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Special thanks to :

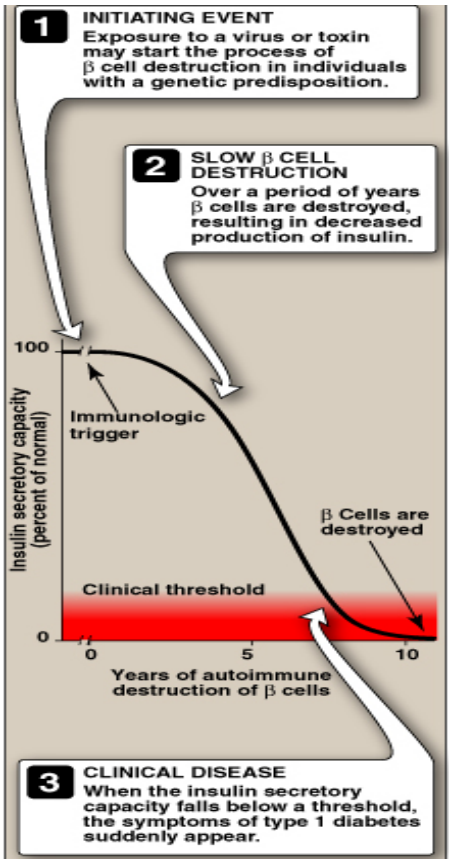
Abdullah alaqeel

Comparison of type 1 and type 2 DM

Imp.

	Type 1 Diabetes (10% of cases)	Type 2 Diabetes (90% of cases)
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 (type 1 Diabetes mellitus)



Disease course :

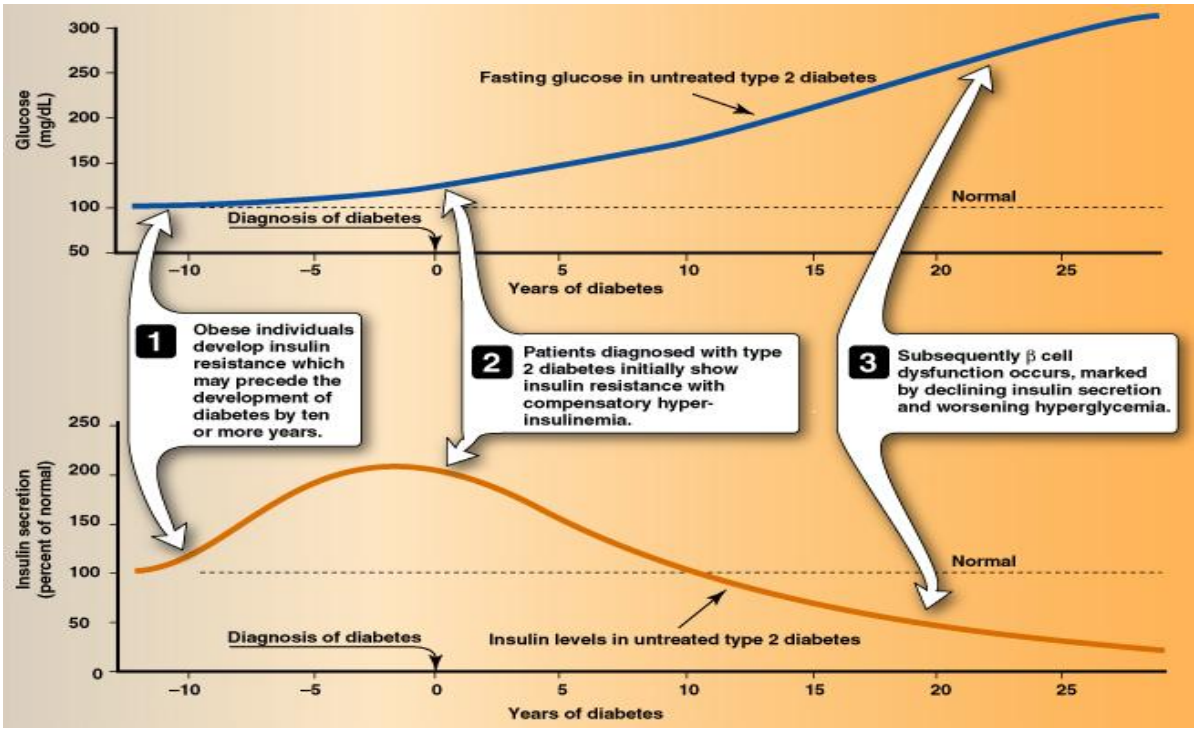
1- In this type there are viral or chemical or genetic abnormality (it is still unknown) lead to destruction of the Beta cells

2- This destruction lead to inflammatory and autoimmunity Reaction

3- the production of Insulin will severely reduce due to the destruction of the source (B cells)

Note : the destruction of beta cells occur during very long time (up to 4 to 5 years or

Progression of T2DM:



The disease course of the type 2 take more than type 1 → it take from 10 to 20 Y to appear

Criteria for Diagnosis of DM*

Criteria for the diagnosis of diabetes

1. A1C ≥6.5 percent. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.* **OR**
2. FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.* **OR**
3. Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. 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.* **OR**
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

A1C: glycated hemoglobin; NGSP: National glycohemoglobin standardization program; DCCT: Diabetes control and complications trial; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test.
* In the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing.
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***American Diabetes Association**

There are 4 testes used to Diagnose diabetes :

Test 1 : measure the amount of Hemoglobin A1C (which is Hb + Glucose bind to it)
If the result is : > 6.5 → it diagnose Diabetes

Test 2 : FPG : Fasting plasma glucose
Procedures : measure the glucose level of subject that has been fasting for at least 8 H
If the result : > 126 → it diagnose Diabetes

Test 3 : 2 h plasma glucose :
Procedures : the subject is given 75 g of glucose after fasting and then measure the glucose level after 2 H
If the result : > 200 → it diagnose Diabetes

Test 4 ; random plasma glucose :
This test is a measure of the level of sugar without any procedures before- this is done in cases of emergency, which is similar to the result of the preceding test

Notes : To concerted from MMOL → MG (we * 18)

Categories of increased risk for diabetes*

FPG 100-125 mg/dL (5.6-6.9 mmol/L) [IFG]
2-h PG on the 75-g OGTT 140-199 mg/dL (7.8-11.0 mmol/L) [IGT]
A1C 5.7-6.4 percent

FPG: fasting plasma glucose; IFG: impaired fasting glucose; PG: post glucose; OGTT: oral glucose tolerance test; IGT: impaired glucose tolerance; A1C: glycated hemoglobin.

If the results from the previous test become just below the – diagnostic result – the patient is consider at high risk group

HEMOGLOBIN A1C:

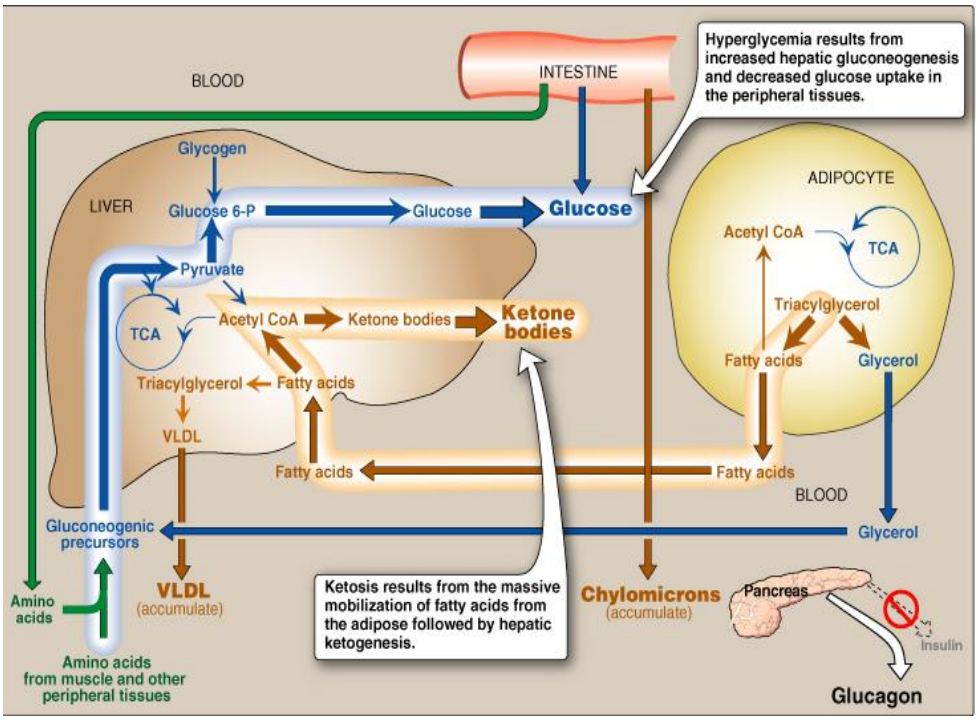
- Hemoglobin A1C (A1C) **is the result of** non enzymatic covalent glycosylation of hemoglobin
- Recently, A1C **is recommended for** the detection of T2DM
- A1C and fasting plasma glucose (FPG) were found to be similarly effective in diagnosing diabetes.
- A1C cut-off point **of >** 6.5 % is used to 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).
- It is used to estimate glycemic control **in the last 1-2 months**

هذا الاختبار كان في السابق يستخدم لمتابعه العلاج لمرضى السكر فقط – وكان يستخدم لمتابعه العلاج كل شهر الى شهرين لان الهيموجلوبين يتجدد كل فتره شهر الى شهرين بعد ذلك تم عمل اجراء موحد دولي لهذا الاختبار واصبح مقياس معتمد لتشخيص مرض السكر

Metabolic Effects of Diabetes Mellitus

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

Intertissue Relationship in T1DM



CHO metabolism

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

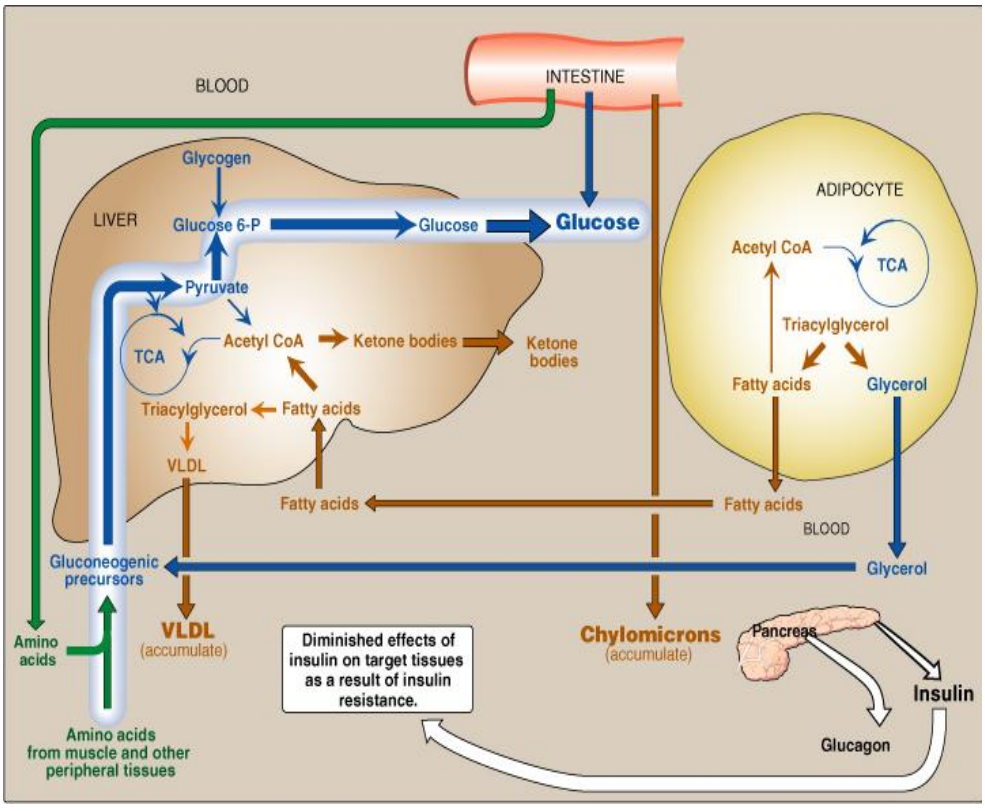
Lipid metabolism

- ↑ Lipolysis
- ↑ Fatty acid oxidation
- ↑ Production of Ketone bodies (very large quantity)

Protein metabolism

- ↓ Protein synthesis
- ↑ Protein degradation

Intertissue Relationship in T2DM



CHO metabolism

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

Lipid metabolism

- ↑ Lipolysis
- ↑ Fatty acid oxidation
- ↑ Production of Ketone bodies (less than previous one)

Protein metabolism

- ↓ Protein synthesis
- ↑ Protein degradation

Major Metabolic changes in DM

Absolute (type 1) or relative (type 2) 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
1- Hepatic Glucose Output

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

2- Mechanisms of Decrease of Peripheral Glucose Uptake

Muscle:

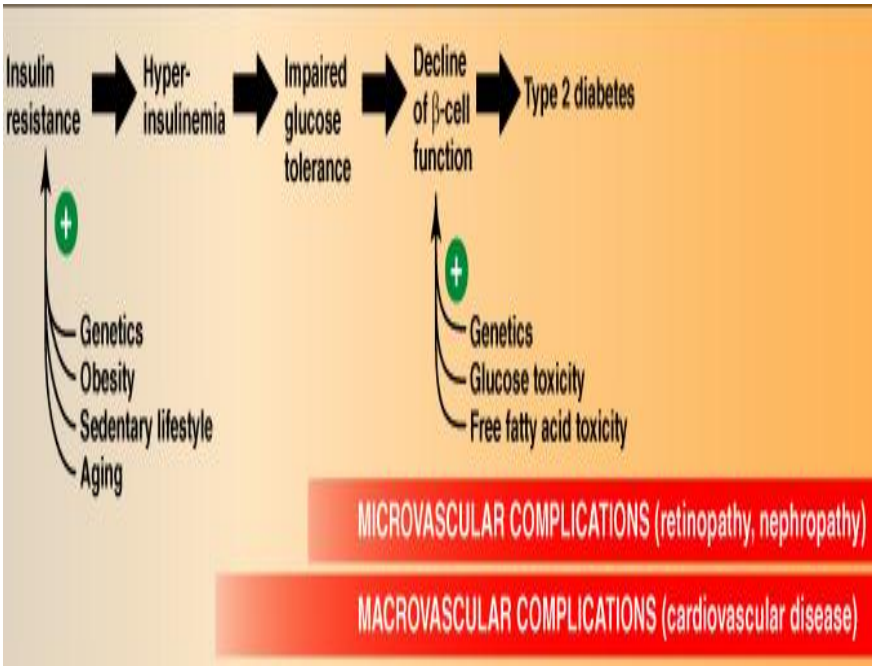
↓ Insulin → ↑ Glucose & amino acid uptake & ↑Protein breakdown → ↑ Plasma glucose ↑Plasma amino acids

Adipose Tissue:

↓ Insulin → ↓ **Glucose uptake** → ↑ **Plasma glucose**

Mechanisms of Diabetic Complications

Typical Progression of T2DM



2 types of complication appears

1- microvascular complications

(will be explained)

2- macrovascular complications

(not our topic in this lec.)

General Mechanisms for Diabetic Microvascular Complications

1- Chronic hyperglycemia →

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

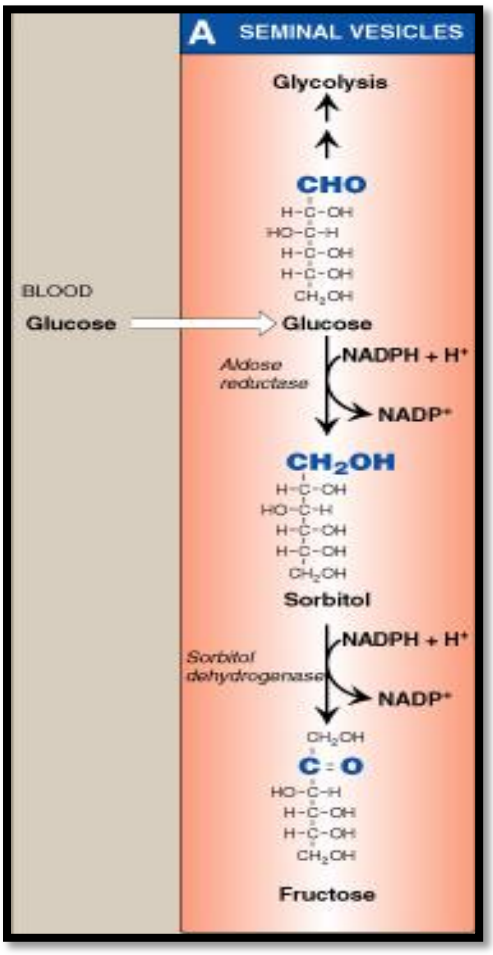
2- Advanced Glycosylation End Products (AGEs)

- **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**

3- Polyol pathway

- **Glucose is metabolized to sorbitol within the cells by aldose reductase Sorbitol**
- **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
A Mechanism for Diabetic Complications



في كل خلايا الجسم ما عدا :

الكليه – العدسه – الرتينا – الجهاز العصبي

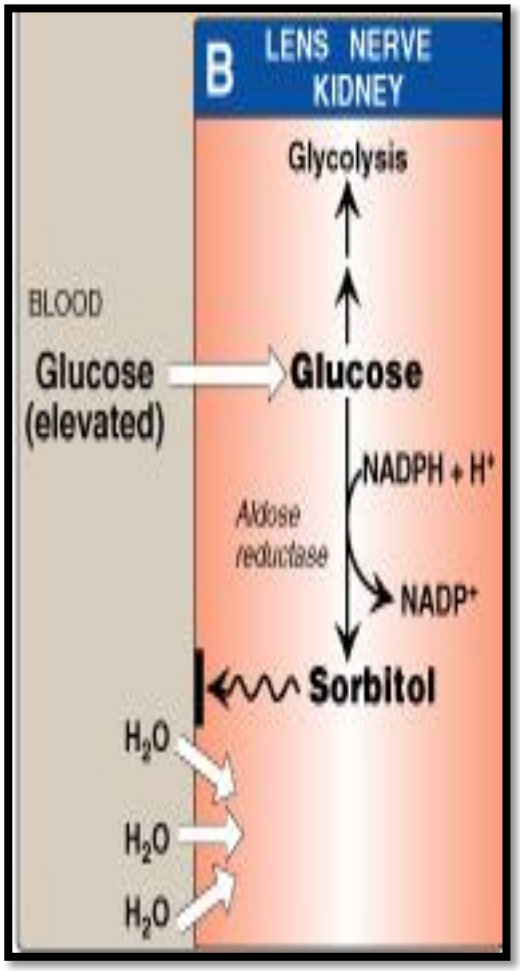
يوجد انزيم

Sorbitol dehydrogenase

الذي يحول الماده السامه الى

Fructose

هذا يشرح سبب لماذا ان الكليه و باقي الاعضاء التي في الاعلى اكثر تعرضا لمضاعفات مرض السكر



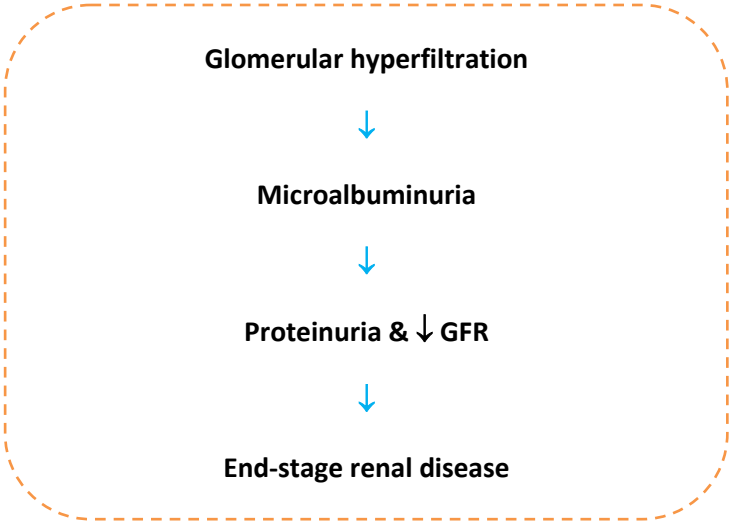
Diabetic Retinopathy:

- 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



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