Pathogenesis of CKD in Diabetes

6th HiD Program 2022

Diabetes Kidney Disease- Closing the Loop in CardioRenal Protection

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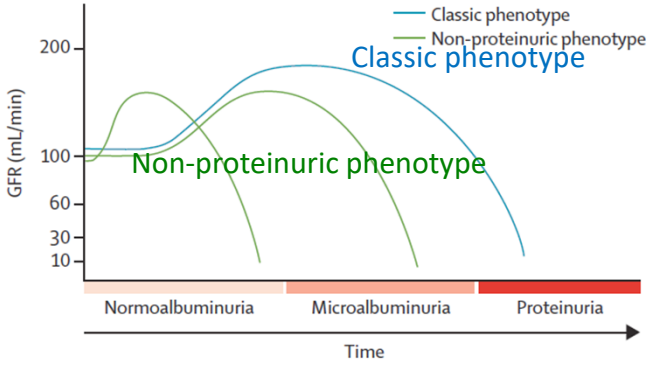
Learning objectives

- Review the natural history of chronic kidney disease in diabetes
- Describe glomerular and tubular pathology in diabetic kidney disease (DKD)
- Describe the pathogenic mechanisms involved in DKD
- Discuss the processes of renal inflammation, oxidative stress, and accelerated fibrosis in DKD

- **Terminology of kidney disease in patients with diabetes**

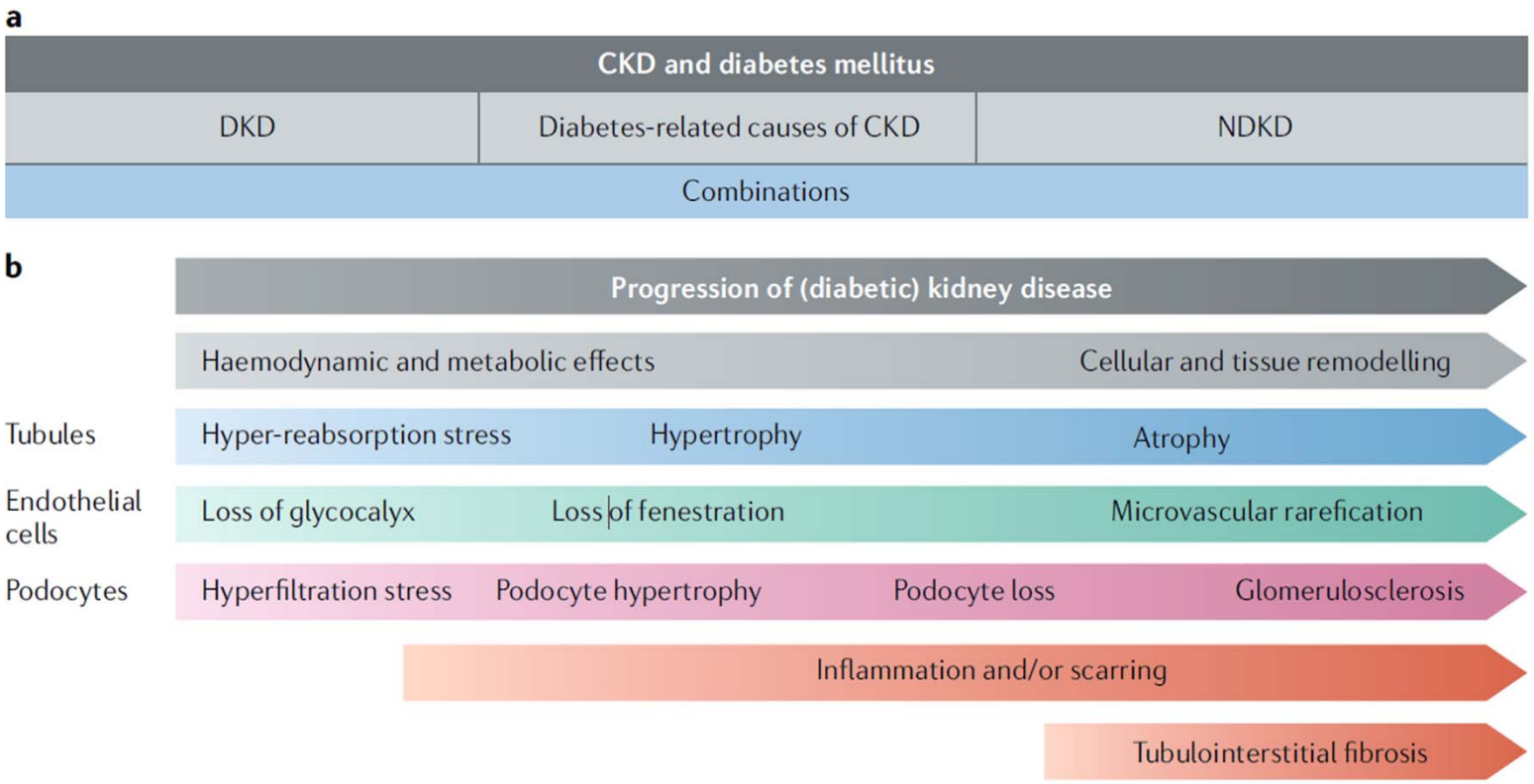
Terminology of kidney disease in diabetes mellitus (DM)

- Diabetic nephropathy (DN)
  - *Intercapillary Glomerulosclerosis* or *Kimmelstiel-Wilson Syndrome*, 1936
  - clinico-pathological syndrome:
    - hypertension, renal failure, albuminuria, edema, retinitis, longstanding type 1 or type 2 diabetes
    - Typical, classical nodular lesions on kidney biopsy
- Diabetic kidney disease (DKD)
  - Heterogeneous clinical presentation of DN, *Mogensen*, 1983
  - Chronic kidney disease (CKD) is due to DM
  - Incipient nephropathy
  - Overt nephropathy



Kimmelstiel, Wilson *Am J Path* 1936
Mogensen *DIABETES*,1983

CKD in DM



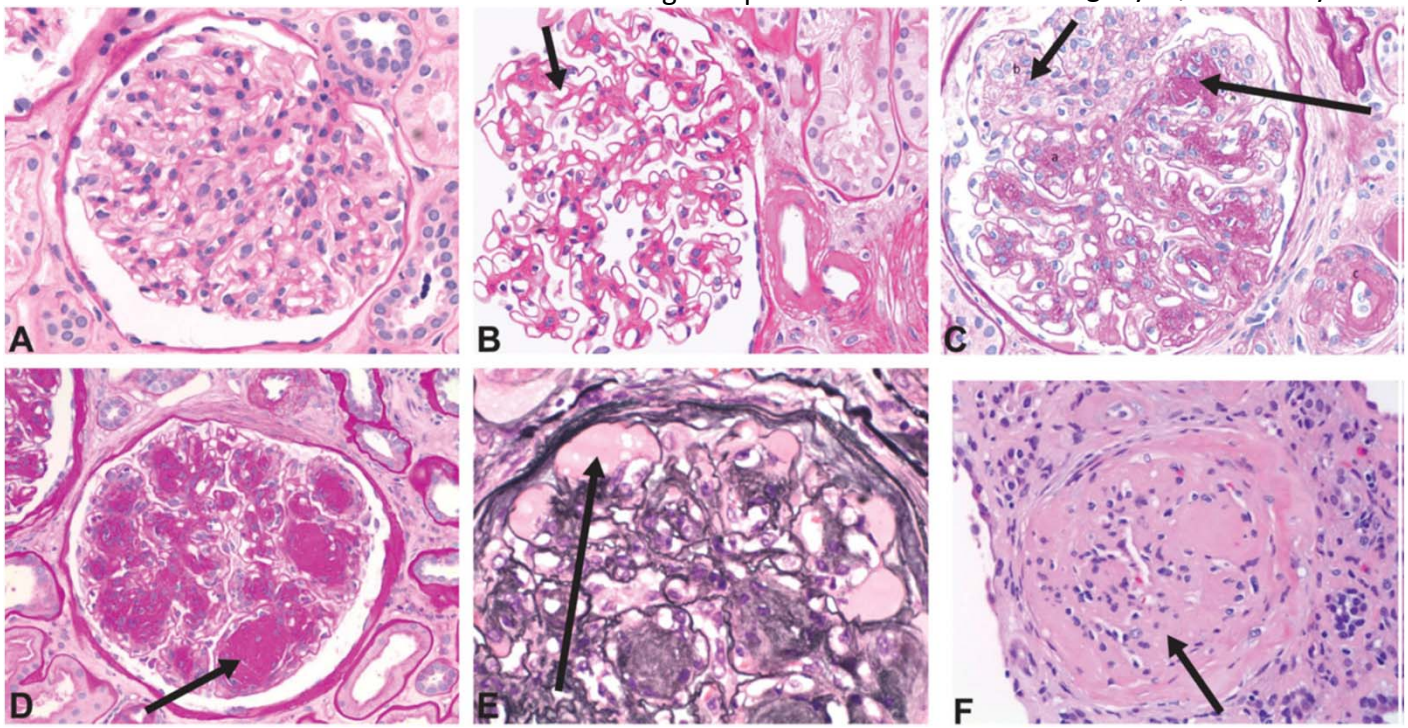
Opens doors to novel therapies → precision medicine

Distinction between DKD and DN

CKD in patients with diabetes	Diagnosis
Diabetic kidney disease (DKD)	• Clinical diagnosis of CKD in patients with diabetes based on laboratory for eGFR <60 ml/min/1.73 m^2, or UACR >30 mg/g, or both • clinical signs of diabetes
Diabetic nephropathy	• Long-standing diabetes, UACR ≥300 mg/g • Kidney biopsy- showing structural features associated with glomerular pathologic changes particularly in patients with type 1 diabetes • glomerular basement membrane thickening, mesangial expansion and nodules, podocyte loss, and endothelial disruption

Nicholas, Tuttle. *NephSAP* vol 19, No 2, 2020; Tervaert et al *JASN* 2019

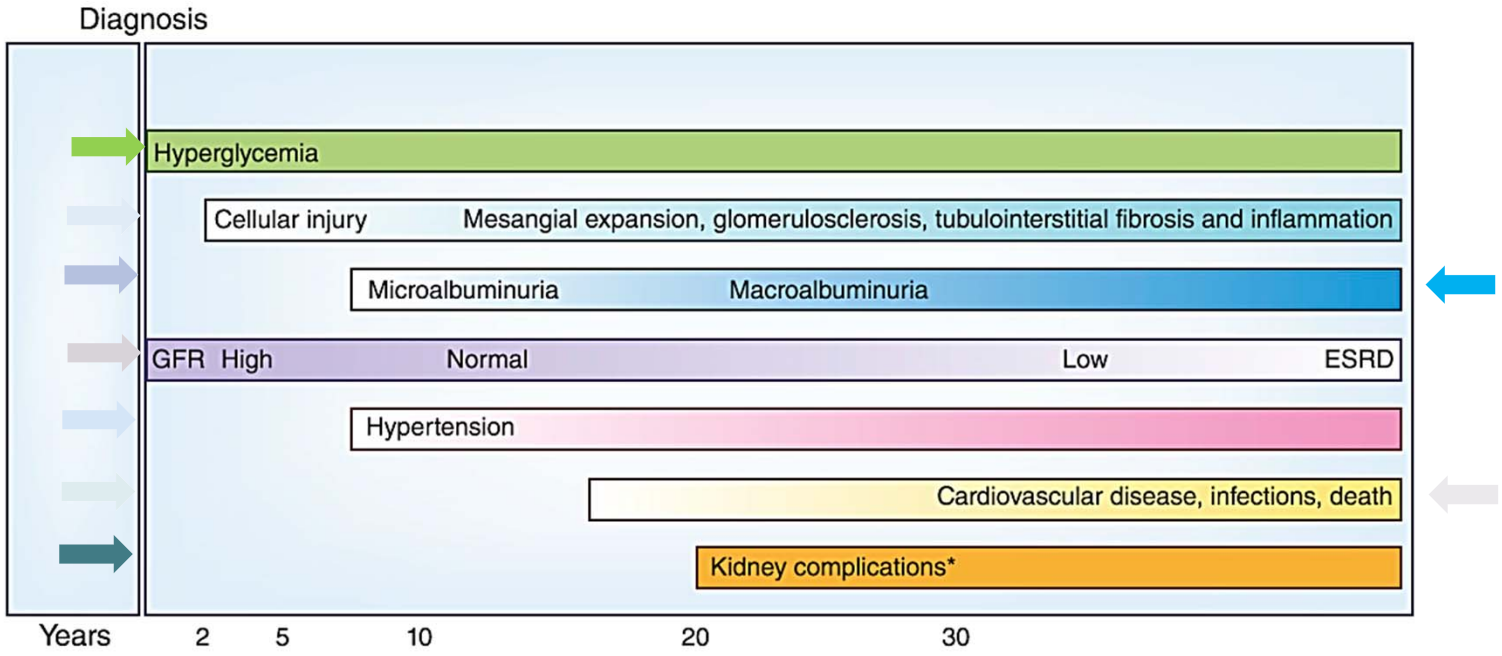
Glomerular changes in diabetic glomerulopathy



Alicic, R. Z. (2017). Diabetic Kidney Disease. *CJASN, 12*(12), 2032-2045.

- **The natural history of DKD**

Natural History of DKD



Progression to kidney failure in 25-30 years

Alicic R et al *CJASN* 2017

DKD in type 1 versus DKD in type 2 diabetes

Type 1 DKD

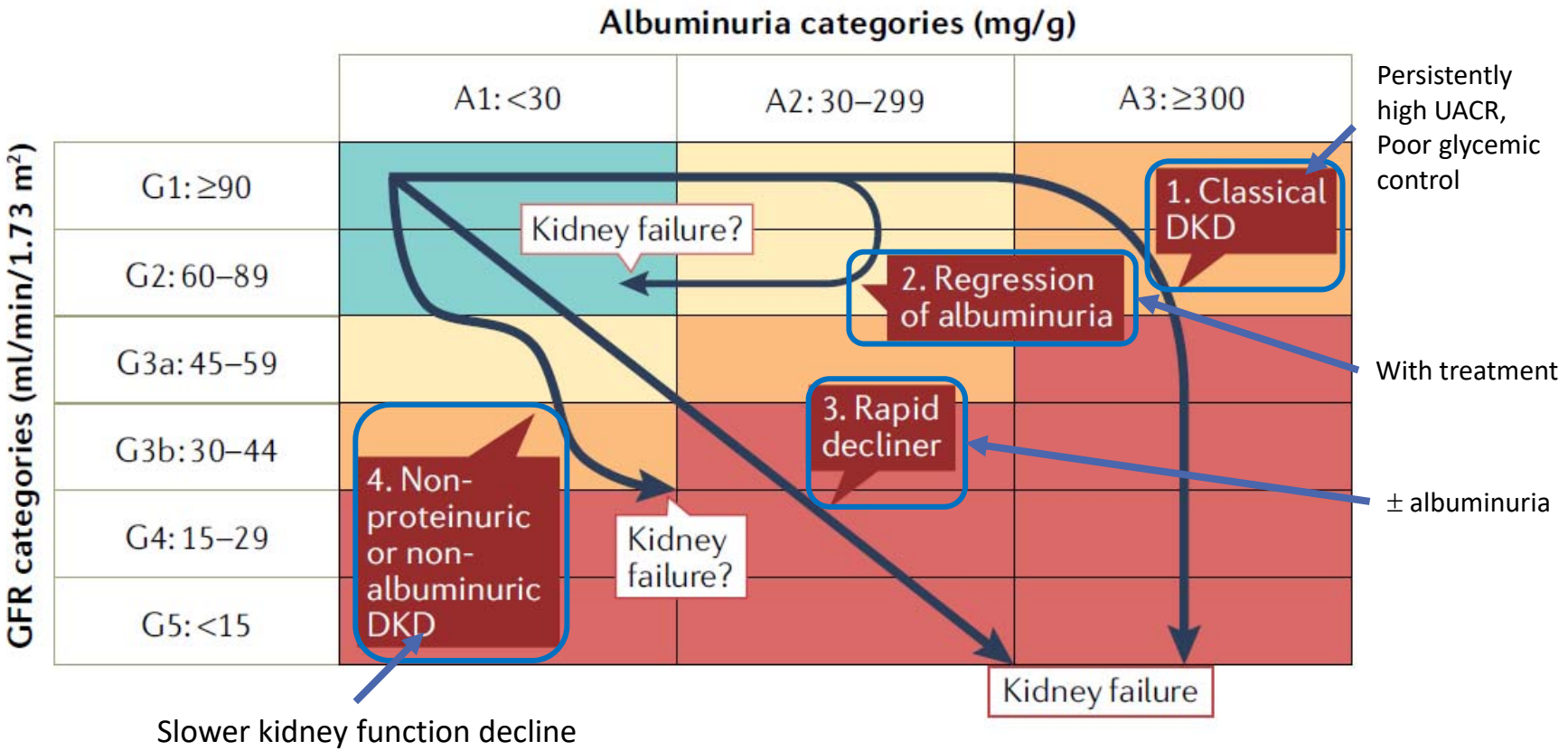
- Classical lesions
- Early: GBM thickening
  - Within 2 years of onset
  - Correlates with *DM duration* and *albumin excretion*
- Later: Mesangial expansion
  - Extracellular matrix accumulation
    - Fibronectin, collagen, laminin
  - Correlates with *declining kidney function*
- Advanced: Kimmelstiel-Wilson nodules (DMGS)
- Arteriolar hyalinosis: afferent and efferent arterioles
- Tubules: normal or atrophic

Type 2 DKD

- Very heterogeneous lesions
  - In patients with microalbuminuria or proteinuria
- Category I: normal or near-normal structure
  - 35% patients with microalbuminuria
  - 10% patients with proteinuria
- Category II: predominant DM glomerulopathy
  - 30% patients with microalbuminuria
  - 50% patients with proteinuria
- Category III: atypical renal lesions
  - Mild glomerular lesions
  - Disproportionately severe tubulointerstitital and/or vascular lesions (arteriolar hyalinosis, atherosclerotic lesions, global glomerulosclerosis
- Unclear if variability is due to other factors (HTN, aging) or T2D pathophysiology

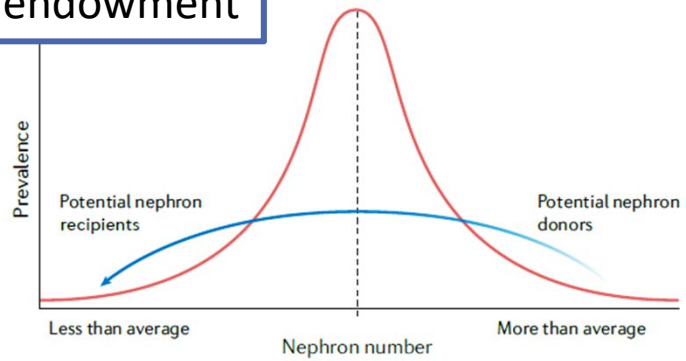
Di vencenzo et al *J of Neph*, 2020

Heterogeneity of the clinical presentation of DKD



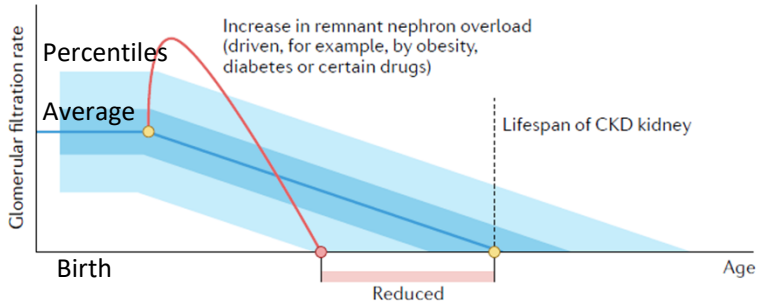
The goal is to prolong kidney lifespan

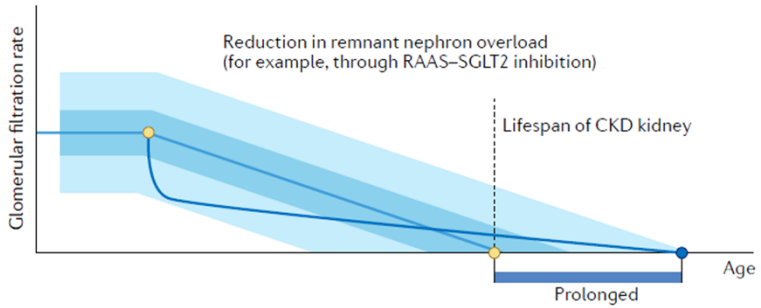
Nephron endowment



Renal functional reserve	None or poor	Sufficient	Excellent
Preeclampsia risk	High	Low	Low
Hypertension onset	Early in life	Late in life	None or very late in life
Proteinuria level relative to disease stage	High	Adequate	Low
Trigger for sudden SCr↑ or AKI	Mild injury	Modest injury	Severe injury
CKD progression	Fast	Slow	Minimal
Obesity	High risk of adaptive FSGS	Low risk	No adaptive FSGS
Diabetes	Risk of early nephropathy	Late nephropathy	No nephropathy
Glomerulonephritis	Fast CKD progression	Slow progression	Minimal progression
Post-donation kidney failure risk	High	Low	No risk for donor

Nephron adaptation



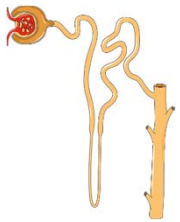


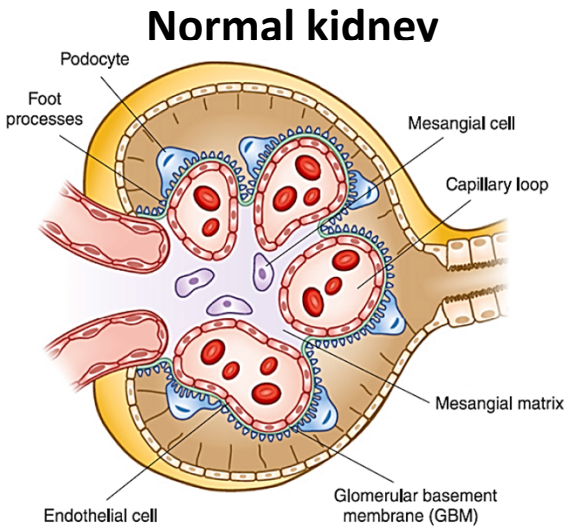
Luyckx et al *Nat Rev*, 2022

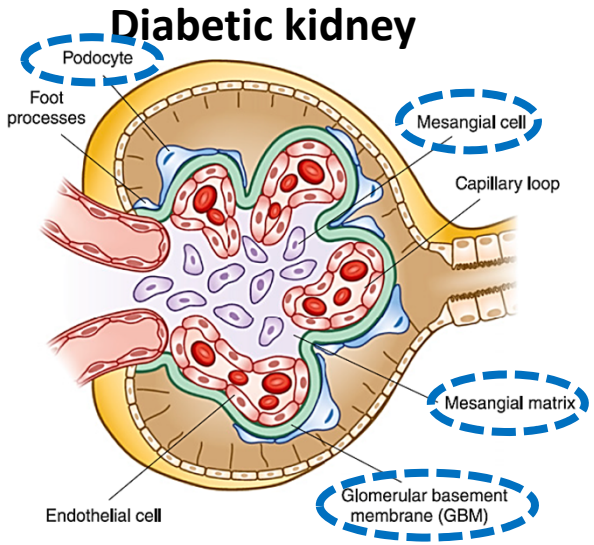
- **Glomerular and tubular pathology**

Normal kidney morphology and structural changes in DKD

~1 million nephrons per kidney



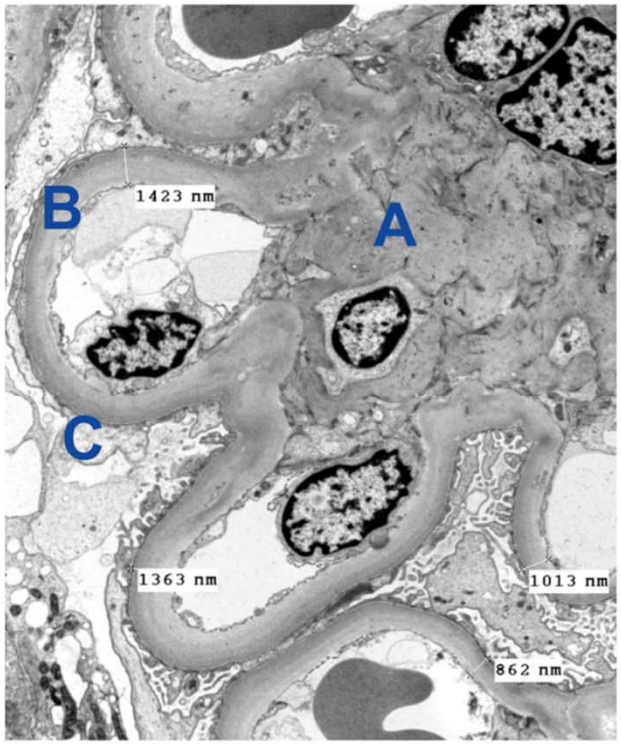




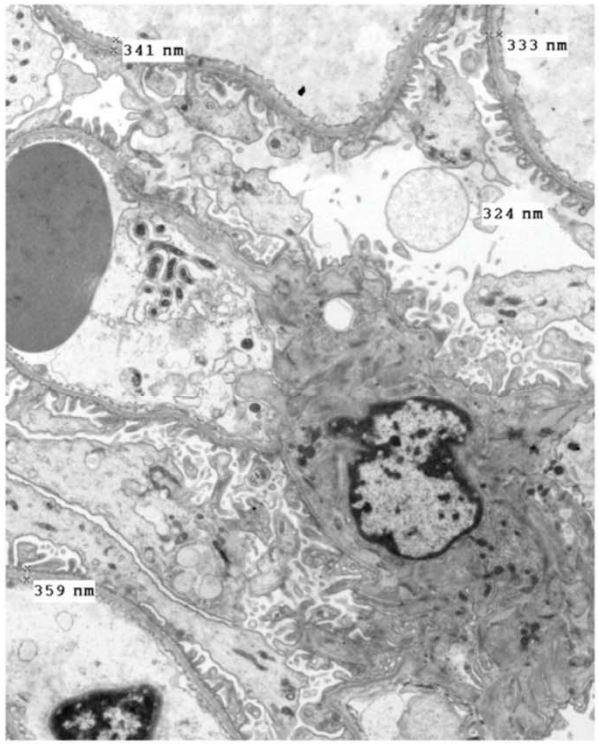
Hemodynamic + metabolic imbalance → Glomerular hypertrophy, hyperplasia ECM accumulation → Clinical presentation: albuminuria, hypertension, decline in renal function

Alicic et al CJASN 2017

Diabetic glomerulopathy-EM



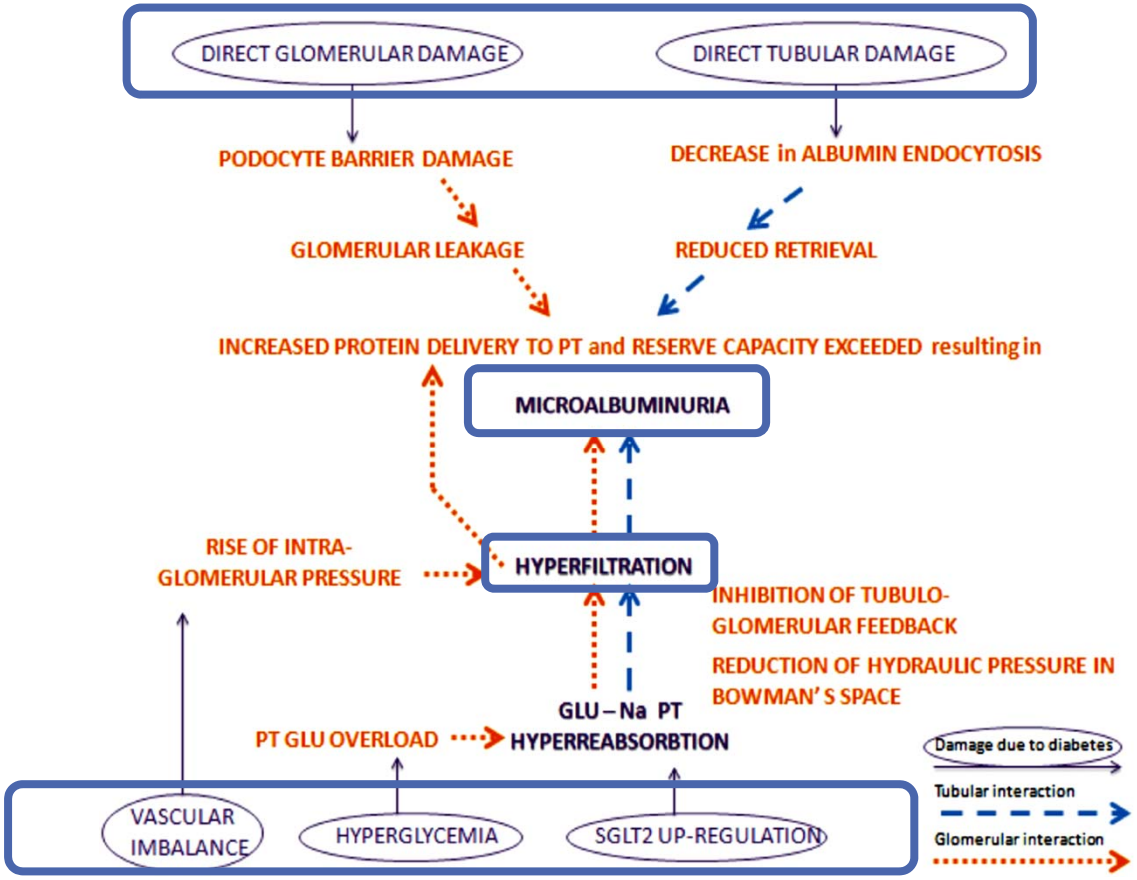
Diabetic Glomerulopathy



Normal Glomerulus

Alicic R et al *CJASN* 2017

Glomerular and tubular damage in the DKD



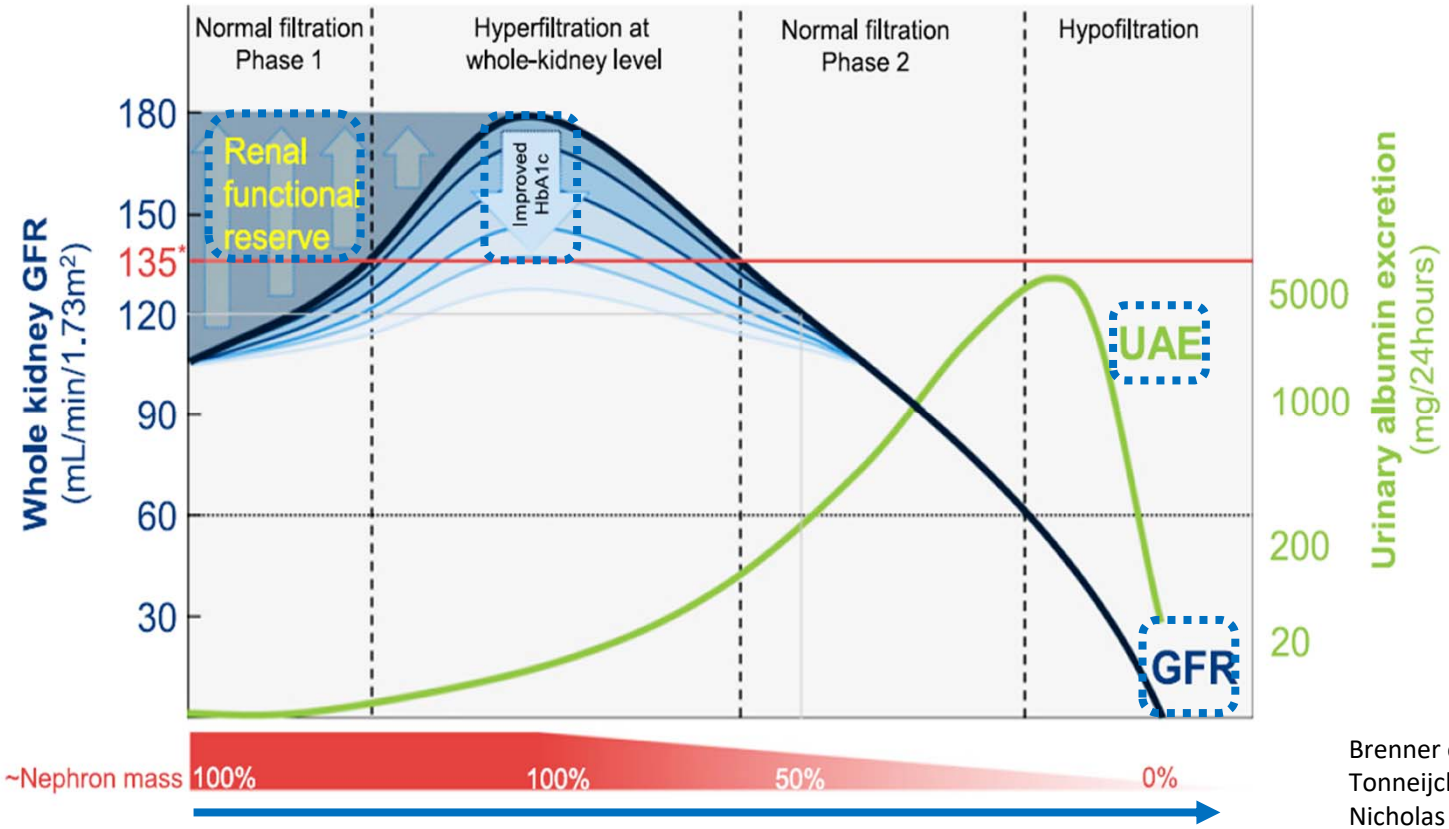
Zeni et al *J Nephrol* 2017
Nicholas and Tuttle, *NephSAP* 2020

Definition of glomerular hyperfiltration in DKD

- eGFR 120-175 mL/min/1.73 m^2 or >2 SD increase in eGFR above mean in healthy age-matched individuals
- 70% of patients with T1D, 50% in T2D
- Predicts:
  - glomerular structural pathology and
  - progressive ↓ in GFR
  - CV events
  - all-cause mortality in T2D

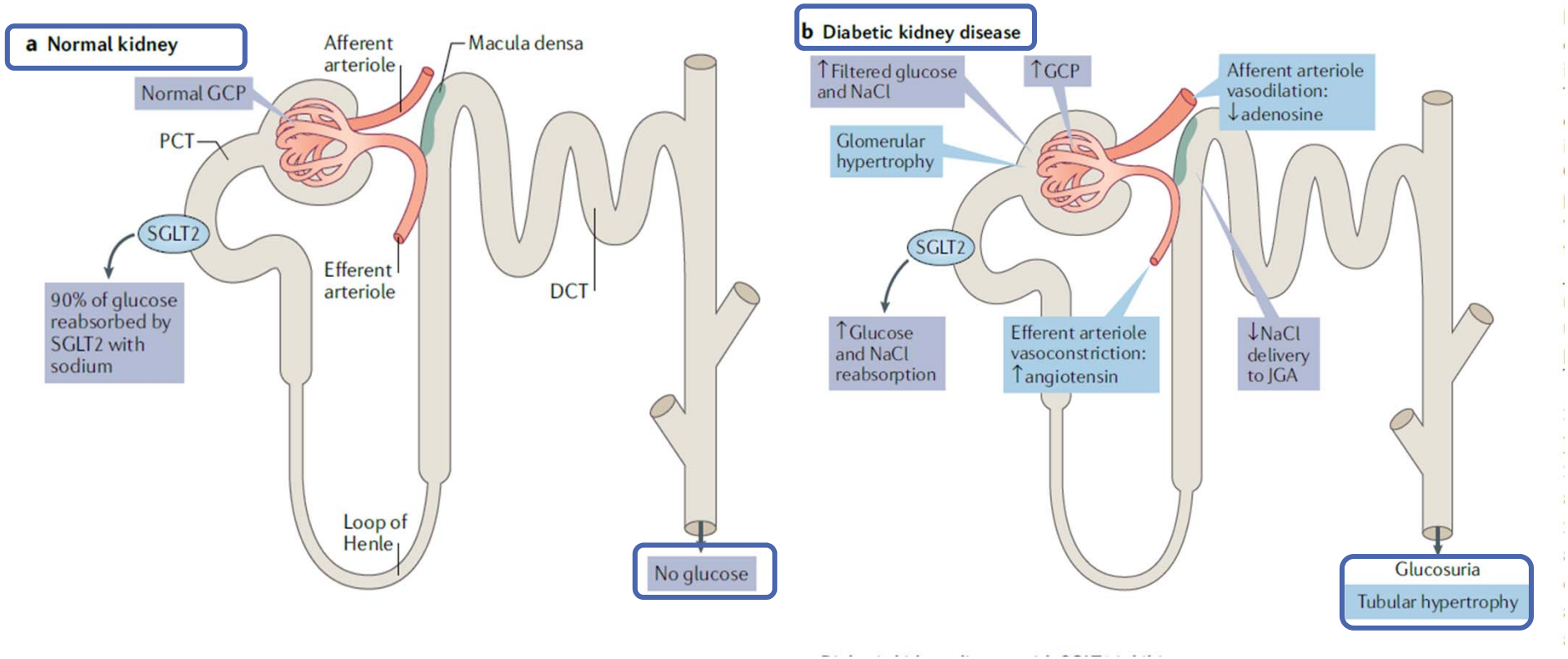
Nicholas and Tuttle, *NephSAP* 2020
Yang and Xu *Frontiers in Endo* 2022

Four phases of hyperfiltration and relation to whole kidney GFR and urine albumin excretion



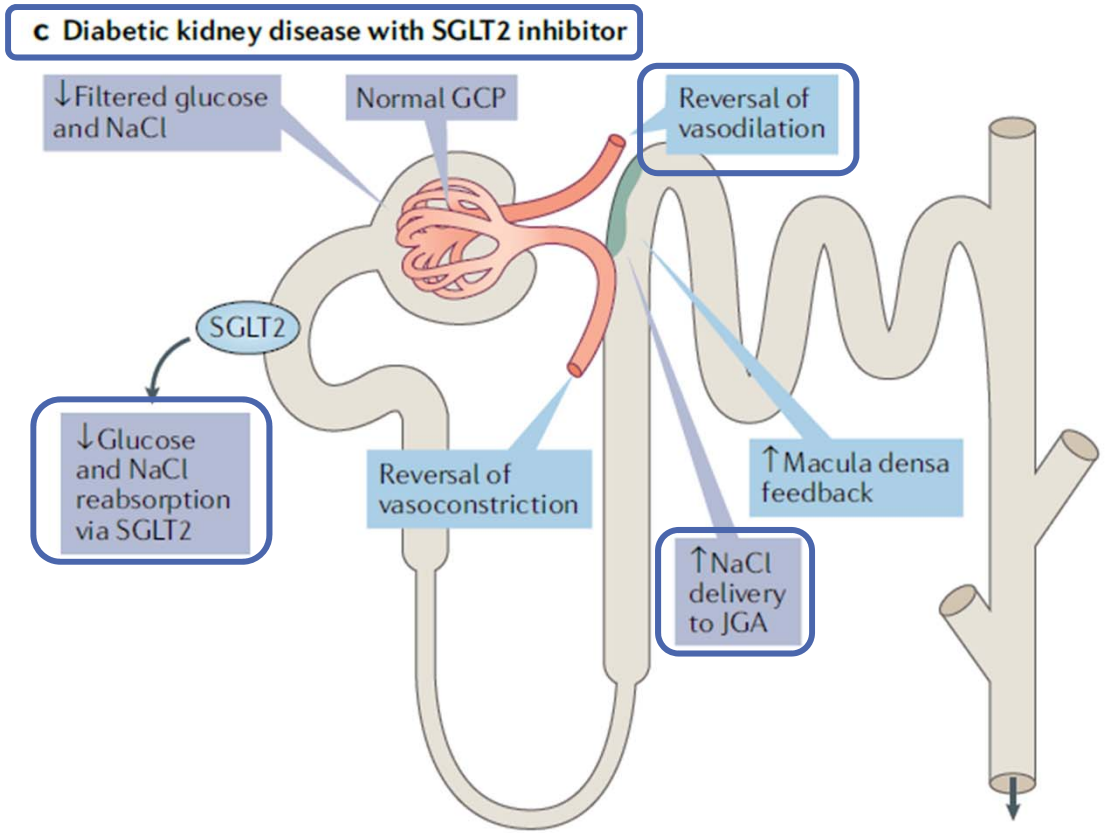
Brenner et al *KI* 1996
Tonneijck et al *JASN*, 2017
Nicholas and Tuttle, *NephSAP* 2020

Hemodynamic changes in DKD



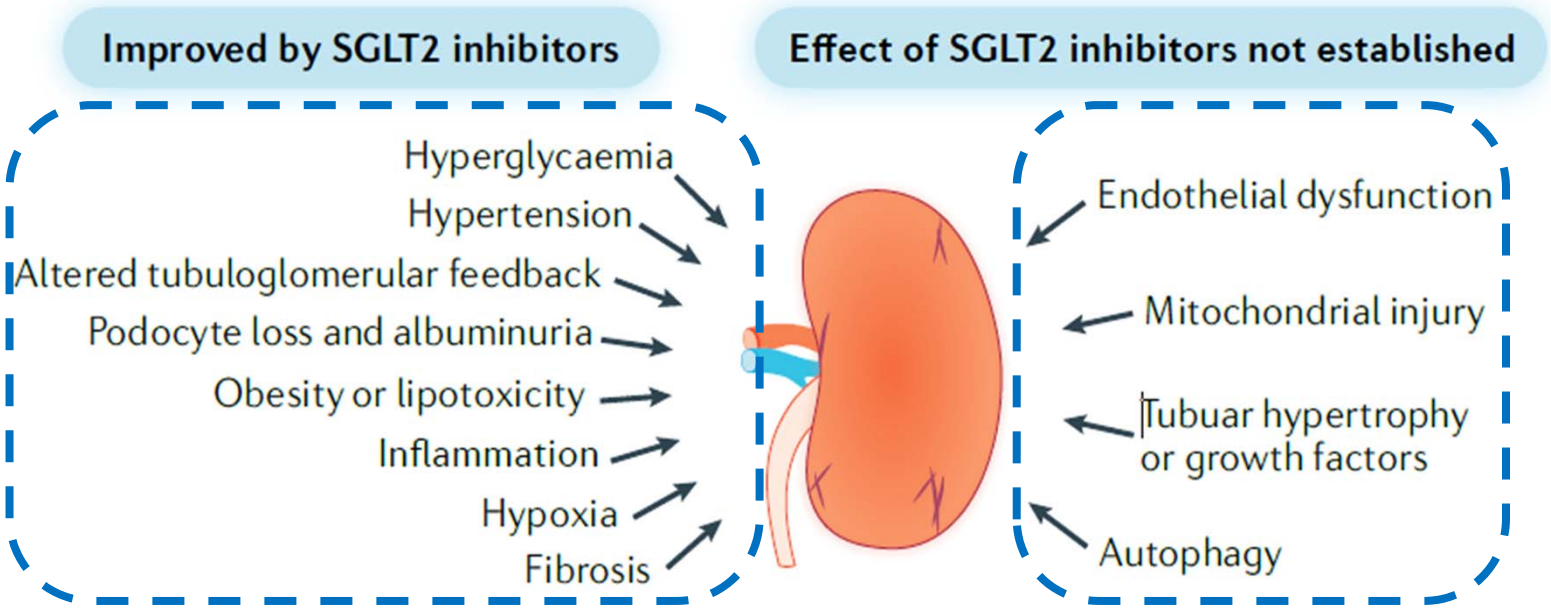
DeFronzo et al, *Nat Rev* 2021

Hemodynamic action of SGLT2 inhibitors



DeFronzo et al, *Nat Rev* 2021

Other possible pleiotropic actions of SGLT2 inhibitors



DeFronzo et al, *Nat Rev* 2021

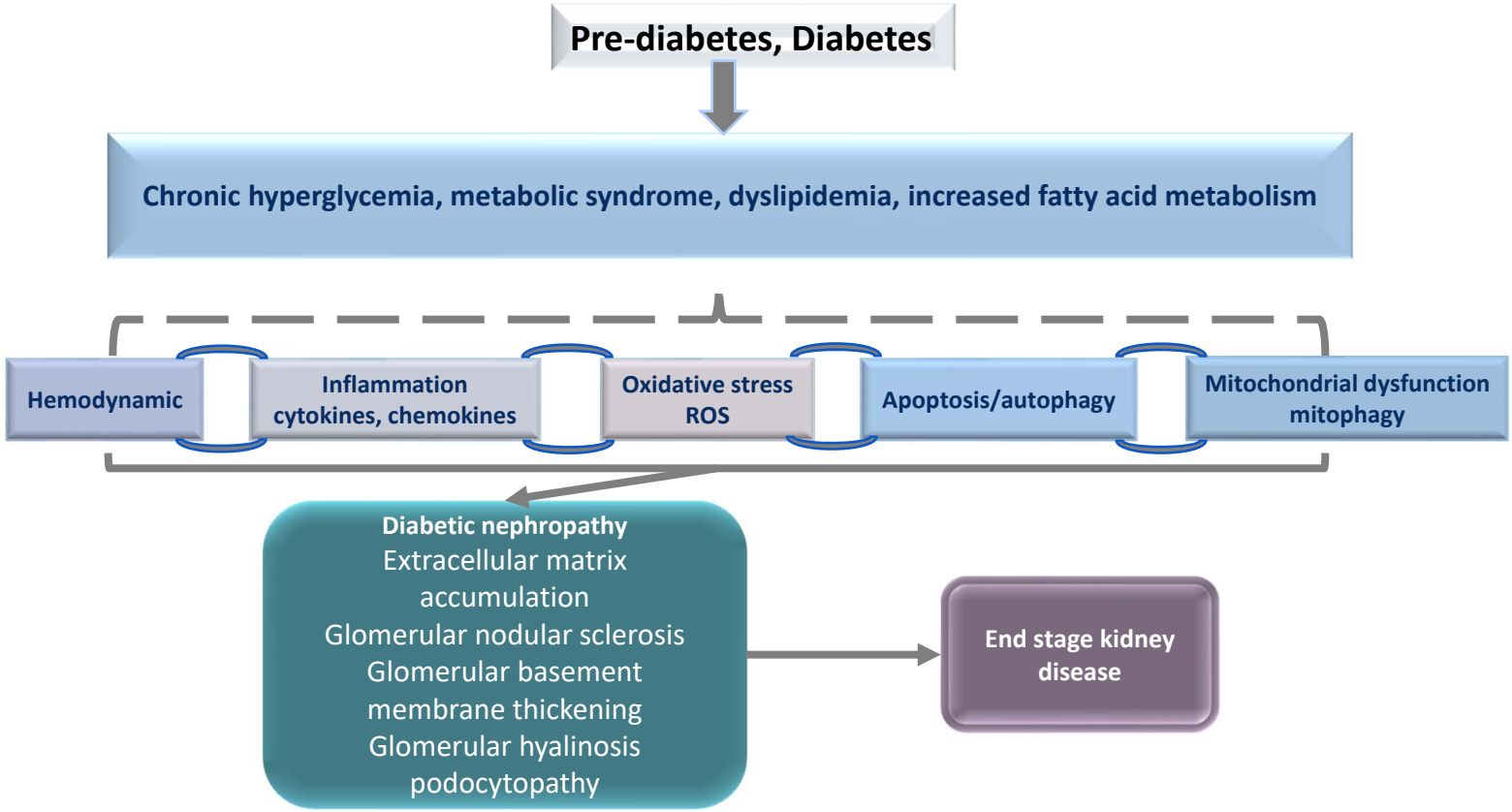
Classification of tubular urinary biomarkers in DKD

Urinary Biomarkers in DKD		
Structural Biomarkers	**Functional Biomarkers**	**Pathophysiological Biomarkers**
▪ **Biomarkers reflecting glomerular endothelial cells and podocytes** (α-actinin-4, Glycosaminoglycans, Lipocalin-Type, Prostaglandin-D Synthase, Nephrin, Podocalyxin, Podocin, Synaptopodin, Vascular endothelial growth factor A, Wilms'Tumor-1) ▪ **Biomarkers of glomerular and tubular basement membrane and extracellular matrix proteins alterations** (Fibronectin, Laminin, Matrix metalloproteinase-9, Transforming Growth factor-β-induced protein h3, Type I collagen fragments, Type IV collagen) ▪ **Biomarkers of tubular epithelial cells damage** (Alkaline phosphatase and ɣ-Glutamyltransferase, Cubilin and Megalin, Glycoprotein non-metastatic melanoma protein B, Kidney injury molecule-1, Liver-type fatty acid binding protein, Neutrophil gelatinase-associated lipocalin, N-acetyl-β-D-glucosaminidase)	▪ **Functional glomerular barrier damage** (Albumin, Angiotensinogen, Ceruloplasmin, Immunoglobulin G, Transferrin) ▪ **Functional tubular reabsorptive damage** (α_1-macroglobulin, β_2-macroglobulin, Albumin, Cystatin C, Retinol Binding Protein 4)	▪ **Oxidative stress** (Advanced Glycation end products, Heart fatty acid binding protein, Pentosidine, 8-hydroxy-2'-deoxyguanosine, 8-oxo-7,8-dihydro-2'-deoxyguanosine) ▪ **Inflammation** (Interleukin-6, monocyte chemoattractant protein-1, nitric oxide, orosomucoid, tumor necrosis factor-α) ▪ **Intra-renal renin-angiotensin system** (Urine/plasma renin ratio) ▪ **Growth factors** (Connective tissue growth factor, Transforming growth factor β1)

Zeni. J Nephrol. 2017;30:701.

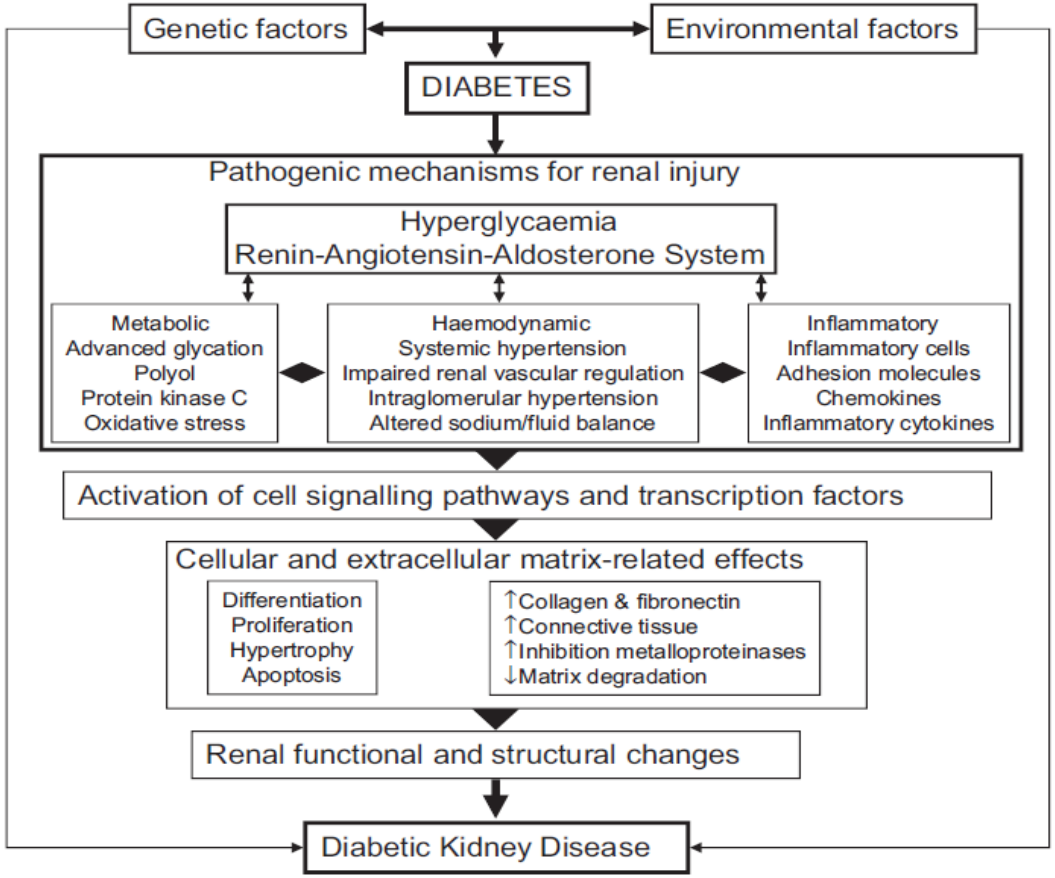
- **Pathogenic mechanisms involved in DKD**

Mechanistic links between pre-diabetes, diabetes and DKD and end stage kidney disease



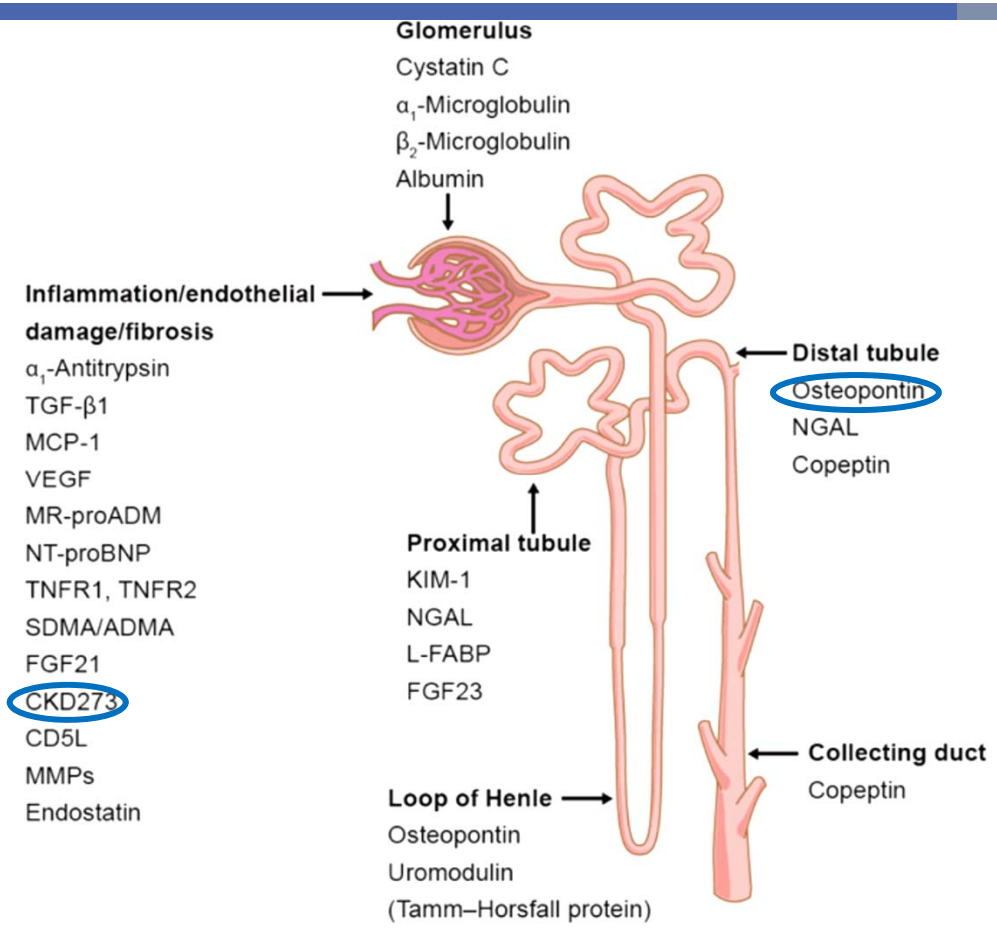
Nicholas and Tuttle, *NephSAP* 2020

Schematic of the pathogenic mechanisms of DKD



Mora-Fernández C. et al *J Physiol* 2014

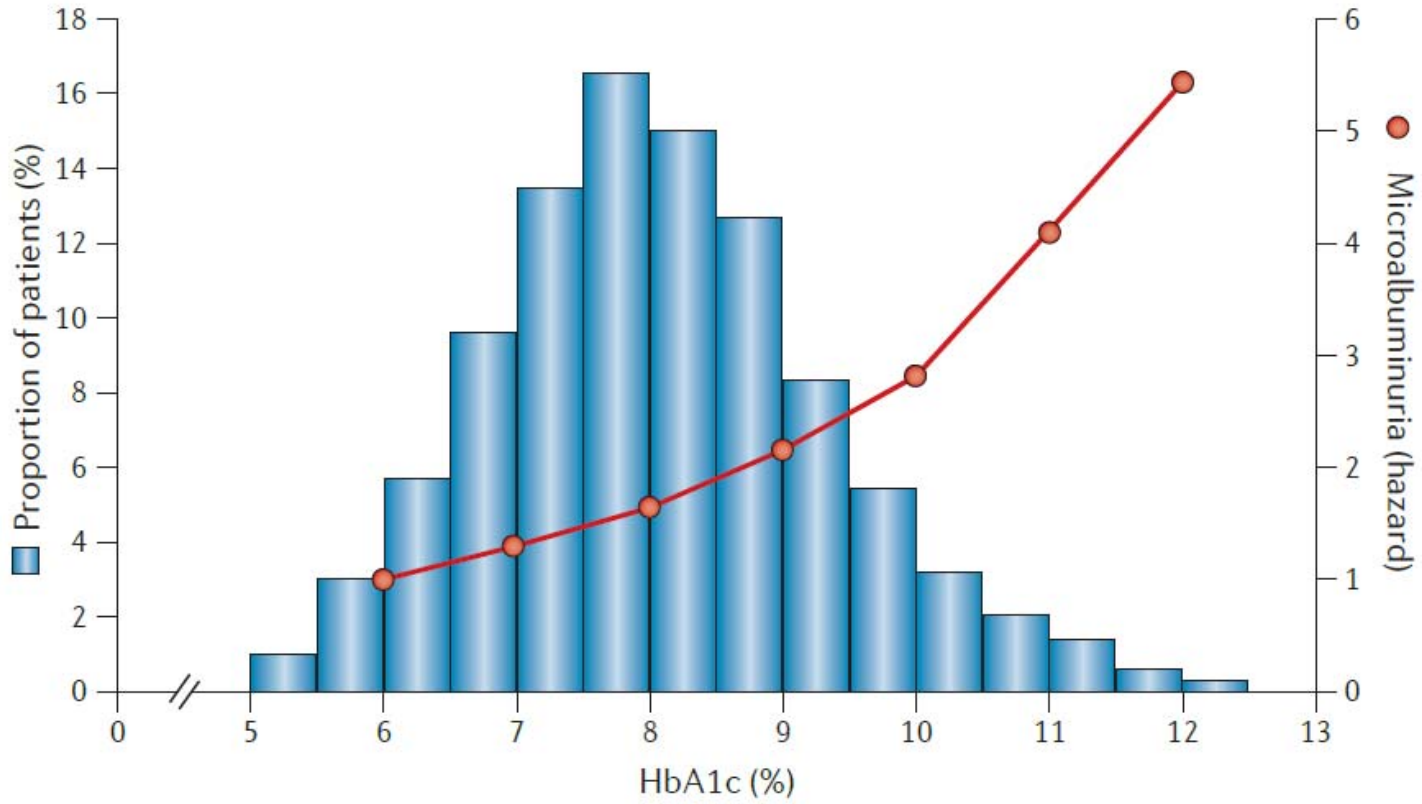
Presumed sites of commonly associated markers predictive of DKD



Colhoun and Marchvechhio *Diabetologia* 2018

- **Renal inflammation, oxidative stress and renal fibrosis**

The relationship between glycemic control and the residual incidence of CKD



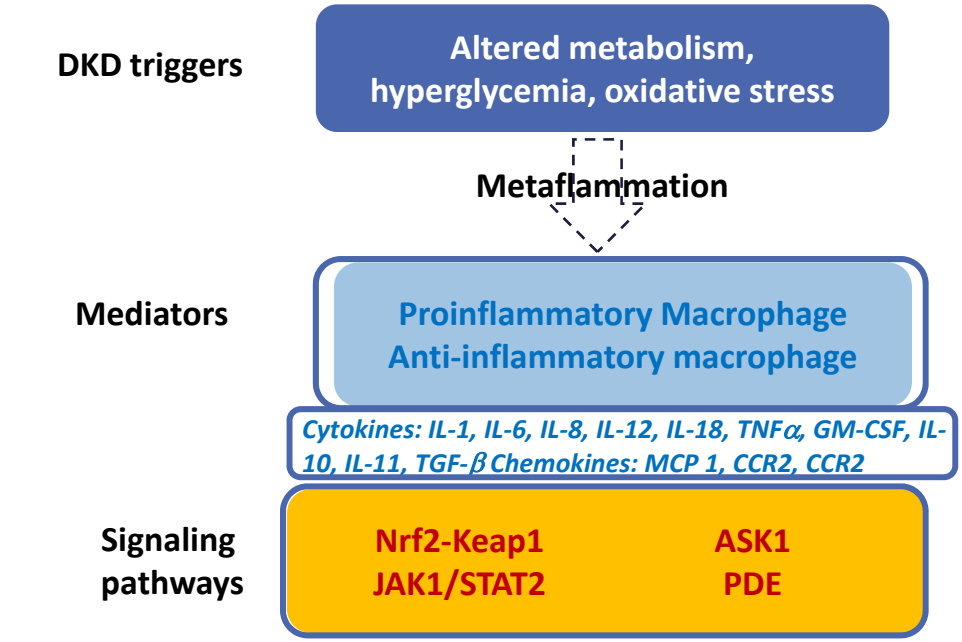
Thomas MC et al *Nat Rev* 2015

Inflammation and oxidative stress in DKD

- Glomerular and tubular injury in DKD
- Also marked by chronic low-grade inflammation and oxidative stress
- Dysregulation of homeostatic processes of apoptosis and autophagy may lead to podocyte loss, albuminuria and tubular damage in DKD
- Both glomerular and tubular damage contribute to albuminuria and both processes can be targeted in DKD management

Nicholas and Tuttle, *NephSAP* 2020
Nicholas *Adv Chronic Kidney Dis*. 2021;28(4):378-390

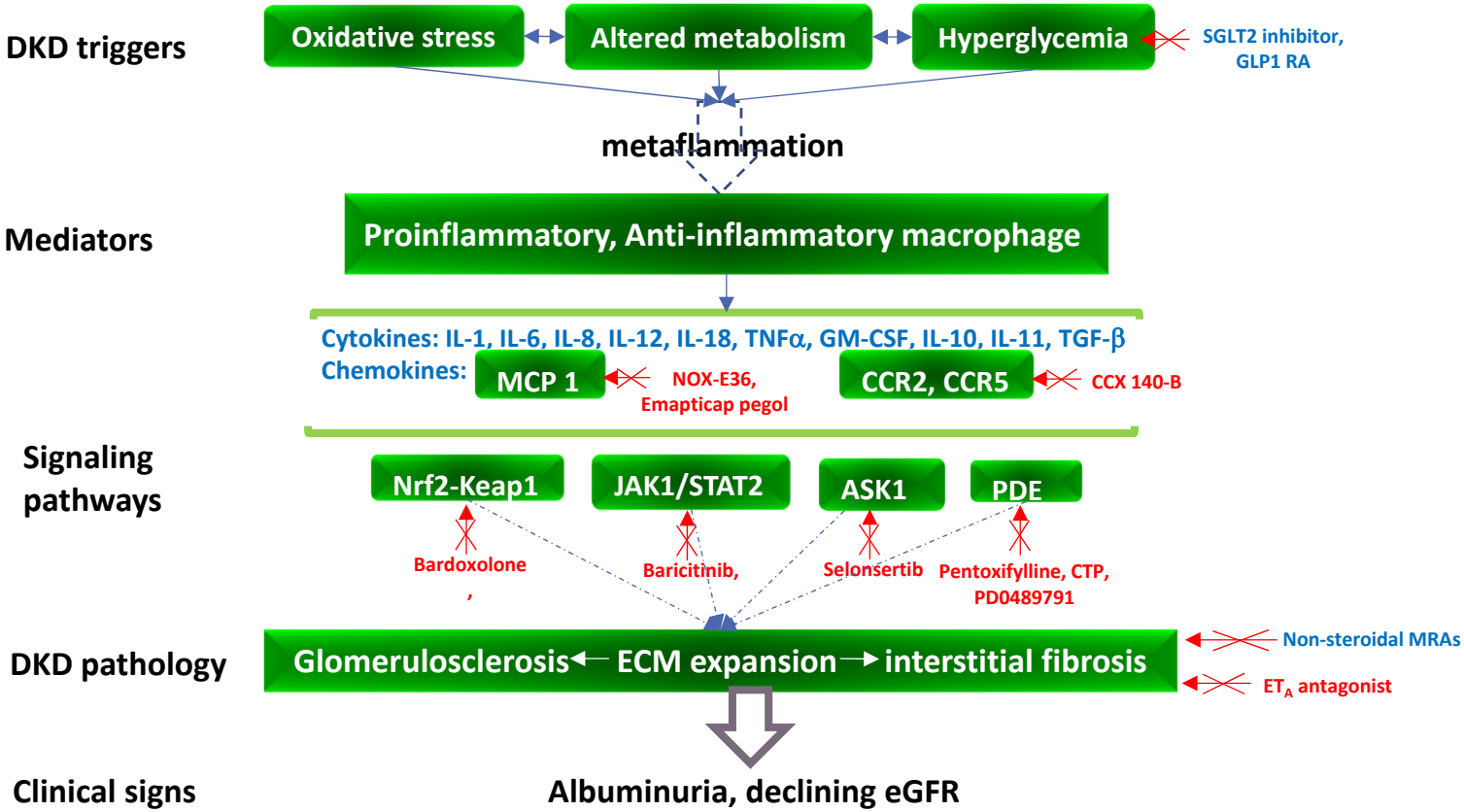
Inflammatory pathways in DKD



Nicholas *Adv Chronic Kidney Dis*. 2021;28(4):378-390

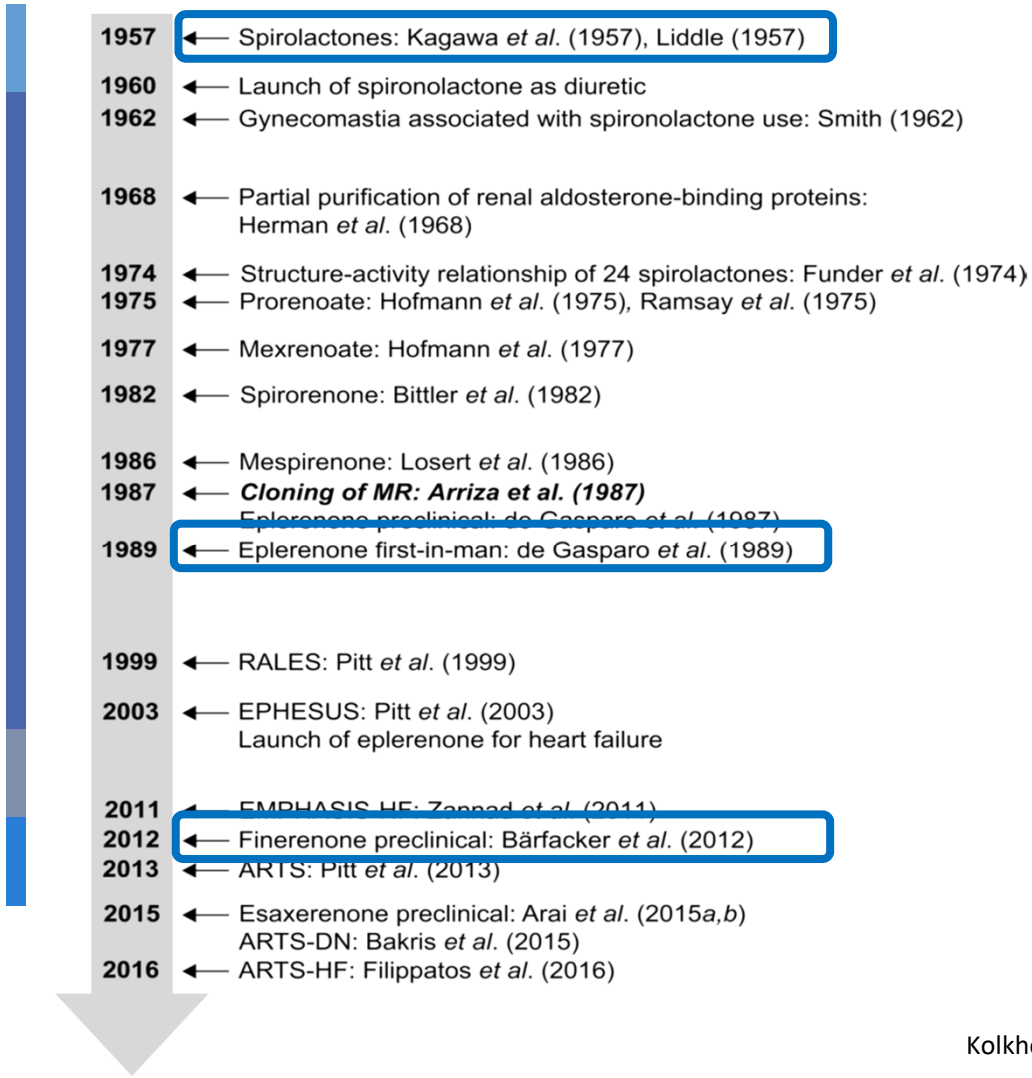
clinicaloptions.com

Novel inflammatory and fibrosis pathways in DKD



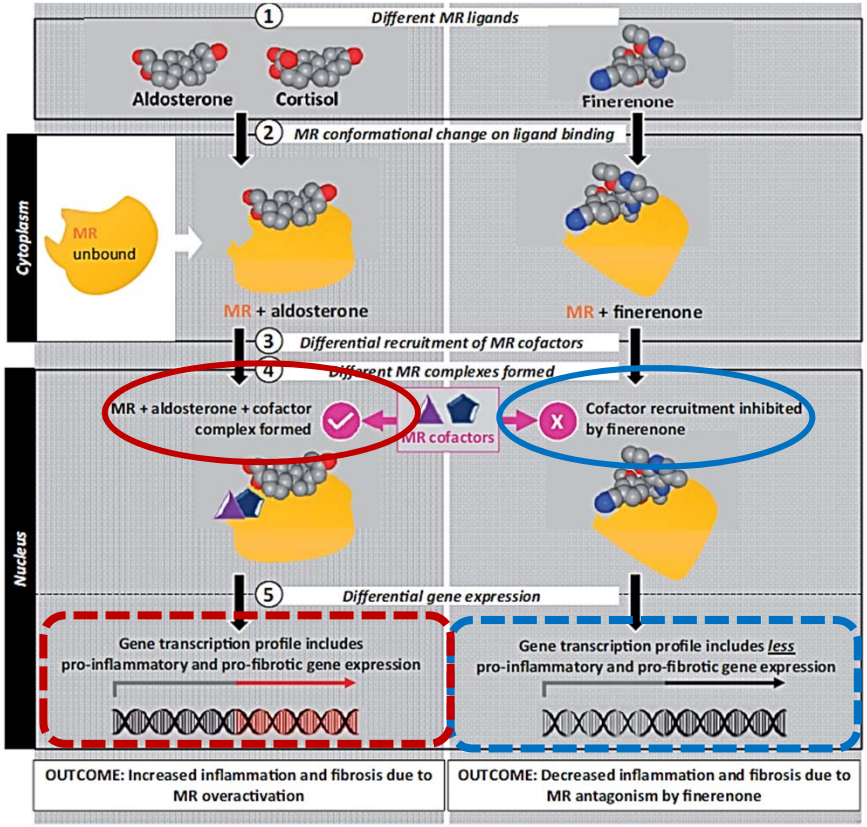
Nicholas *Adv Chronic Kidney Dis*. 2021;28(4):378-390

MRAs: 60 years of research and development



Kolkhof and Bärfacker *J Endocrin* 2017

Finerenone reduces downstream pro-inflammatory and pro-fibrotic factors



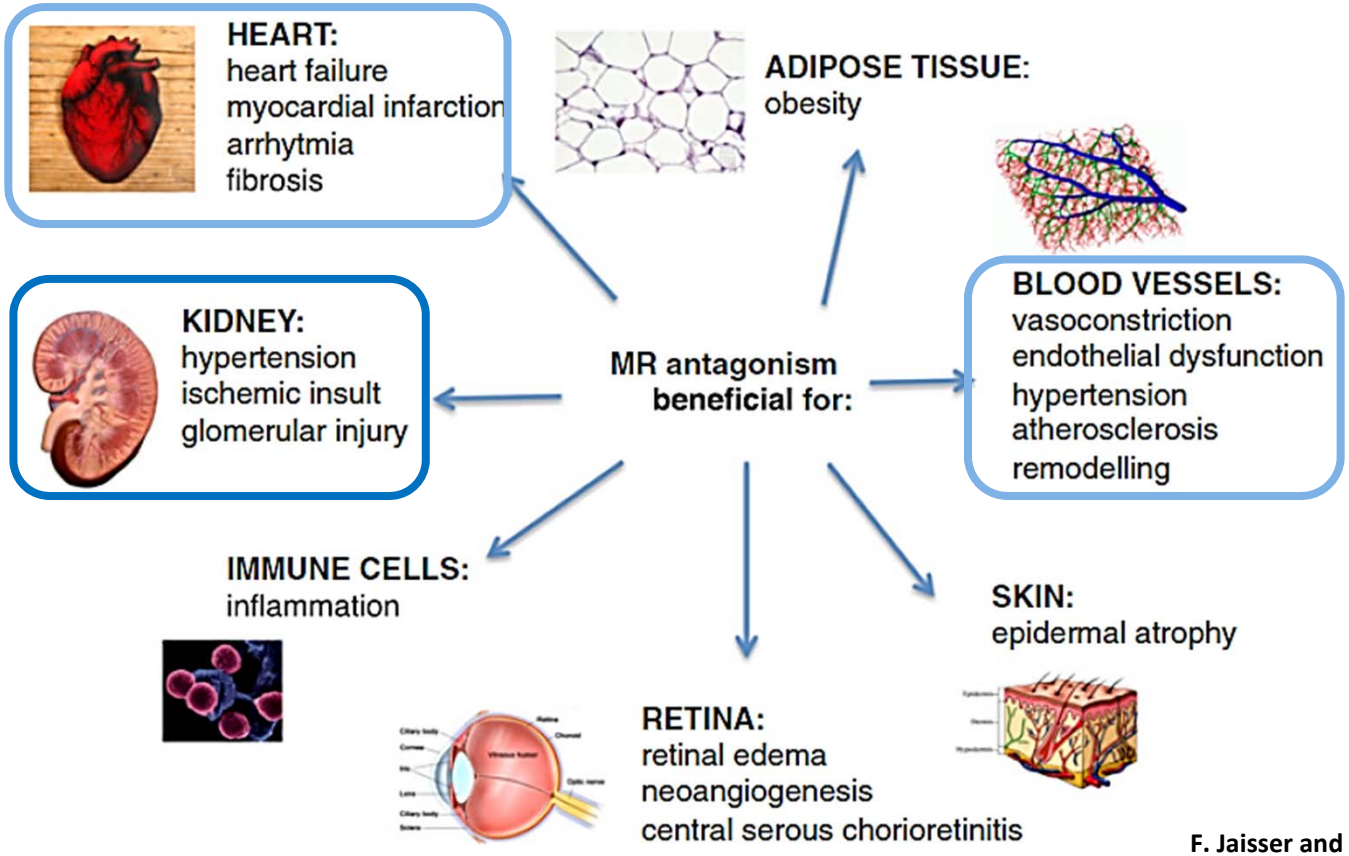
Agarwal. *European Heart J.* 2021;42:152
clinicaloptions.com

In Vitro Potency of MR Antagonists

Agonist	Antagonist		
	Spironolactone IC_{50} (nM)	Eplerenone IC_{50} (nM)	Finerenone IC_{50} (nM)
Aldosterone	24	990	18
Cortisol	19	360	5
Corticosterone	41	940	24

Kolkhof. *J Endocrinol*. 2017;234:T125

Beneficial effects of MR antagonism



F. Jaisser and N. Farman *Pharmacol Rev*. 2016

Take-home points

- Terminology: DN, DKD, CKD in DM
- The mechanisms involved in the pathogenesis of DKD include:
  - Altered hemodynamics - hyperfiltration
  - Metabolic - hyperglycemia
- Direct glomerular and tubular injury
  - SLGT2 inhibitors target tubuloglomerular feedback, other pleiotropic effects
- Structural, functional and pathophysiological biomarkers
- Residual incidence of CKD
  - oxidative stress, inflammation and fibrosis
- Antagonism of the MR
  - Finerenone is more potent than spironolactone or eplerenone
- There are still other potential targets for therapies as we advance care in *precision medicine*


Thank you