جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

Metabolic changes in diabetes mellitus

Biochemistry Team 437

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Doctors slides
Doctor's notes
Extra information
Highlights

Endocrine block

Lecture outlines:

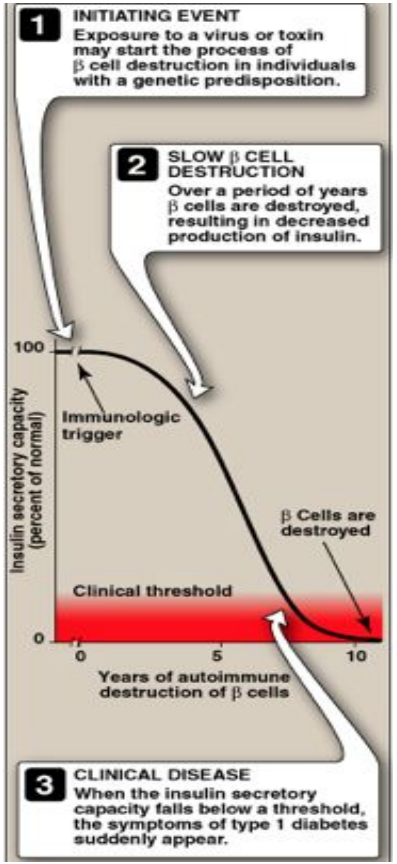
- **Background**
  - Differences between type 1 and type 2 DM
  - Natural course of T1DM
  - Natural course of T2DM
- **Diagnostic criteria for DM**
- **Metabolic changes in DM**
  - Increase of hepatic glucose output
  - Decrease of glucose uptake
  - Inter-organ relationship in T1DM and T2DM
- **Mechanisms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

Comparison of type 1 and type 2 DM

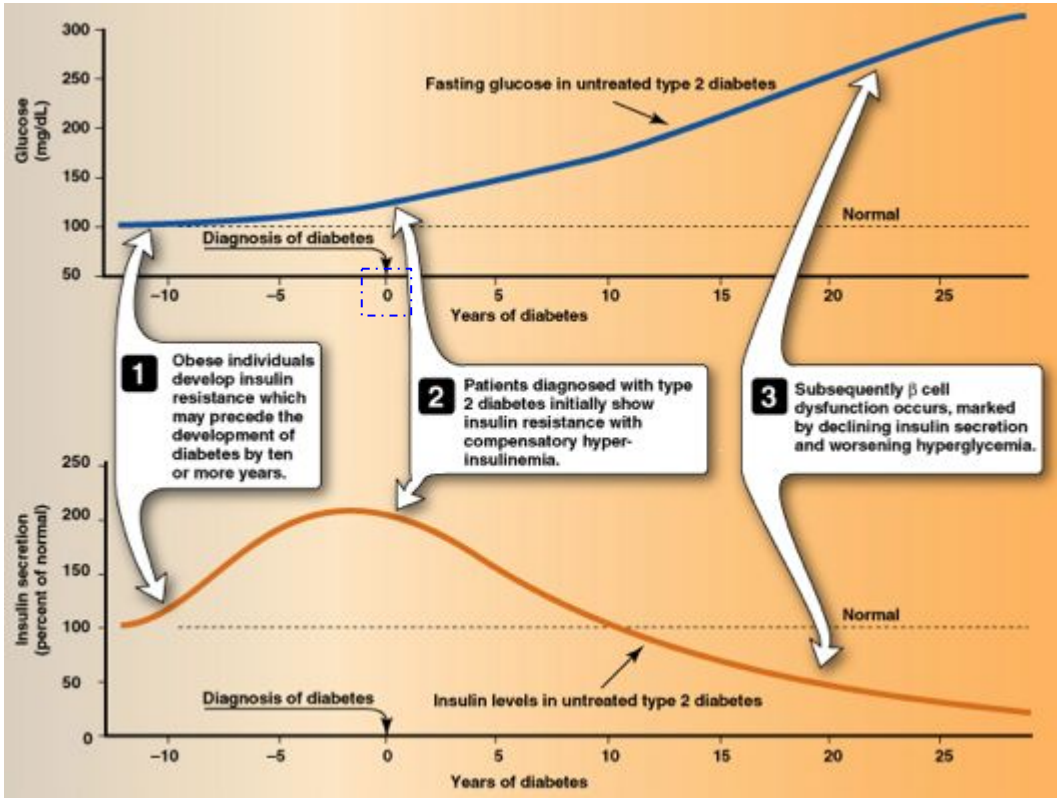
	Type 1 Diabetes	Type 2 Diabetes
AGE OF ONSET	Usually during childhood or puberty; symptoms develop rapidly	Frequently after age 35; symptoms develop gradually
NUTRITIONAL STATUS AT TIME OF DISEASE ONSET	Frequently undernourished	Obesity usually present
PREVALENCE	900,000 = 10% of diagnosed diabetics	10 Million = 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 coma
TREATMENT WITH ORAL HYPOGLYCEMIC DRUGS	Unresponsive	Responsive
TREATMENT	Insulin is always necessary	Diet, exercise, oral hypoglycemic drugs, +/– insulin

Natural course of T1DM

- 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



- 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.

the diagnosis happens at point zero

Criteria for Diagnosis of DM*

*American Diabetes Association (ADA), 2010

Test:	About test:	Increased risk for diabetes: (pre diabetic state)	Diagnosis of diabetes: هنا نكون متأكدين ان المريض عنده سكر إذا ظهرت لنا أحد هذي النتائج
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. يعطون الشخص ٧٥ جرام جلوكوز ويقيسونه بعد ساعتين بالحالة النورمال الجلوكوز بيرتفع بعدين بيرجع نورمال ليه؟ لأن فيه هوميوستيسس.. اذا الشخص يعاني من مشاكل ماراح يرجع نورمال	7.8 - 11 mmol/L (IGT) 140 - 199 mg/dL	11 mmol/L ≥200 mg/dL
HbA1c:	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	هنا نقيس مستوى الجلوكوز (عشوائيا) بدون تهيئة ظروف معينة "مانعطيهم جلوكوز من نفسه مرتفع" هالتست يستخدم لمن الشخص يجي ومعاه اعراض الهايبر جلاسيميا الكلاسيكال.	-	≥11.1 mmol ≥200 mg/dL + classic symptoms of hyperglycemia.

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.

To convert from mmol\L to mg\dl use this equation: (mmol\L * 18 = mg\L)

HEMOGLOBIN A1C

Hemoglobin A1C (A1C)	• Is the result of non enzymatic covalent glycosylation of hemoglobin
Used for	• Recently, A1C is recommended for the detection of T2DM • It is used to estimate glycemic control in the last 1-2 months • A1C and fasting plasma glucose (FPG) were found to be similarly effective in diagnosing diabetes.
Notes	• 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[1] or relative[2] insulin deficiency
↓ Glucose uptake (muscle & adipose tissue)
↑ Glucose production (liver)

1: Absolute insulin deficiency → DMT1
2: relative insulin deficiency → DMT2

Intertissue Relationship in T1DM

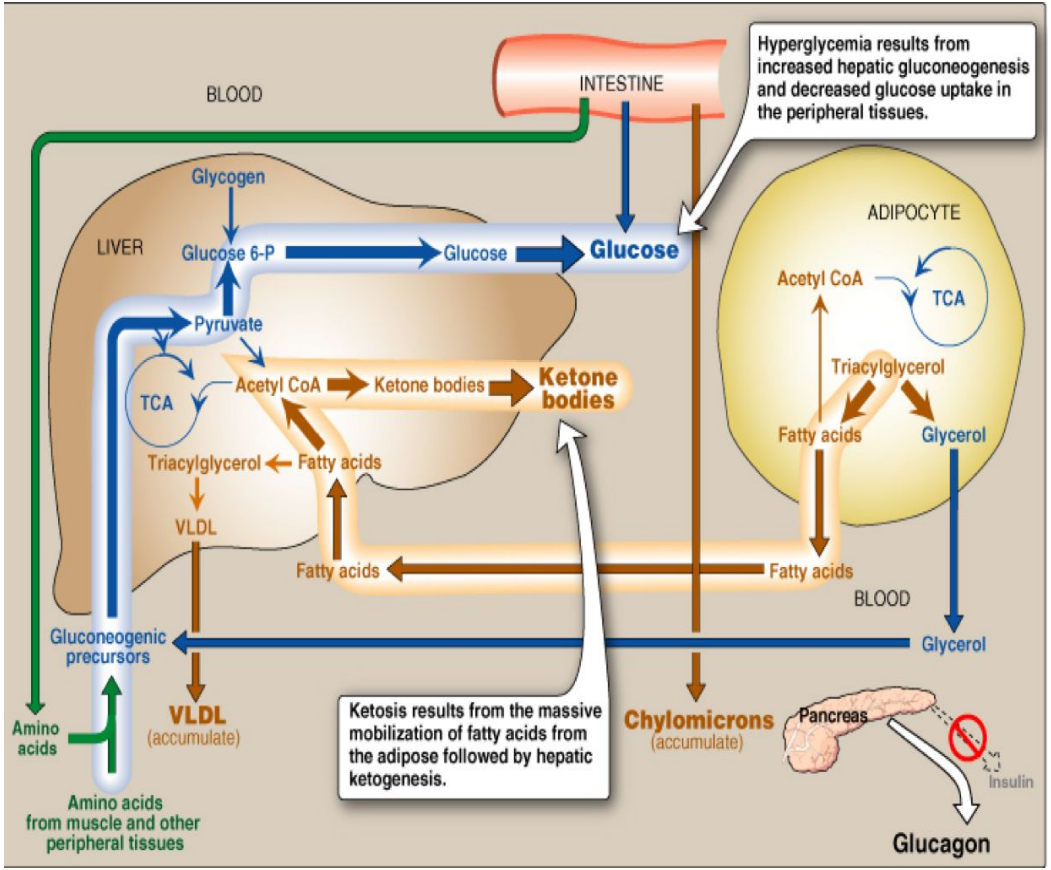
the pancreas is not secreting insulin but it is secreting glucagon which has 2 effects, gluconeogenesis and glycogenolysis.

1) gluconeogenesis
   - The intestine absorbs glucose, and amino acids which are delivered to the liver along with the amino acids coming from muscle breakdown, these substances are used for gluconeogenesis

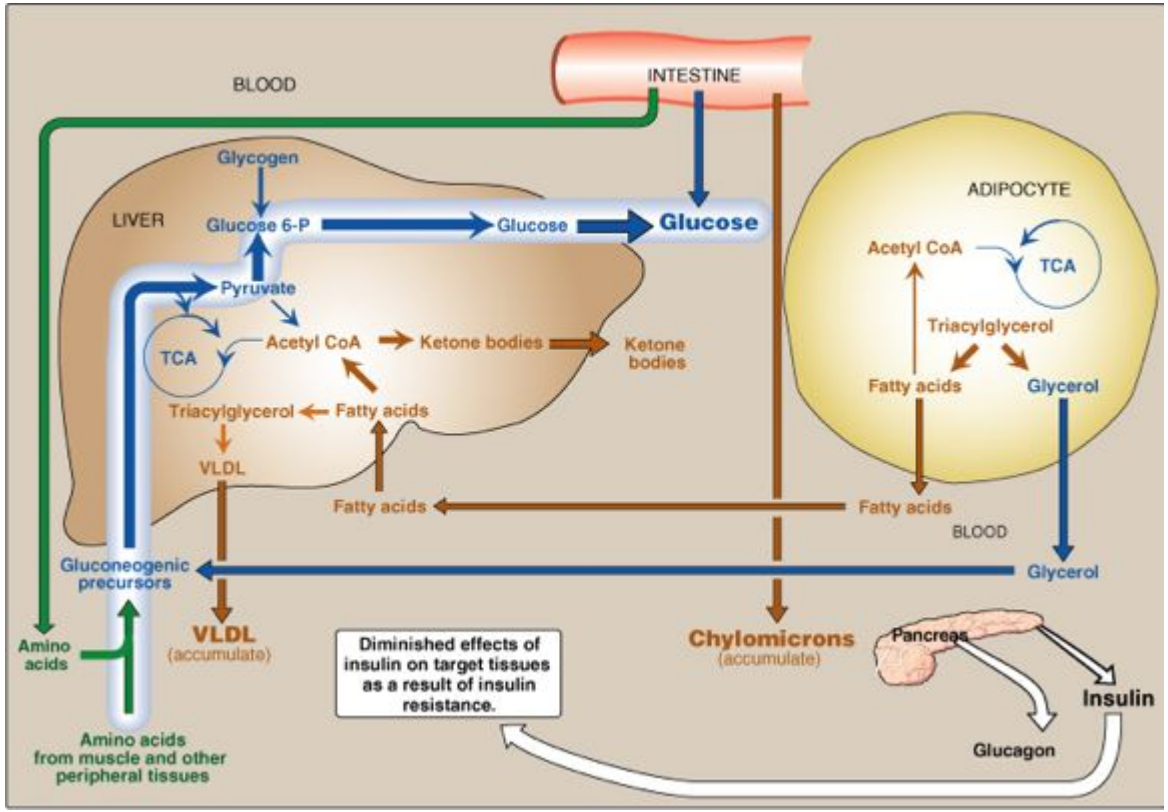
2) glycogenolysis
   - Glycogen is broken down in the liver which releases glucose

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 T2DM



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

Major Metabolic changes in DM

Absolute or relative insulin deficiency

↓

Multiple metabolic effects

CHO metabolism

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

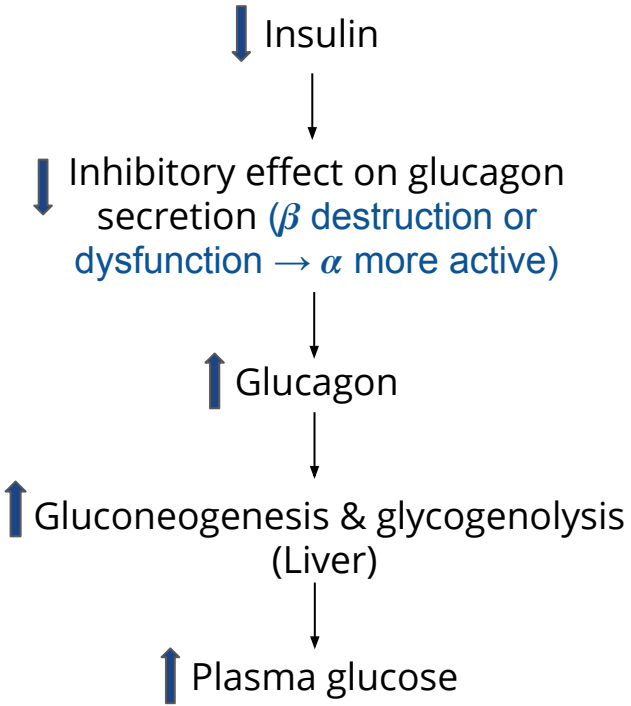
Lipid metabolism

- ↑ Lipolysis
- ↑ Fatty acid oxidation
- ↑ Production of Ketone bodies

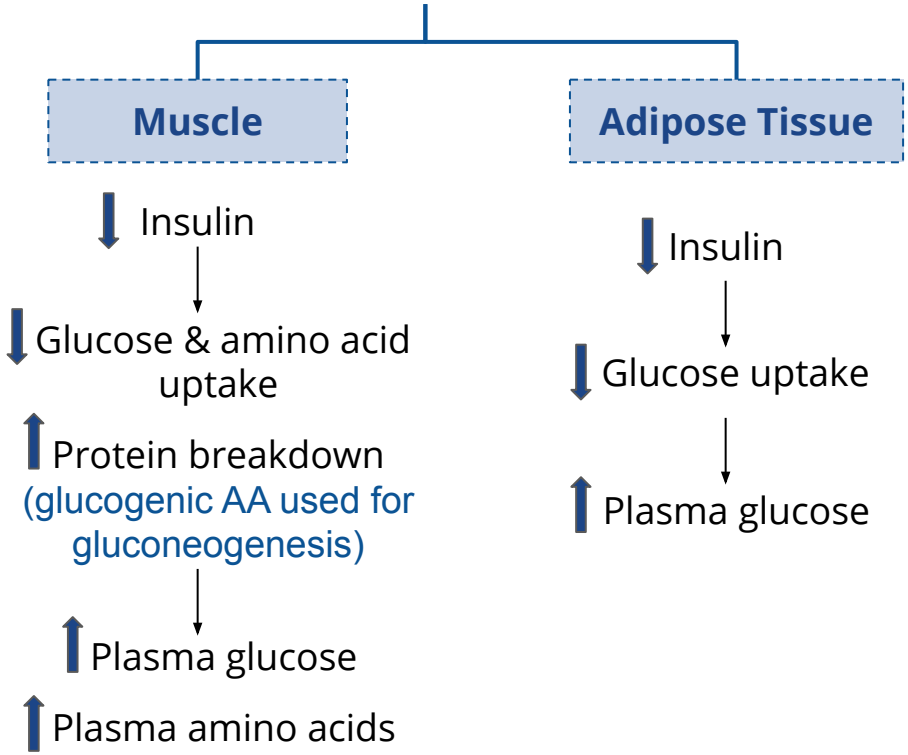
Protein metabolism

- ↓ Protein synthesis
- ↑ Protein degradation

Mechanisms of Increase Hepatic Glucose Output



Mechanisms of Decrease of Peripheral Glucose Uptake



Mechanisms of Diabetic Complications

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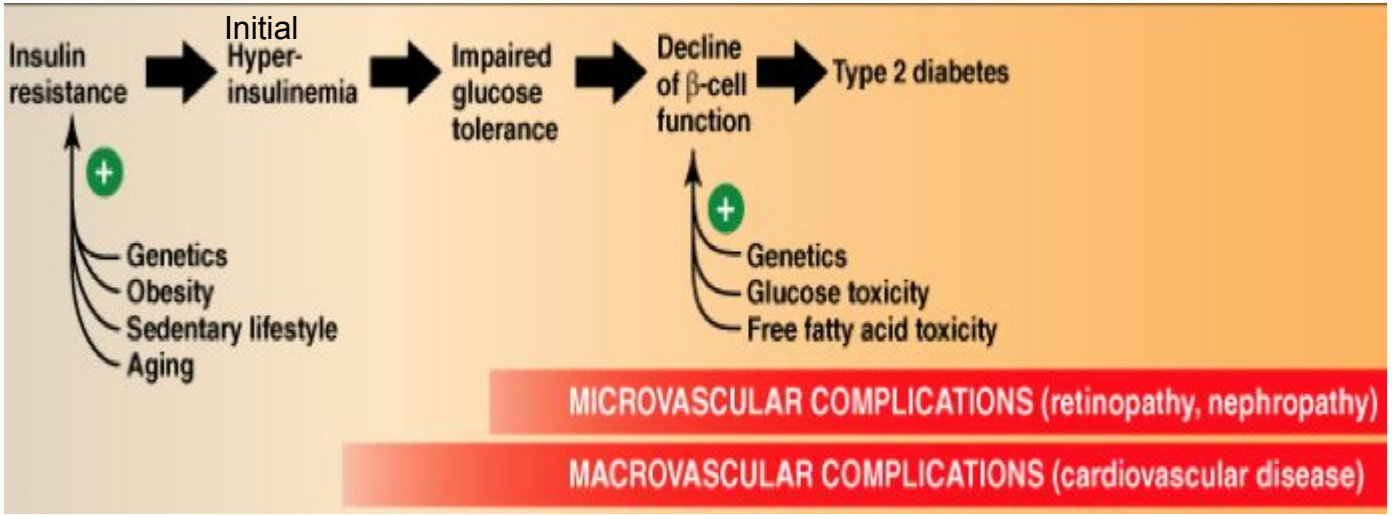
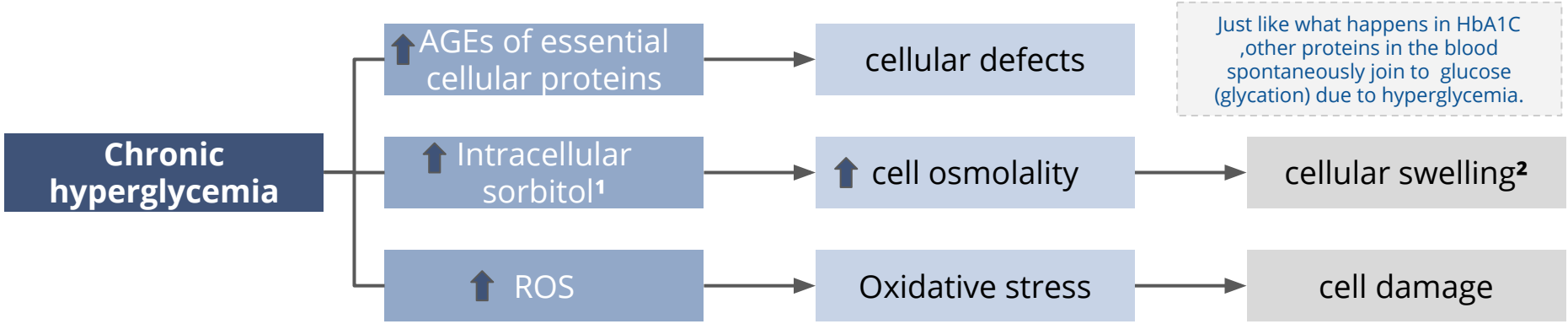
Typical Progression of T2DM



+neuropathy

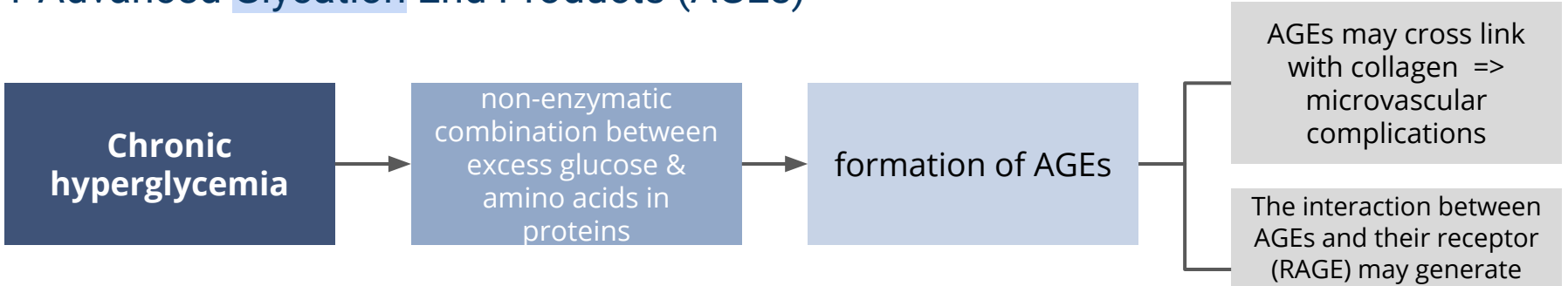
e.g. Atherosclerosis

General Mechanisms for Diabetic Microvascular Complications



Just like what happens in HbA1C ,other proteins in the blood spontaneously join to glucose (glycation) due to hyperglycemia.

1-Advanced Glycation End Products (AGEs)



1: Sorbitol is sugar made from unused glucose in the cells, and it is osmotically active .

2: This is one of the mechanisms involved in Retinopathy

2- Polyol pathway

sorbitol formation pathway

Sorbitol Metabolism

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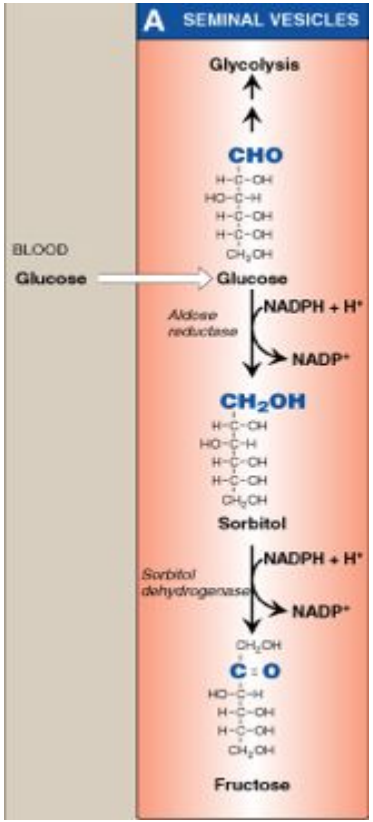
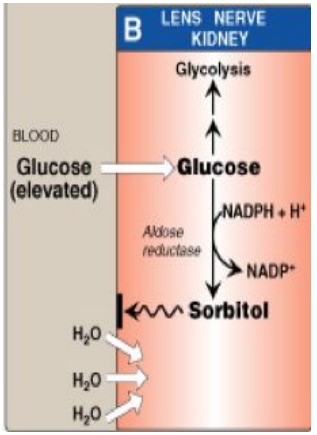
- **Excess** Glucose is metabolized to sorbitol within the cells by aldose reductase
- The role of sorbitol in the pathogenesis of diabetic complications is uncertain. Hypotheses are:

1. During sorbitol production, consumption of NADPH → oxidative stress. Remmember NADPH is important for antioxidant pathway
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 (protein kinase C) → altered VEGF (vascular endothelial growth factor) activity → altered vascular permeability

Remmeber, sorbitol is osmotically active





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

Diabetic Microvascular Complications

Diabetic Retinopathy	Diabetic Nephropathy	Diabetic Neuropathy
- 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	- 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	- 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

Sequence of Events in Diabetic Nephropathy

1: Glomerular hyperfiltration is due to hypertension

Glomerular hyperfiltration[1] → Microalbuminuria → Proteinuria & ↓ GFR → End-stage renal disease

Summary

- **T1DM** results from destruction of beta cells of the pancreas while **T2DM** is due to the development of insulin resistance.
- **Genetics**, **Obesity** , **sedentary lifestyle** and **aging** are the factors which may contribute in the development of insulin resistance.
- Criteria for diagnosis of DM includes assessment of FPG - OGTT - A1C .
- Complica.ons of DM are classified into :
  - **Macrovascular** (CVS diseases)
  - **microvascular** (Neuropathy , Retinopathy)
- General Mechanisms for Diabetic Microvascular Complications:

↑ Advanced Glycation End products (AGEs) of essential cellular proteins a cellular defects

↑Intracellular sorbitol ↑ cell osmolality a cellular swelling

↑ Reactive Oxygen Species (ROS) a oxidative stress a cell damage

- The earliest clinical finding of diabetic nephropathy is **microalbuminuria** then progression to **proteinuria** and **decrease GFR** and may end with **end-stage renal** disease .

MCQS

1.Which test used to estimate glycemic control in the last 1-2 months?
A) HbA1C
B) 2 hours in FPG
C) Random blood glucose
D) OGTT

2.Which one of the following is not a metabolic effect happens with insulin deficiency?
A) increase glycogenolysis
B) increase protein synthesis
C) increase FA oxidation
D) decrease glucose uptake

3.Diabetic nephropathy occurs
A) Type 1 DM
B) Type 2 DM
C) Gestational diabetes
D) both types 1 and 2

4.(From 436team)Microalbuminuria progresses into which of the following?
A) Nephritic syndrome
B) Pyelonephritis
C) Glucosuria
D) Decreased GFR

5.(From 436team)Which one of the following may cross link with AGEs?
A) Glucose
B) Proteins
C) Keratin
D) Collagen

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

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Girls team

- رزان الزهراني
- منيرة المسعد
- مها القحطاني
- رهف الشنيبر
- اروى الجهني

Boys team

Team leaders

- رهام الحلبي
- معاذ الحمود

@biochemistry437

teambiochem437@gmail.com