How Does Diabetes Cause Harm To Our Kidneys?

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Introduction ..

- Diabetes mellitus (DM) a metabolic disease that is due to either insufficient insulin production (type 1 DM) or defective responsiveness to insulin (type 2 DM) all of which lead to increased blood glucose level (hyperglycemia).
- Diabetes Mellitus is the most frequent cause of chronic kidney failure in both developed and developing countries.
- Diabetic Nephropathy remains a leading cause of end stage renal disease (ESRD) in western societies.
- Approximately 50-60% of patients with diabetic nephropathy have type 2 diabetes, and 30-40% of patients with diabetic nephropathy have type 1 diabetes.
- Most of the available experimental and clinical evidence suggests that the complications of diabetes are a consequence of metabolic derangements, mainly hyperglycemia.

Hemodynamic Pathway ..

Advanced glycosylation end-products (AGE) :

Glucose + free amino groups ⟶ early glycosylation products
Early glycosylation products ⟶ glycosylation end products (ages).[1]

In non-diabetic mice, the infusion of early products of glycosylation up to the concentration seen in diabetic mice increases the kidneys blood flow, GFR, and intraglomerular pressure, which are characteristic of untreated DM.[2]

A- Glycosylation of the basement membrane in the efferent arteriole leads to it's thickening ⟶ increased intra glomerular pressure ⟶ increased filtration rate.

B- Glycosylation of heparin sulfate lining the glomerular endothelium ⟶ changes the negative charge of the glycocalyx ⟶ increased albumin permeability of the glomerular filtration membrane.

C- AGE-receptor signaling. AGEs bind to their receptors located on endothelial cells, mesangial cells, and macrophages leading to :

↑ Activation of macrophages and enhancing their cytokines release.
↑ Proliferation and synthesis of extracellular matrix by fibroblasts.

D- Mesangial expansion (proliferation and growth in size) due to increased glomerular pressure and excessive matrix deposition.[1]

Metabolic Pathway ..

Hyperglycemia-induced abnormality of intracellular metabolism:

A- Activation of protein kinase C:
Intracellular hyperglycemia ⟶ ↑ de novo synthesis of DAG ⟶ ↑ activation of PKC.

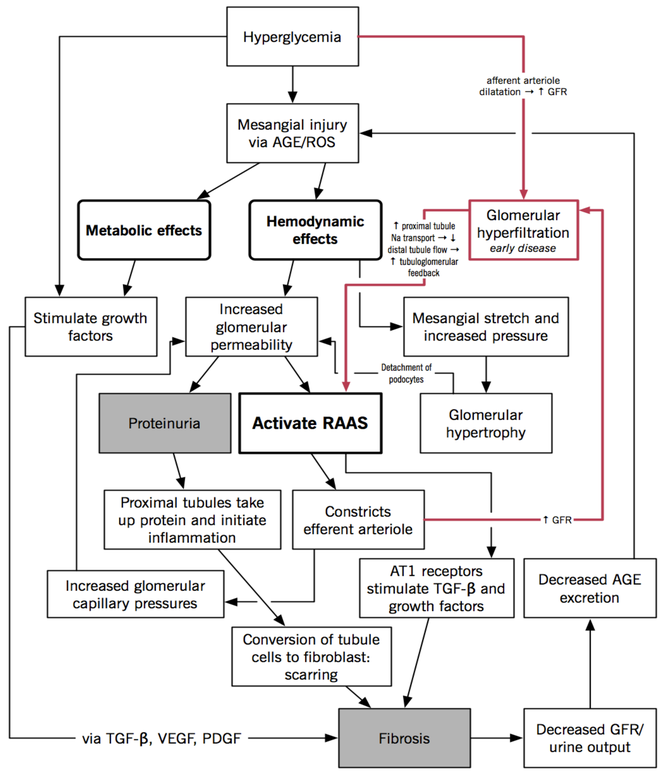
PCK activation stimulates the production of pro-fibrogenic molecules (such as transforming growth factor beta) leading to:

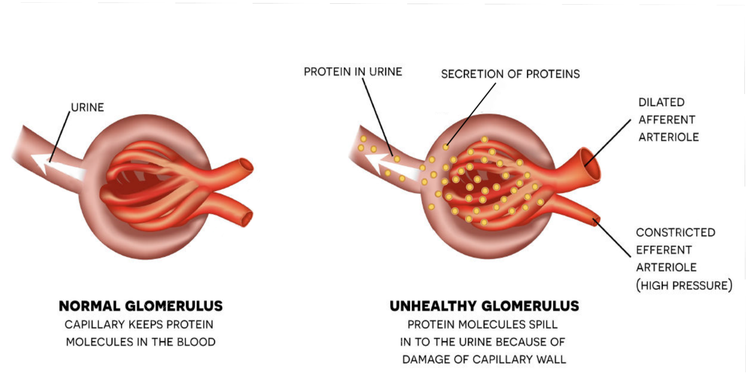
↑ Vascular permeability.
↑ Synthesis of extracellular matrix components.
↑ Production of reactive oxygen species (ROS), which are important mediators of kidney injury.

B- Sorbitol pathway activation:
increased Intercellular glucose ⟶ ↑ Sorbitol ⟶ ↑ Fructose

- Accumulated sorbitol and fructose cause injury via:
↑ Intracellular osmolarity and water influx.
↑ Cellular susceptibility to oxidative stress.[1]

Research in patients with type 1 DM and known hyperfiltration has shown that the infusion of aldose reductase inhibitor decreases GFR to normal values.[3]





Conclusion ..

- Diabetic nephropathy is a chronic complication of both type 1 DM (beta cell destruction – absolute lack of insulin) and type 2 DM (insulin resistance and/or decreased secretion of insulin).
- It is a characterized by albuminuria, permanent and irreversible decrease in glomerular filtration rate (GFR), and arterial hypertension.
- It is multifactorial (both hemodynamic and metabolic induced) but mainly as a consequence of an increased blood glucose level (hyperglycemia).

References ..

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