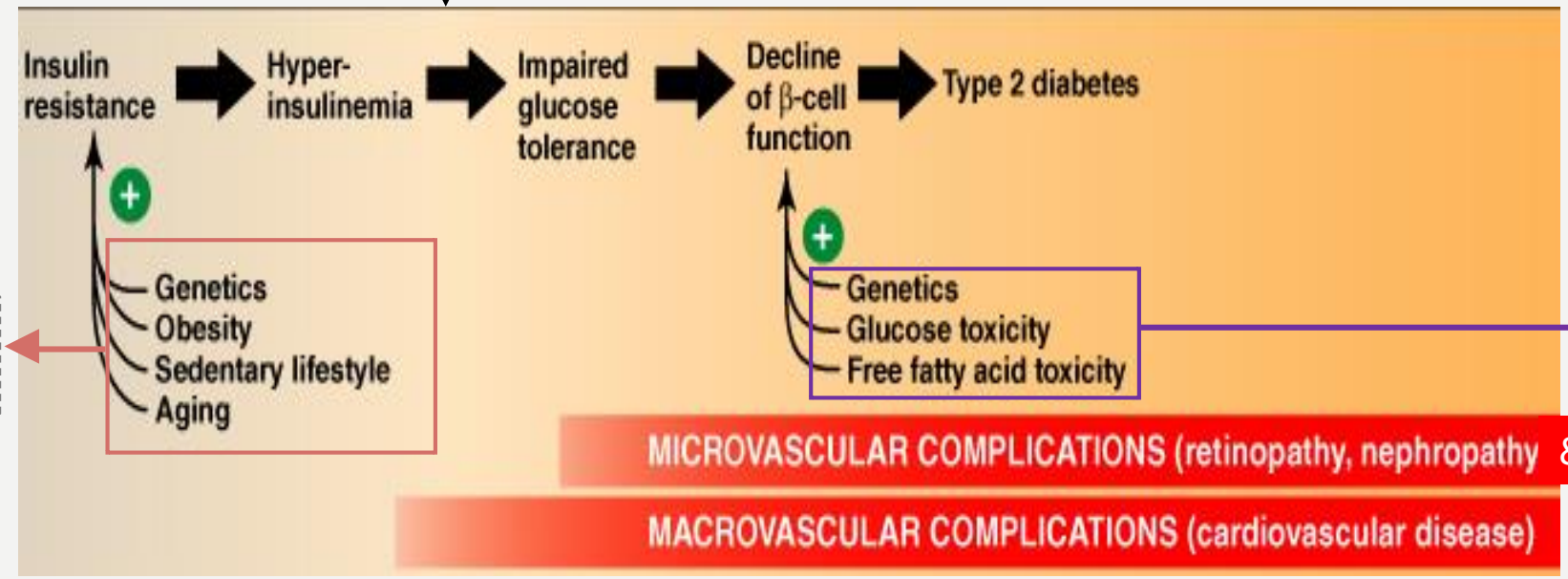
Mechanisms of Increase Hepatic Glucose Output

❑ ↓ Insulin → ↓ Inhibitory effect on glucagon secretion → ↑Glucagon → ↑Gluconeogenesis & glycogenolysis in liver → ↑Plasma glucose.

*Absolute deficiency as in type I.
**Relative deficiency as in type II.

TYPICAL PROGRESSION OF T2DM

نفس الكلام الي قلناه في السلايد رقم 5



عوامل تزيد من مقاومة الانسجة للانسولين.

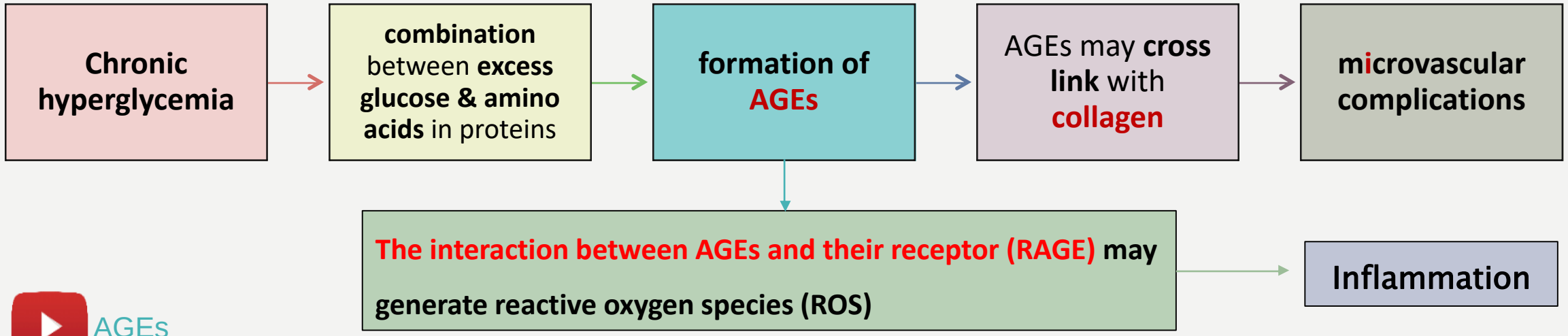
عوامل تسرع من موت البيتا سيلز في البنكرياس.

GENERAL MECHANISMS FOR DIABETIC MICROVASCULAR COMPLICATIONS

Chronic hyperglycemia leads to:

1. ↑ **Advanced Glycation End products (AGEs)** of essential cellular proteins → **cellular defects**.
2. ↑**Intracellular sorbitol** → ↑ cell **osmolality** → cellular swelling.
3. ↑ Reactive Oxygen Species (ROS) → **oxidative stress** → cell damage.

1-ADVANCED GLYCOSYLATION END PRODUCTS (AGES)

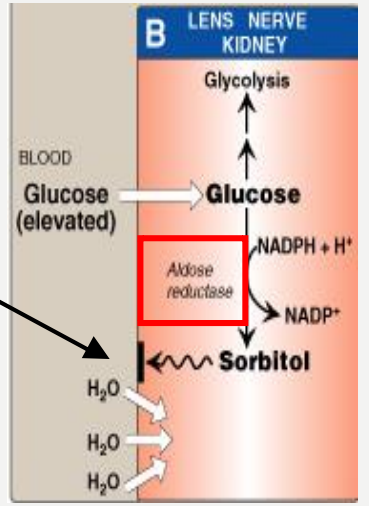


AGEs

2- SORBITOL METABOLISM: POLYOL PATHWAY

❖ **Polyol Pathway:** A pathway in which **glucose** is metabolized to **sorbitol** within the cells by **aldose reductase**. This enzyme is present in all cells of the body.

Why it's metabolized to sorbitol? Due to the excess amount of glucose in blood (the body tries to reduce it).



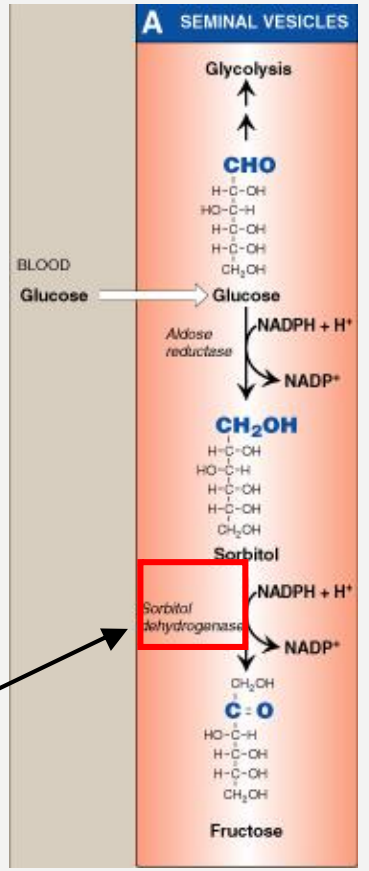
❖ **The role of sorbitol in the pathogenesis of diabetic complications is uncertain. Hypotheses are:**

1- During sorbitol production, consumption of **NADPH** → oxidative stress. (Same as AGEs with their receptors). by affecting the glutathione system. الناد بي اتش بيقل فأكيد بيأثر على الجلوتاثايون وبيسبب سترس

2- Sorbitol accumulation:

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

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



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, which is in turn is needed for some biochemical reactions in these tissues.

MICROVASCULAR COMPLICATIONS

	Diabetic Retinopathy	Diabetic Neuropathy	Diabetic Nephropathy
Definition:	A progressive **microvascular** complication of DM, affecting the retina of the eye.	Loss of both **myelinated** and **unmyelinated** nerve fibers.	Glomerular **hyper**filtration → **Microalbuminuria** → **Proteinuria** & ↓ **GFR** → **End-stage renal disease**
Occurs in:	After **20 years** of the disease: It's present in almost **all** T1DM & in **50 – 80%** of T2DM	**Both** type 1 & type 2 DM	**Both** type 1 & type 2 DM.
Info. :	➢ Major cause of morbidity in DM (may lead to **blindness**) ➢ Its prevalence ↑ with increasing duration of disease in both type **1** & **2** DM	It correlates with the **duration of DM** & with **glycemic control**.	➢ **The earliest clinical finding of diabetic nephropathy is microalbuminuria.** ✓ 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.** ✓ 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**

Diabetic retinopathy

Diabetic nephropathy

Check your understanding!

Q1: Absolute or relative metabolic activity will affect?

A. Lipid metabolism
B. .CHO metabolism
C. Protein metabolism
D. All of the above

Q2: Sorbitol is converted to fructose by which enzyme?

A. Aldose reductase
B. Sorbitol dehydrogenase
C. Sorbitol hydroxlyase
D. Dglucokinase

Q3: the earliest clinical finding in diabetic nephropathy is :

A. Microalbuminuria.
B. Macroalbuminuria.
C. Proteinuria.
D. Albumin excretion is normal.

Q4: Testing the levels of which one of the following estimates glycemic control in the last 1-2 months :

A. FBG
B. .HBA1c
C. FFA
D. insulin

Q5: Regarding diabetic retinopathy, which one is incorrect:

A. Higher risk in type 1.
B. Microvascular disease contributes in the progression of diabetic retinopathy.
C. Never happens in type 2
D. Common complication.

Q6:T1DM Is more strongly associated with Genetic than DMT2 :

A. True
B. False

1.D 2.B 3.A 4.B 5.C 6.B

Check your understanding!

Q7: In the beginning of Diabetic nephropathy the GFR will be ?

A. Increased
B. Decreased
C. Normal
D. Highly decreased

Q8: Which of the following is A major cause of morbidity in DM?

A. Blindness
B. end-stage renal disease
C. infection
D. None

Q9: mechanism of Diabetic microvascular complication :

A. Increase intracellular sorbitol
B. Increase cell osmolality
C. Cellular swelling
D. All of them

Q10:Chronic hyperglycemia will lead to non-enzymtic combination between excess glucose and amino acid in protein which is known as?

A. Polyol pathway
B. ROS
C. Advanced glycosylation End product
D. None of the above

Q11: Which one of the following cut-off points of hemoglobin A1C is used to diagnose diabetes?

A. Less than 6.5%
B. More than 6.5%
C. More than 5.6%
D. Less than 5.6%

Q12: decrease in the lipolysis is a metabolic affect of insulin :

A. True
B. False

7.A 8.A 9.D 10.C 11.B 12.A

Done by:

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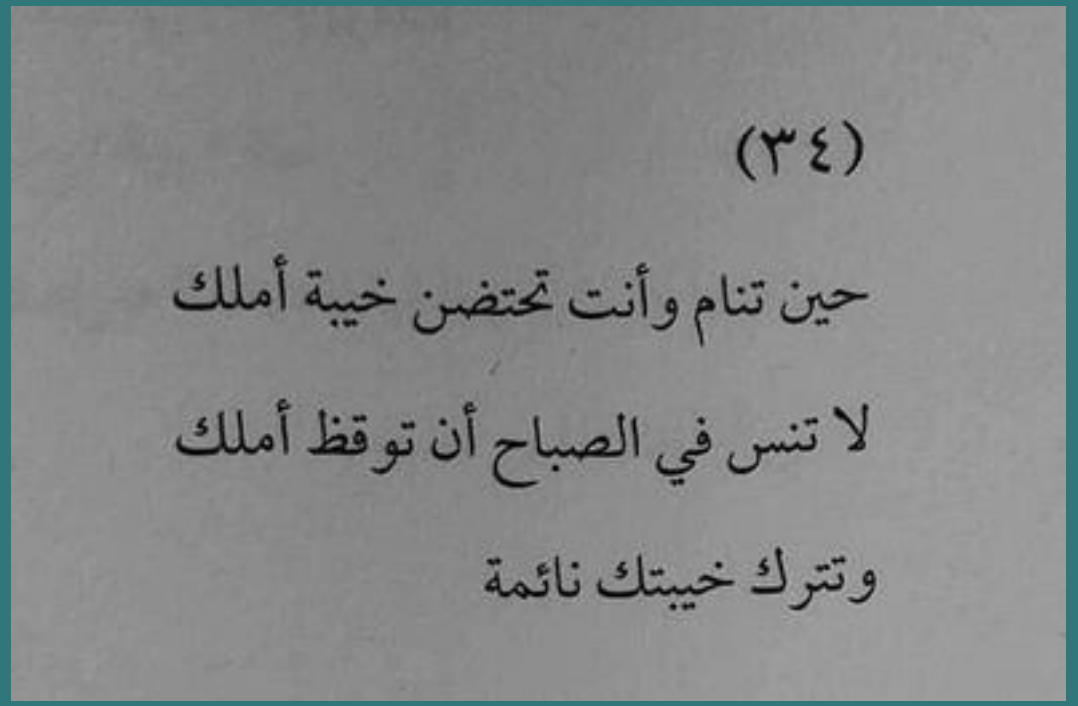
- شهد العنزي.
- عبدالله الشنيفي.
- لينا الشهري.
- أحمد الرويلي.
- نوف الرشيد.



Resources:

- 435's slides and notes.
- Lippincott's illustrated reviews: Biochemistry – sixth edition.

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