Revised & Approved

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BIOCHEMISTRY TEAM
439

MED439
KING SAUD UNIVERSITY

Metabolic changes in DM

Editing File

Color Index

- Main Text
- Important
- Extra
- Dr.'s Notes
- Girls slides
- Boys slides

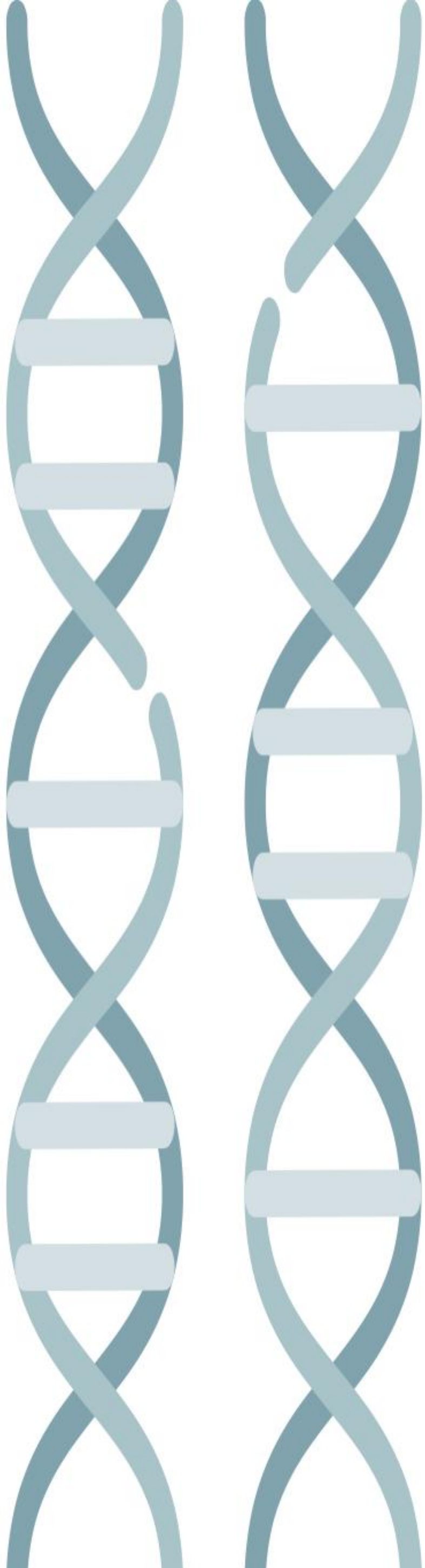
Objectives

Background
o Differences between type 1 and type 2 DM
o Natural course of T1DM
o 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

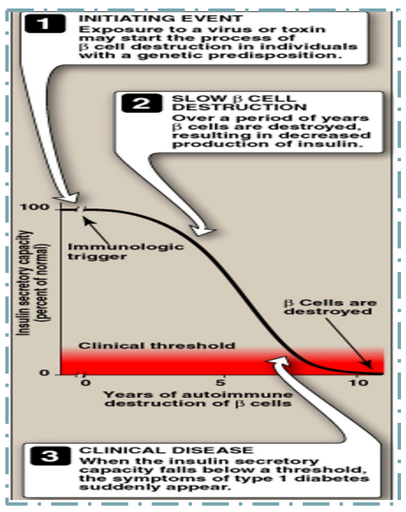
Mechanisms of diabetic complications



Comparison of type 1 and type 2 diabetes mellitus

	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	90,000=10% of diagnosed diabetics	10 millions= 90% of diagnosed diabetics
Genetic predisposition	moderate(Dr sumbl :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
Plasma insulin	Low to absent	High early in disease; low in disease of long duration
Acute complications imp	ketoacidosis	Hyperosmolar coma
Treatment with oral hypoglycemic drugs	Unresponsive	Responsive
Treatment	Insulin is always necessary	diet , exercise, oral hypoglycemic drugs, +/- insulin

Natural course of T1 DM



❖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 rst the insulin level will decreases gradually but you will not see any symptoms because this level is still sufficient to maintain glucose level.

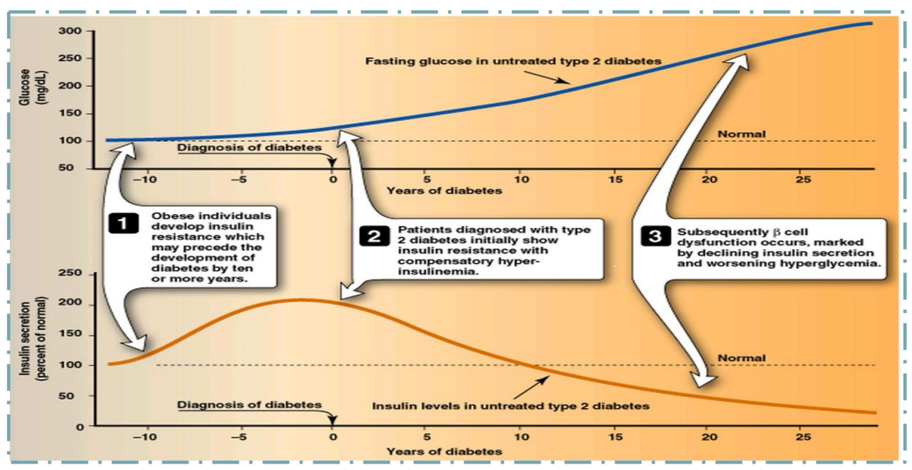
❖after 80%-90% of β cells have been destroyed clinical symptoms will appear, and when the symptoms appears the progression will be fast.

❖So, if you see the clinical symptoms that means the remaining insulin secretory capacity is only 10%-20% (the clinical threshold).

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 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.

Categories of increased risk of diabetes

IFG (impaired fasting glucose)

FPG(fasting plasma glucose) 100-125 mg/dL (5.6-6.9mmol/L)

A1C(glycated hemoglobin)

5.7-6.4% (39-46 mmol/mol)

Or

2h-PG (post glucose) in the 75-g OGTT 140-199 mg/dL (7.8-11.0 mmol/L)

IGT(impaired glucose tolerance)

Criteria for diagnosis of DM

FPG (fasting plasma glucose) great than or equal to 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.
OR

Two-hour plasma glucose greater than or equal to 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 organisaion, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

A1C greater than or equal to 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

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

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

-A1C and fasting plasma glucose (FPG) were found to be similarly effective in diagnosing diabetes.
-A1C cut-off point of greater than 6.5% is used to diagnose diabetes .

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

Recently, A1C is recommended for the detection of T2 DM.
Why T2?
Because it is discovered in a regular check (slow)

A1C values also correlate with the prevalence of retinopathy.

Metabolic Effects of Diabetes Mellitus

Absolute or relative insulin deficiency

Absolute = T1DM
Relative = T2DM

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

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 sumbl : excessive in T1 because there is absolute deficiency of insulin

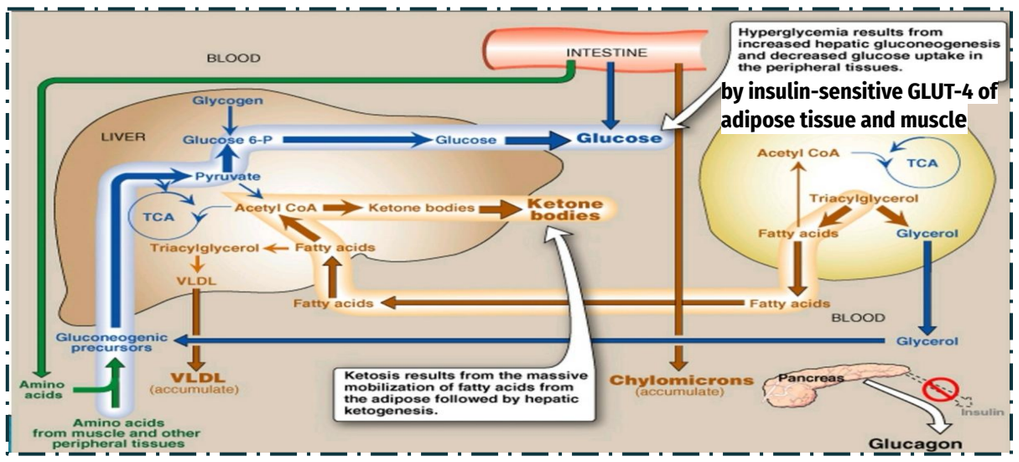
Protein metabolism
- Decrease protein synthesis
- Increase protein degradation

Can be utilized in guocogengesis .

Mechanisms of Increase Hepatic Glucose Output

Decrease insulin → Decrease inhibitory effect on glucagon secretion → Increase glucagon → Increase gluconeogenesis and glycogenolysis (liver) → Increase plasma glucose

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:

- 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:

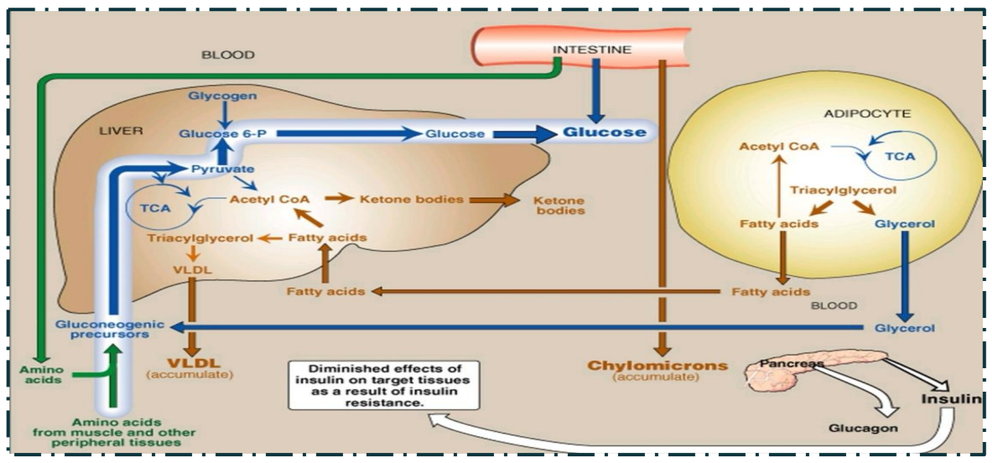
- Glycogen is broken down in the liver which releases glucose.

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).

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.

mechanisms of Decrease of Peripheral Glucose Uptake

Muscle

Decrease insulin

↓

- decrease glucose and amino acid uptake
- Increase protein breakdown

↓

- Increase plasma glucose
- Increase plasma amino acid

Adipose Tissue

Decrease insulin

↓

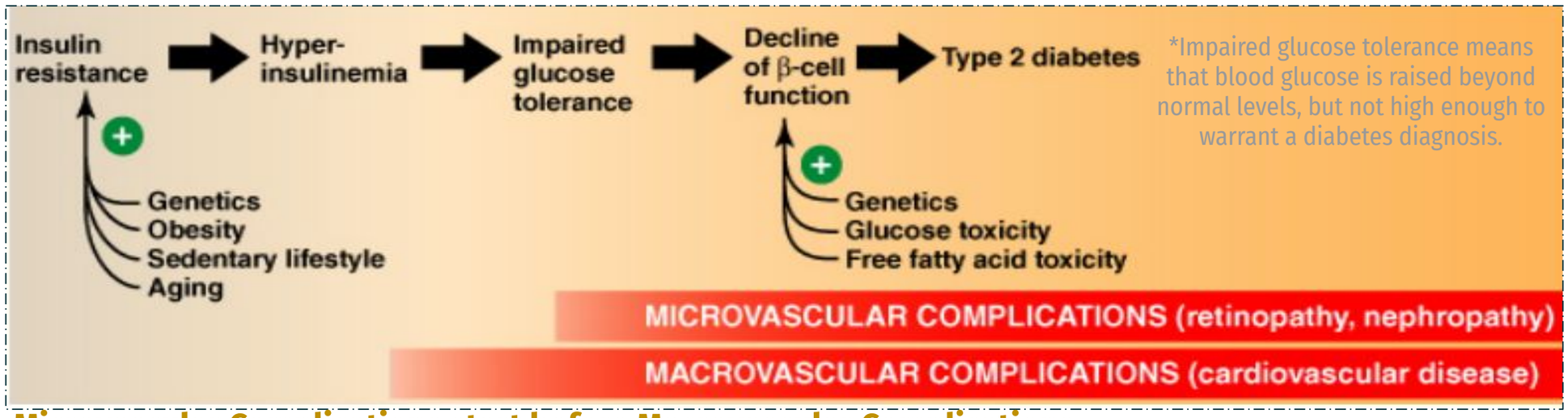
Decrease glucose uptake

↓

Increase plasma glucose

Mechanisms of Diabetic Complications

Typical progression of T2DM



Microvascular Complications start before Macrovascular Complications

General Mechanisms for (Diabetic Microvascular Complications)

Chronic Hyperglycemia

- ↑ **AGEs of essential cellular proteins** → Cellular Defects
- ↑ **Intracellular Sorbitol** → ↑cell osmolality → Cellular Swelling
- ↑**ROS** → Oxidative stress → Cell Damage

Advanced Glycation End Products (AGEs)

Chronic <u>Hyper</u>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.

(Advanced Glycation End Products): Like what happens in HbA1C ,other proteins in the blood spontaneously join to glucose (glycation) due to hyperglycemia.

Polyol pathway

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:

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

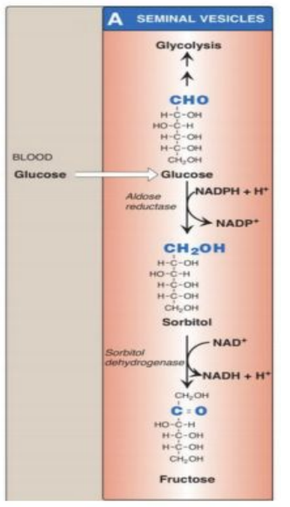
الزبدة هو: alcoholic form of glucose

Remember glutathione pathway?

1 During sorbitol production, consumption of NADPH2 → 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 (protein kinase C) → altered VEGF (vascular endothelial growth factor) activity → altered vascular permeability.



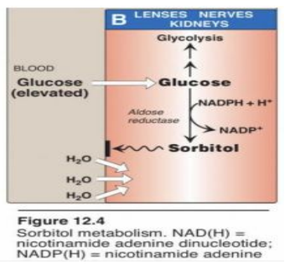


Figure 12.4
Sorbitol metabolism. NAD(H) = nicotinamide adenine dinucleotide; NADP(H) = nicotinamide adenine

Diabetic Microvascular Complications

1 - 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 - Is present in **almost all** T1DM. 2 - Is present in **50 – 80%** of T2DM.

2 - Diabetic Nephropathy

- Occurs in both type 1 & type 2 DM.
- The earliest clinical finding of diabetic nephropathy is microalbuminuria(أصغر albumin حجم لأن):
  (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(مع الوقت بتطلع كل البروتينات):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**

3 - 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

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

MCQs

1- 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
2- Absolute or relative insulin deficiency causes all of the following <u>except :</u>			
A-Increase lipolysis	B-Decrease protein synthesis	C- Decrease protein degradation	D- Increase glycogenolysis
3- Decrease insulin in muscle will lead to :			
A- Increase protein breakdown	B- Decrease glucose uptake	C- Decrease amino acid uptake	D- All of the above
4- which of the following considered as Microvascular complication of DM?			
A- CVD	B- Neuropathy	C- Stroke	D- Peripheral arterial disease
5- Which one of the following may cross link with AGEs?			
A- Glucose	B- Proteins	C- Keratin	D-Collagen
6- Diabetic nephropathy occurs ?			
A-Type 1 DM	B- Type 2 DM	C-both types 1 and 2	D- Gestational diabetes

Answers key

1- B 2- C 3- D 4- B 5 - D 6- C

SAQs

1- what is hemoglobin A1C ?

Hemoglobin A1C is the result of non enzymatic covalent glycosylation of HB.

2- What are the General mechanisms for microvascular complications in DM?

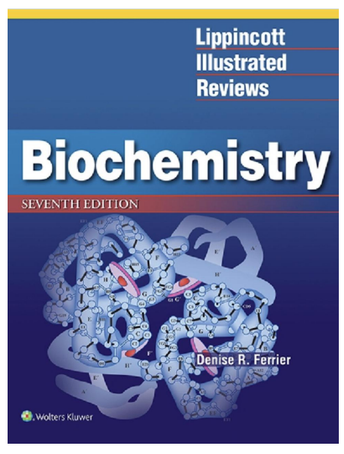
Slide 11

3- Sequence of Events in Diabetic Nephropathy?

Glomerular hyperfiltration - Microalbuminuria - Proteinuria & ↓ GFR - End-stage renal disease .

Resources

Click on the book to download the resource



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