Glomerulus in diabetic nephropathy

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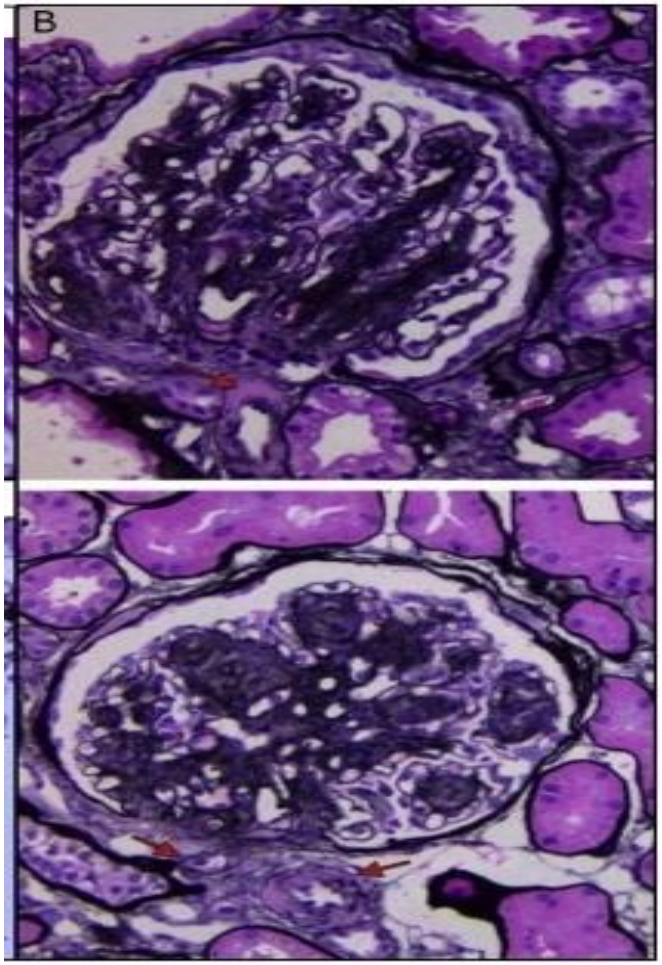
Professor Of Nephrology

TUMS



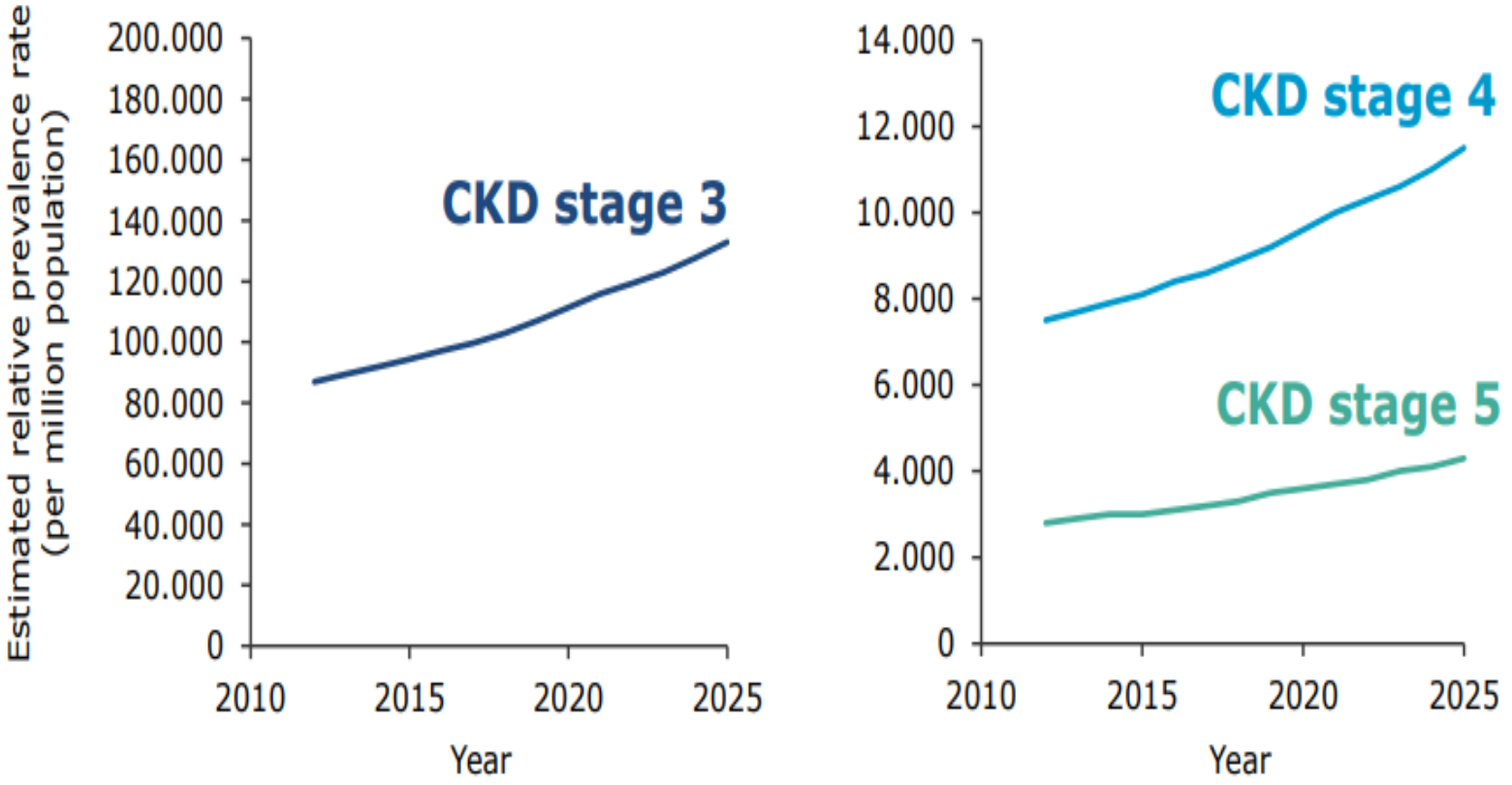
Diabetic Nephopathy (DN)

- **Diabetic Nephopathy (DN)** is the most common cause of end-stage renal disease
- Kidney disease secondary to diabetes mellitus, termed as diabetic nephropathy (DN), accounts for over 40% of end-stage renal disease (ESRD)
- Ten years after the diagnosis of type 2 diabetes, about 25% patients have DN
- It is estimated that **20-40%** of all diabetic patients will develop diabetic nephropathy
- Worldwide prevalence of diabetes is rapidly increasing

Diabetic Nephopathy (DN)

- Renal lesions are much more complex in patients with T2Dm than in patients with T1Dm.
- The prevalence of diabetes unrelated lesions in patients with both proteinuria and T2Dm is considered high
- Importantly, the severity of diabetic glomerulopathy is greatly influenced by diabetes duration.

Estimated future prevalence of diabetic nephropathy in Europe*



CKD, chronic kidney disease. *Austria, Belgium, Denmark, Finland, Greece, Iceland, Italy, Netherlands, Norway, Spain, Sweden, UK

Kainz A *et al. Nephrol Dial Transplant* 2015;30:iv1113 (Supplementary data); SYSKID Project

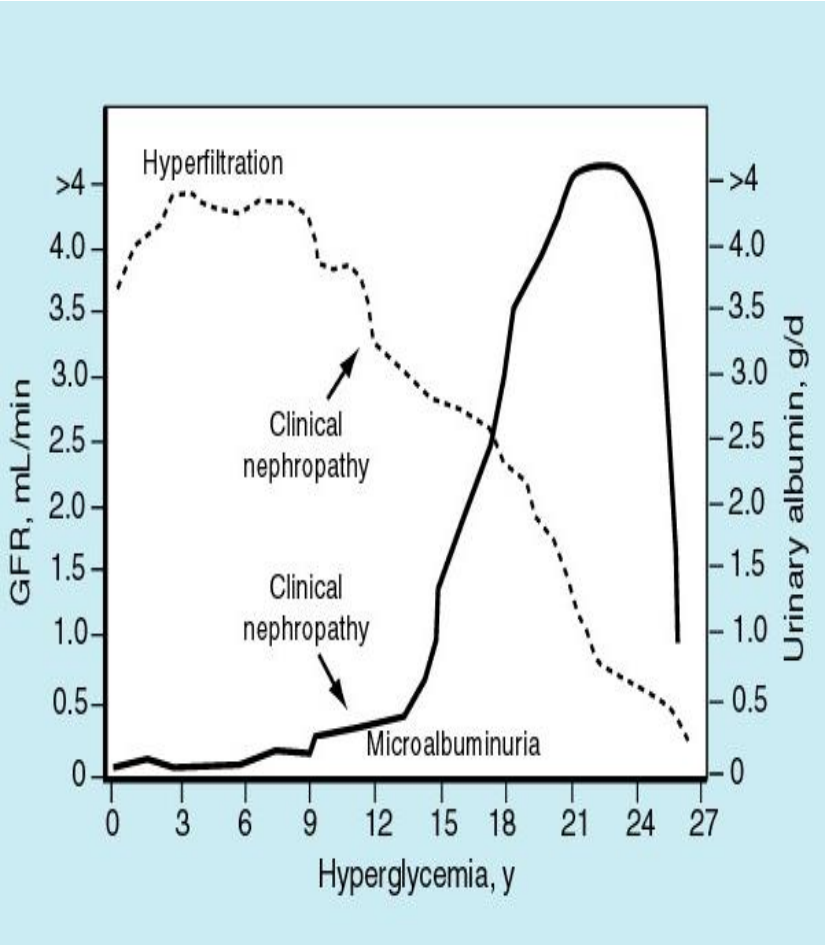
Natural history of diabetic nephropathy

1. Silent clinical phase
   Hyperfiltration
   Increased GFR

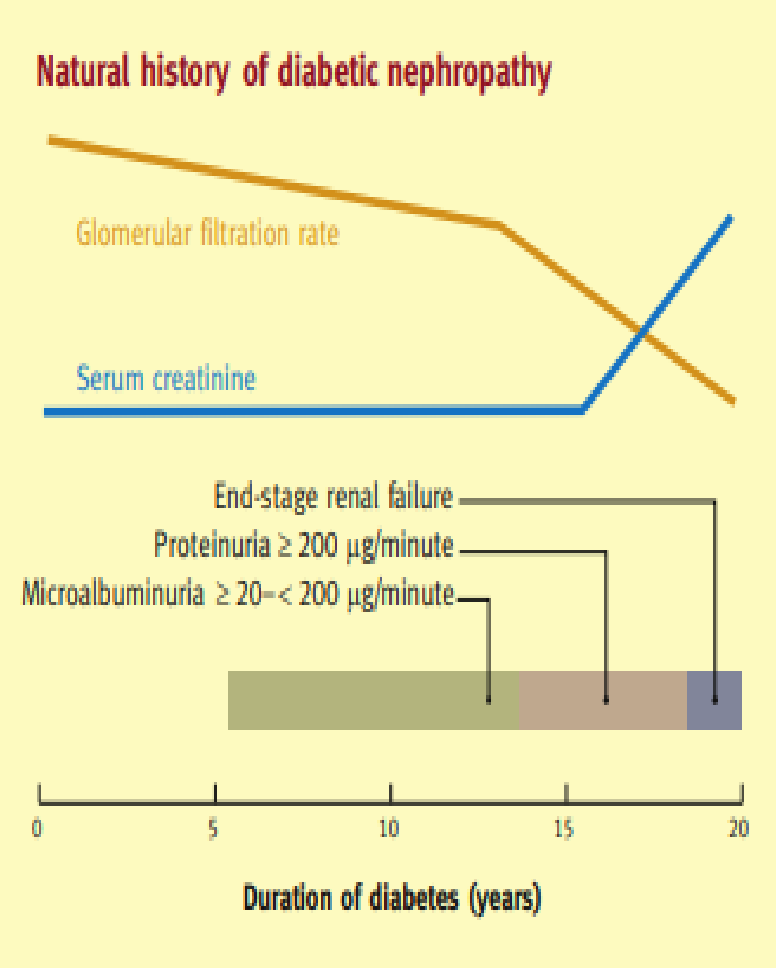
2. Microalbuminuria
   [20 - 200ug/d]

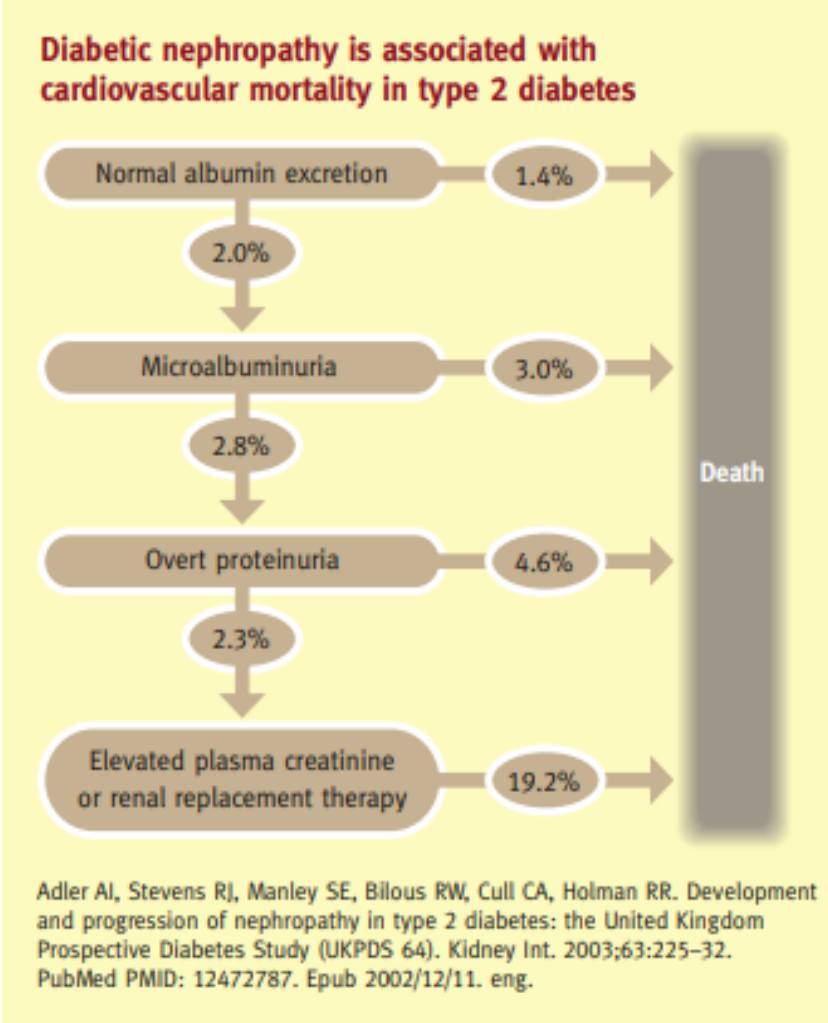
3. Clinical nephropathy
   [proteinuria > 0.5g/d]

4. End -stage renal failure



Natural history of diabetic nephropathy





Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003;63:225–32. PubMed PMID: 12472787. Epub 2002/12/11. eng.

What is the Diabetic Nephropathy?

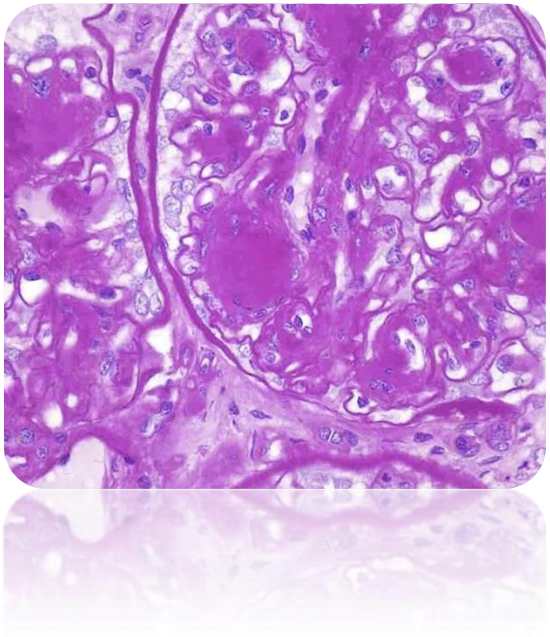
Clinical syndrome

- Persistente proteinuria
- Hypertension
- Progressive decline in renal function

Pathologic renal lesions

- Diabetic microangiopathy – ↑ of basement membrane (BM) material
- Difuse glomerulosclerosis – difuse ↑ in mesangial matrix and thickening of the capillary walls
- Nodular glomerulosclerosis – Kimmelstiel-Wilson lesions
- Insudative lesions – hyalinosis
- Atubular glomeruli
- Difuse linear reaction for IgG along the BM

Diabetic Nephropathy



Diagnostic histopathologic lesions

Glomerular

- Thickening of glomerular basement membrane (GBM)
- Mesangial expansion
- Nodular glomerulosclerosis (Kimmelstiel-Wilson lesions)

Interstitial

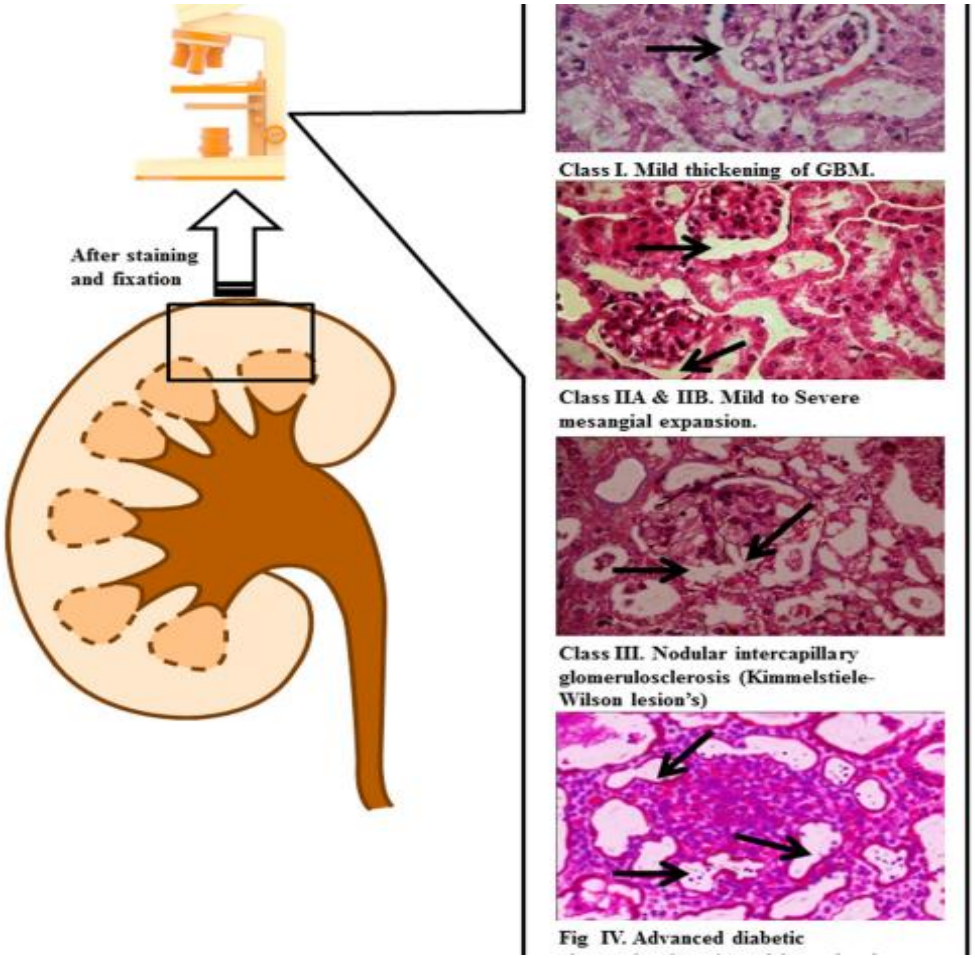
- Thickening of tubular basement membrane (TBM)
- Arteriolar hyalinosis

Tervaert's Pathologic Classification of Diabetic Nephropathy

Class	Description	Inclusion Criteria
I	Mild or nonspecific LM changes and EM-proven GBM thickening	Biopsy does not meet any of the criteria mentioned below for class II, III, or IV GBM > 395 nm in female and >430 nm in male individuals 9 years of age and older[a]
IIa	Mild mesangial expansion	Biopsy does not meet criteria for class III or IV Mild mesangial expansion in >25% of the observed mesangium
IIb	Severe mesangial expansion	Biopsy does not meet criteria for class III or IV Severe mesangial expansion in >25% of the observed mesangium
III	Nodular sclerosis (Kimmelstiel–Wilson lesion)	Biopsy does not meet criteria for class IV At least one convincing Kimmelstiel–Wilson lesion
IV	Advanced diabetic glomerulosclerosis	Global glomerular sclerosis in >50% of glomeruli Lesions from classes I through III

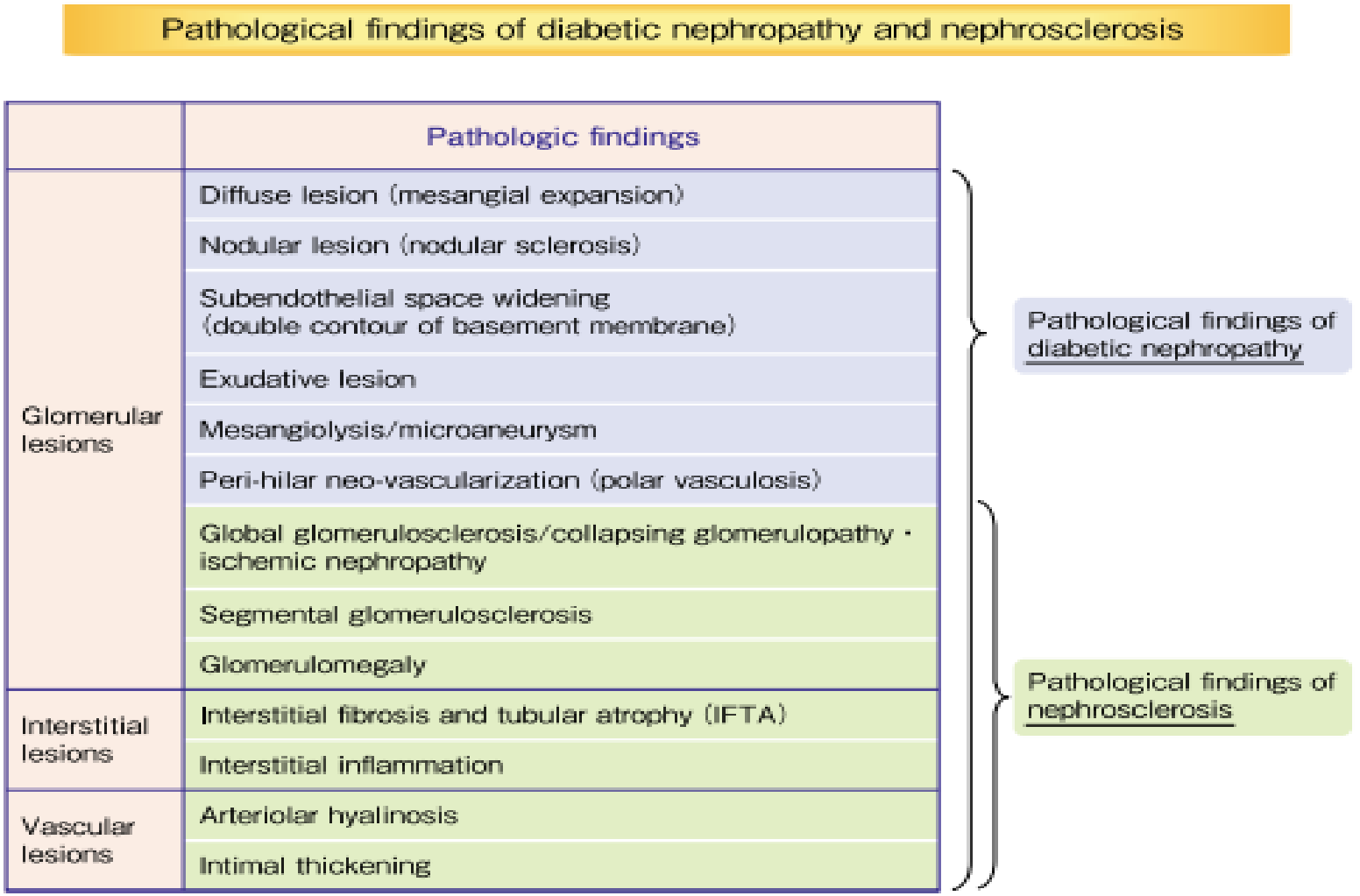
LM, light microscopy.
[a]On the basis of direct measurement of GBM width by EM, these individual cutoff levels may be considered indicative when other GBM measurements are used.

Diagram indicates different stages of diabetic nephropathy



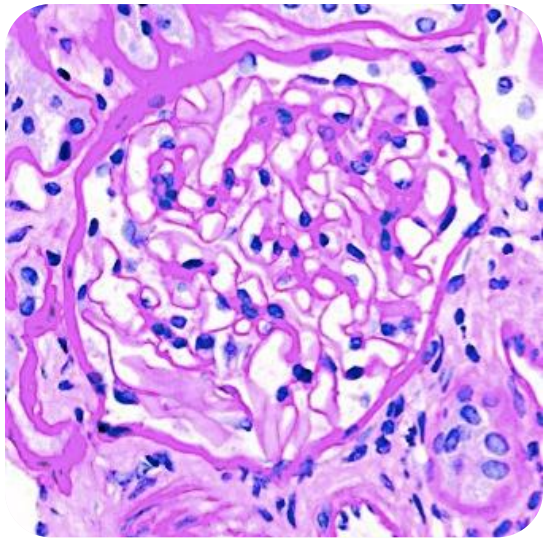
N. Bhattacharjee et al. / European Journal of Pharmacology 791 (2016) 8–24

Pathological findings of diabetic nephropathy and nephrosclerosis



Class I

Glomerular Basement Membrane Thickening

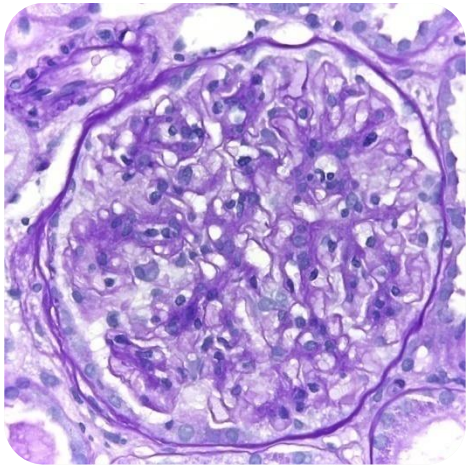


Class I – H & E 400x

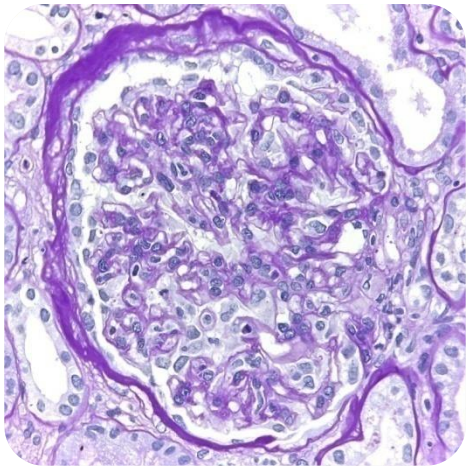
- Biopsy shows **no** or **only mild**, **nonspecific** changes by light microscopy
- **Changes do not meet the criteria of classes II through IV**
  - Absence of mesangial expansion, nodular KW lesions and glomerulosclerosis
- **GBM**, measured with EM is, on average
  - Thicker than 430 nm in males
  - Thicker than 395 nm in females

Class II

Mesangial Expansion
II a – Mild
II b – Severe



Class II a – PAS 400x

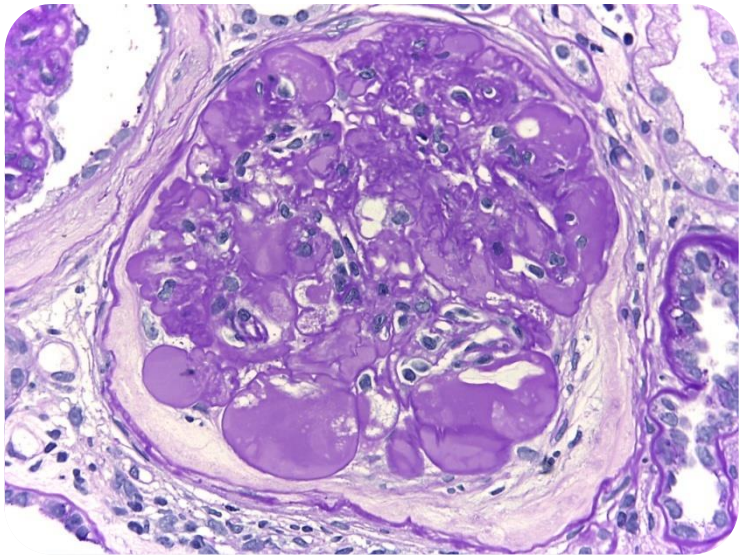


Class II b – PAS 400x

- **Mild** or **severe mesangial expansion**, not meeting the criteria for class II or IV
- **Mesangial expansion** – increase in extracellular material in the mesangium such that the width of the interspace *exceeds two mesangial cell nuclei* in at least two glomerular lobules
  - **Mild** – expanded mesangial area **<** mean area of a capillary lumen
  - **Severe** - expanded mesangial area **>** mean area of a capillary lumen

Class III

Nodular Sclerosis – Kimmelstiel-Wilson lesions.



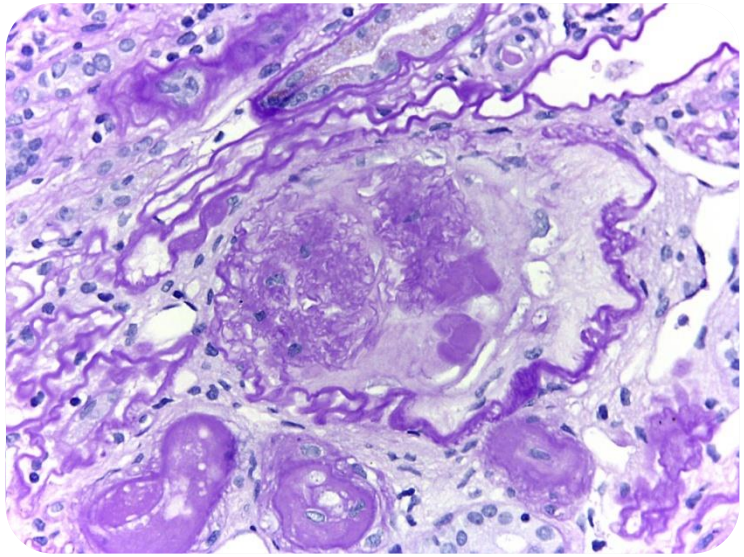
Class III – PAS 400x

- At **least one** convincing Kimmelstiel-Wilson lesion is found
- The biopsy specimen **does not have** more than 50% global glomerulosclerosis (Class III)

- **Kimmelstiel-Wilson lesion** – focal, lobular, round to oval mesangial lesions with an acellular, hyaline/matrix core, rounded peripherally by sparse, crescent-shaped mesangial nuclei

Class IV

Advanced Diabetic Glomerulosclerosis



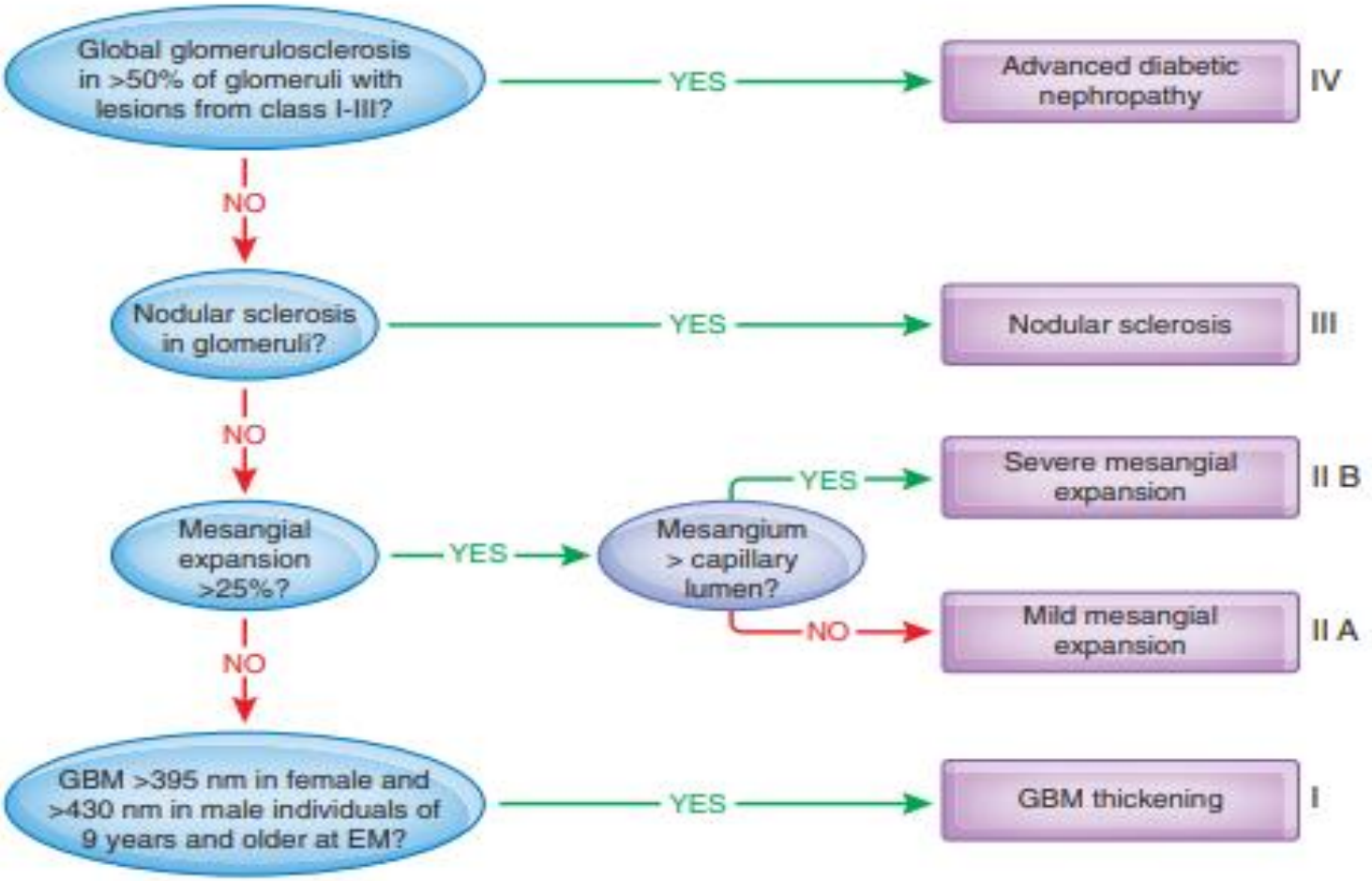
Class IV – PAS 400x

- **Advanced DN**
- **More than 50%** global glomerulosclerosis
- The is clinical or pathological evidence that the sclerosis is attributable to DN

Tervaert's Pathologic Classification of Diabetic Nephropathy

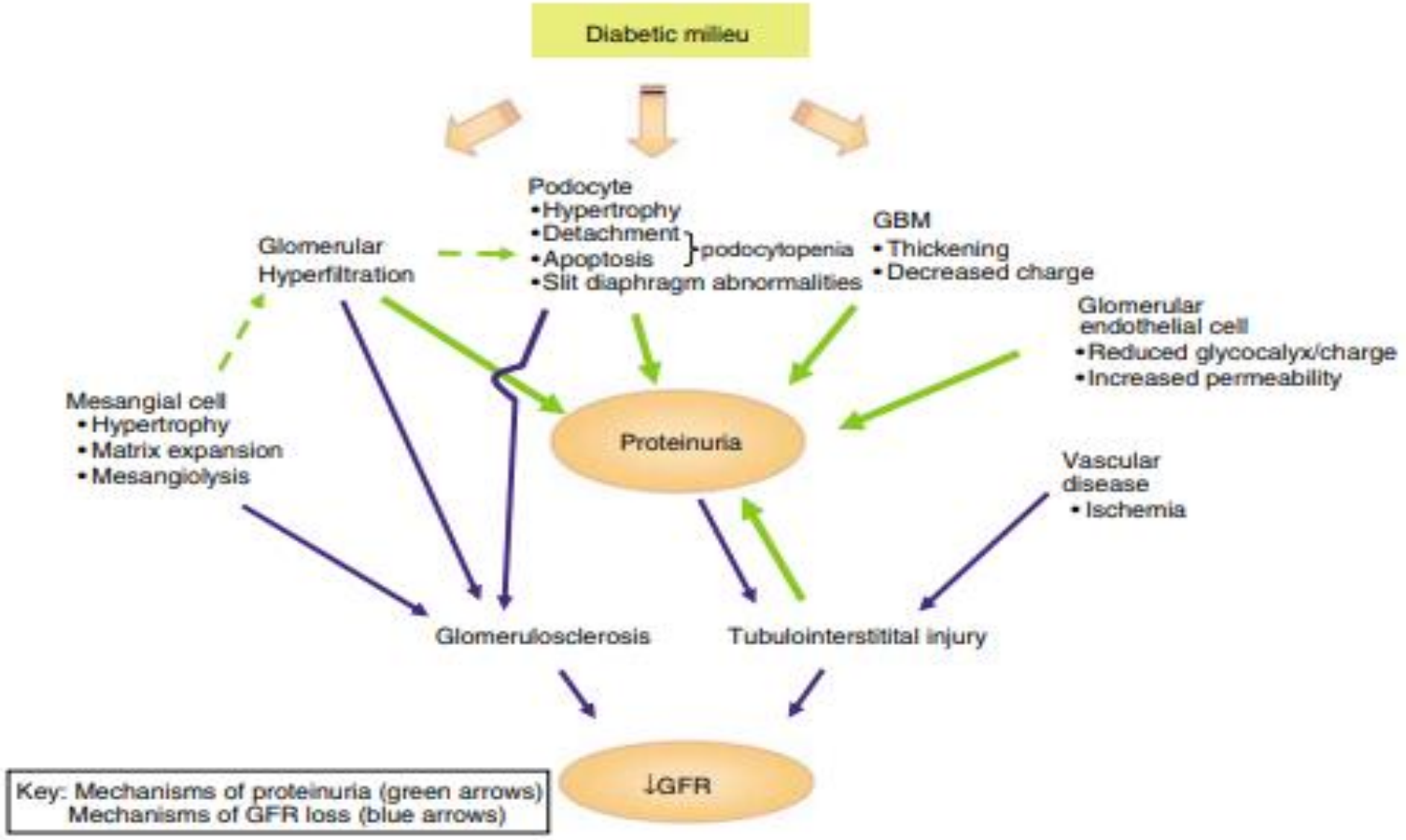
Lesion	Criteria	Score
Interstitial lesions		
IFTA	No IFTA	0
	<25%	1
	25% to 50%	2
	>50%	3
interstitial	Absent	0
inflammation	Infiltration only in relation to IFTA	1
	Infiltration in areas without IFTA	2
Vascular lesions		
arteriolar hyalinosis	Absent	0
	At least one area of arteriolar hyalinosis	1
	More than one area of arteriolar hyalinosis	2
presence of large vessels	–	Yes/no
arteriosclerosis (score worst artery)	No intimal thickening	0
	Intimal thickening less than thickness of media	1
	Intimal thickening greater than thickness of media	2

Flow chart for classifying DN



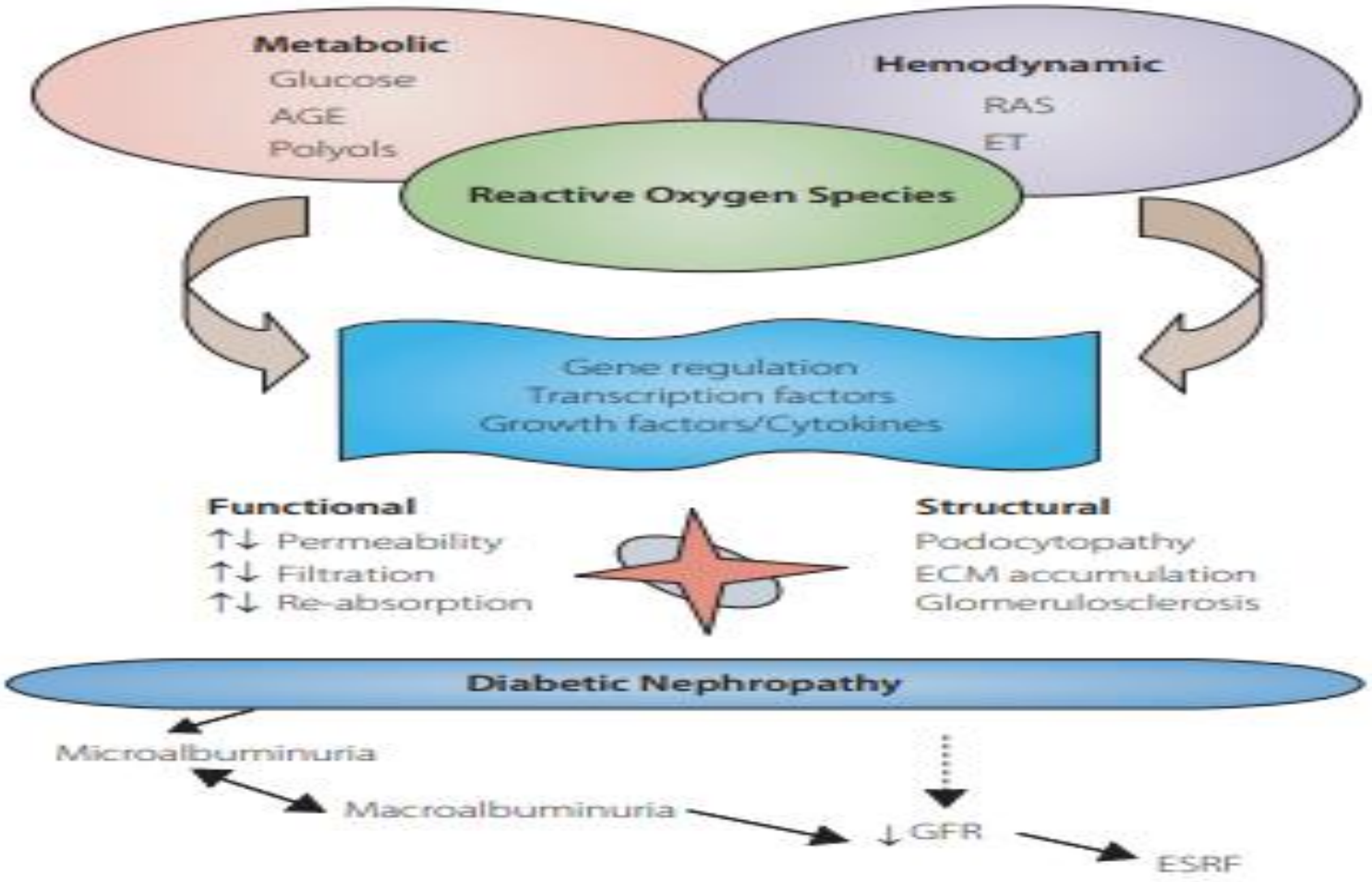
J Am Soc Nephrol 21: 556 –563, 2010

Proposed schema unifying the mechanisms of proteinuria and decrease in GFR in DKD



Kidney International (2008) 74, 22–36

Schema of pathogenesis of diabetic nephropathy



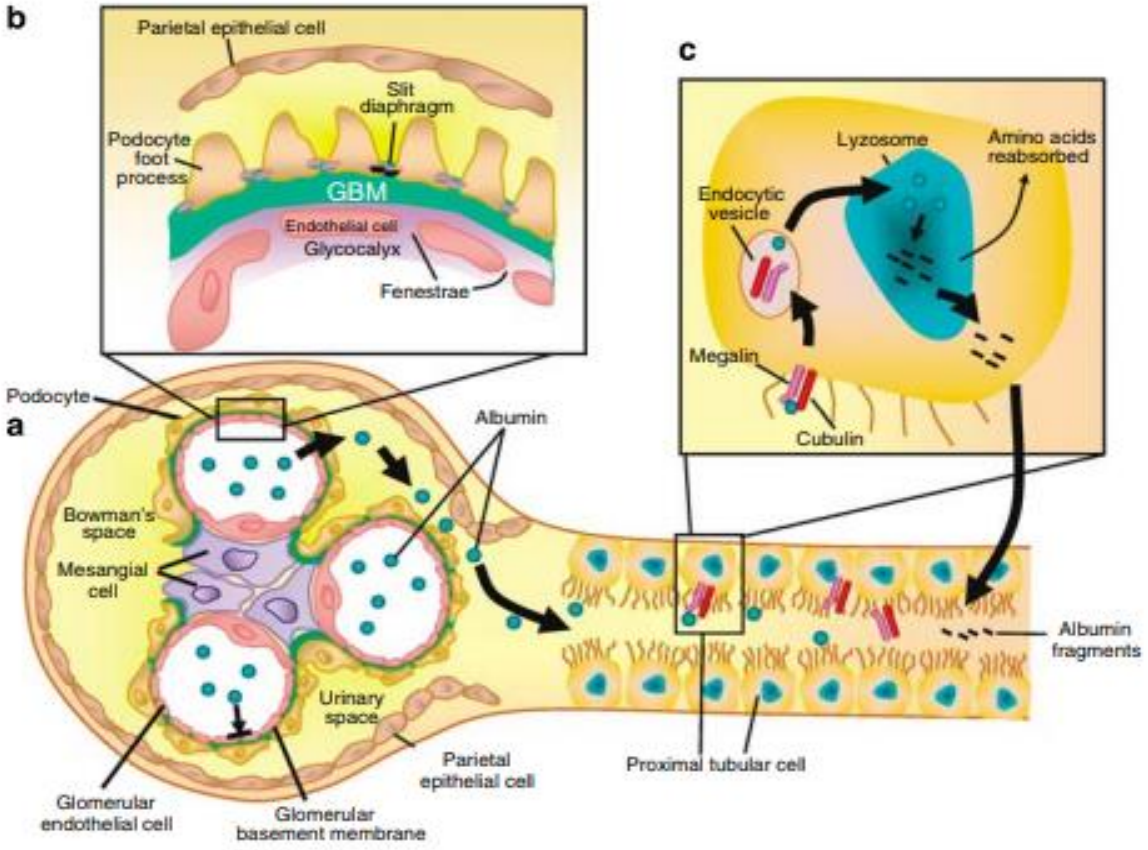
Journal of Diabetes Investigation Volume 2 Issue 4 August 2011

Mechanisms of proteinuria in DKD

Site of injury	Effect	Underlying mechanisms
Glomerular hemodynamics	Glomerular hyperfiltration	Afferent arteriole vasodilatation
		Efferent arteriole vasoconstriction
		↑glomerular capillary pressure
Glomerular endothelial cell	Endothelial cell injury	Hyperglycemia, AGE, ROS
	Diminished endothelial glycocalyx	Endothelial cell injury or enzymatic cleavage
	Altered VEGF signaling	Podocyte injury or loss
GBM	Irregular thickening	↓production and/or ↑degradation of extracellular matrix proteins
	Decreased negative charge	↓ production and/or ↑ degradation of HSPG
Podocyte	Podocytopenia	Detachment
		Apoptosis
		Lack of proliferation
	Loss of slit diaphragm integrity	Decrease or changes in subcellular localization of nephrin
	Foot process widening and effacement	Disrupted actin cytoskeleton
		Loss of slit diaphragm integrity
		Impaired podocyte GBM interaction
	Loss negative charge	↓Podocalyxin
Proximal tubule	Decreased protein reabsorption	Tubular injury and interstitial fibrosis

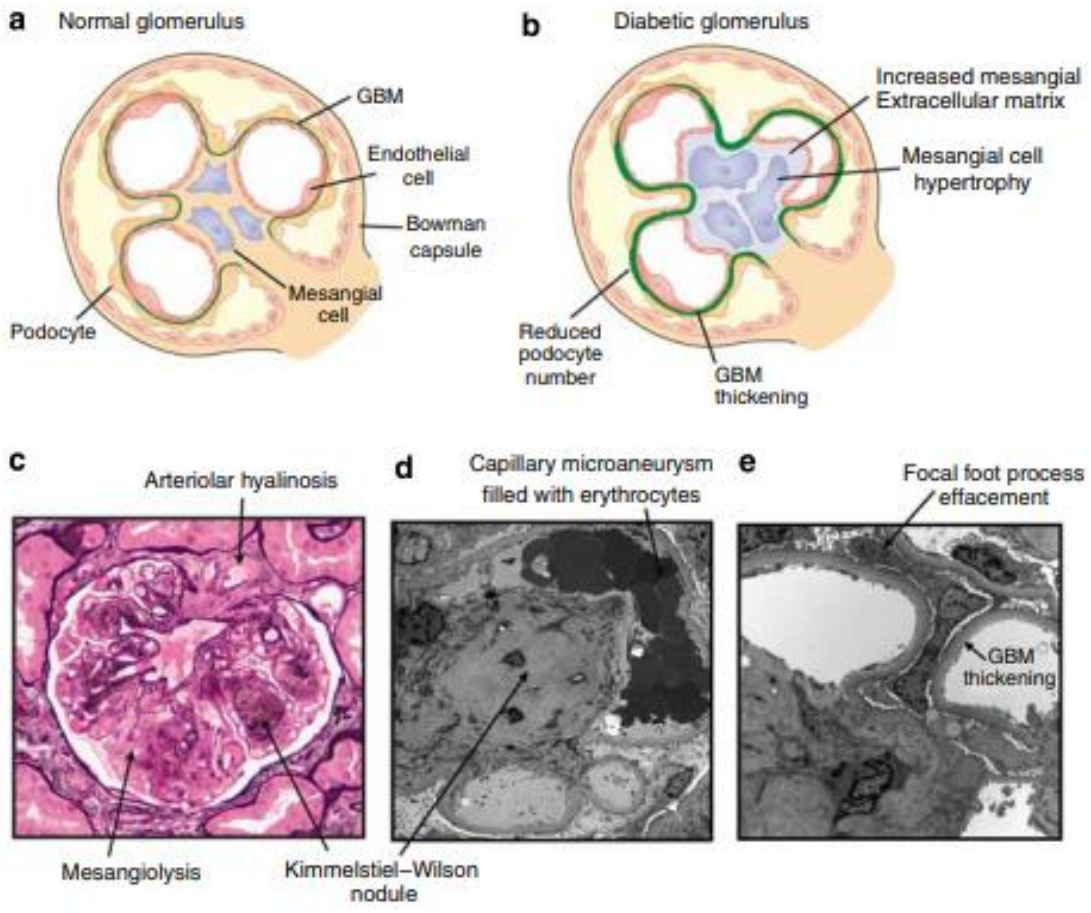
Kidney International (2008) 74, 22–36

Normal renal handling of albumin.



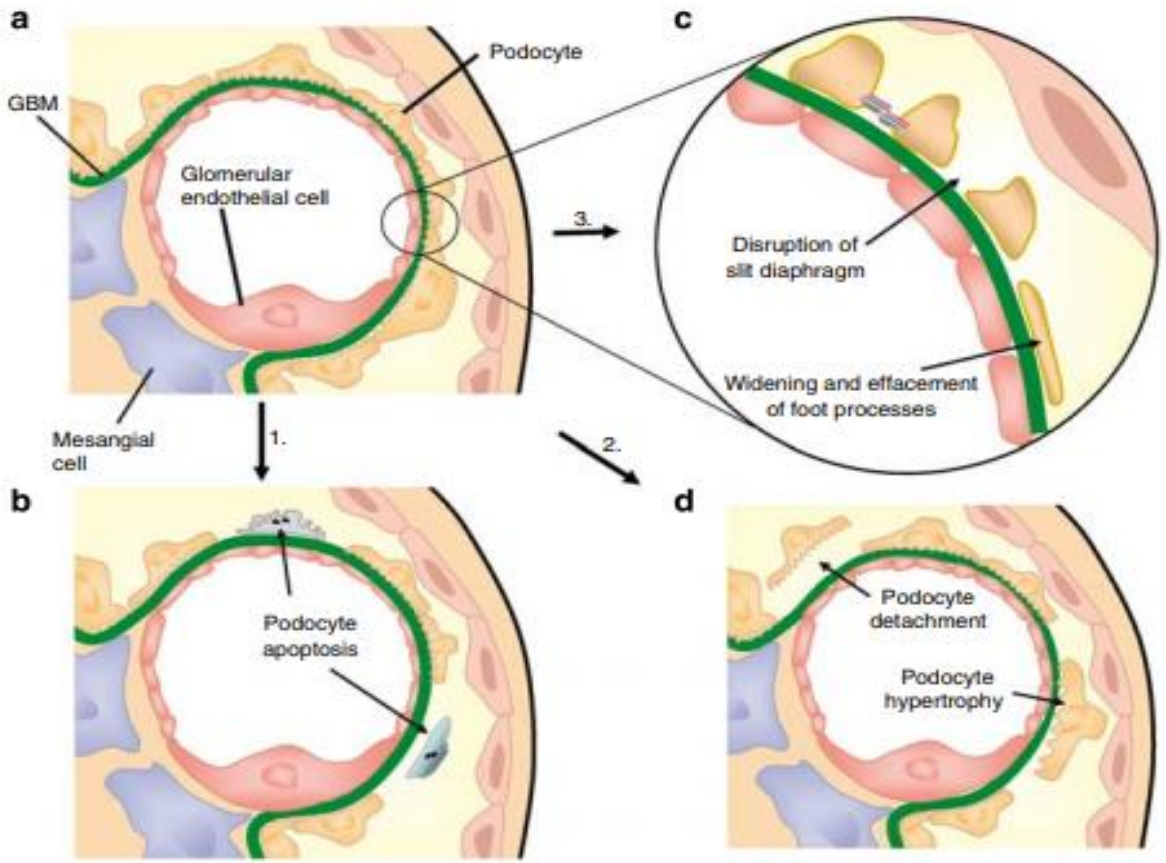
Kidney International (2008) 74, 22–36

Characteristic glomerular changes of DKD



Kidney International (2008) 74, 22–36

Podocyte abnormalities in DKD



Kidney International (2008) 74, 22–36

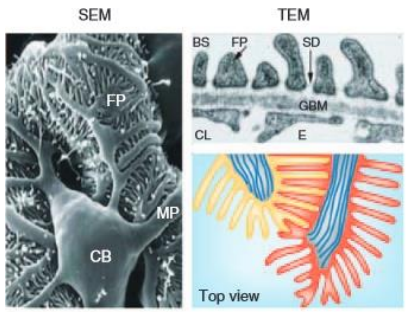
http://www.kidney-international.org

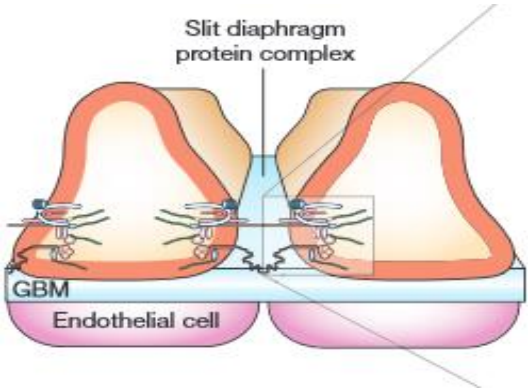
Podocyte biology in diabetic nephropathy

JJ Li[1,2], SJ Kwak[2], DS Jung[2], J-J Kim[2], T-H Yoo[2], D-R Ryu[3], SH Han[2], HY Choi[2], JE Lee[2], SJ Moon[2], DK Kim[2], DS Han[2] and S-W Kang[2]

[1]Department of Internal Medicine, Nephrology and Dialysis Unit, The Affiliated Hospital, YanBian University Medical College, JiLin, China; [2]Department of Internal Medicine, College of Medicine, Brain Korea 21, Yonsei University, Seoul, Korea and [3]Department of Internal Medicine, College of Medicine, Ewha Woman's University, Seoul, Korea

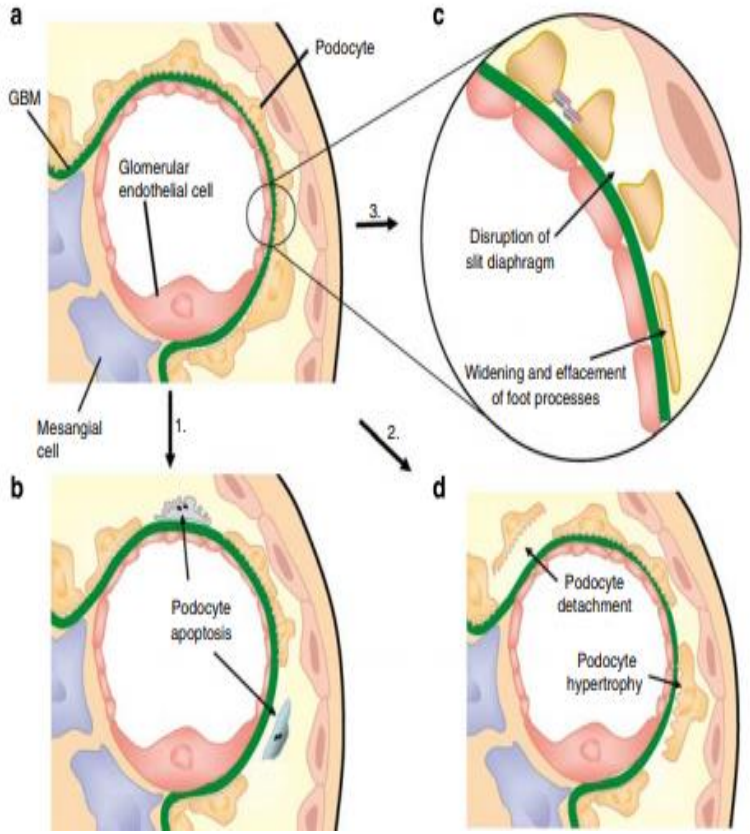
Furthermore, podocytes are known to synthesize matrix molecules to the glomerular basement membrane (GBM), including type IV collagen, laminin, entactin, and agrin. Because diabetic nephropathy is clinically characterized by proteinuria and pathologically by glomerular hypertrophy and GBM thickening with foot process effacement, podocytes have been the focus in the field of research on diabetic nephropathy





FACTORS CAUSING PODOCYTE INJURY IN DIABETIC NEPHROPATHY

- High glucose
- Angiotensin II
- TGF-β
- Mechanical stress



Kidney International (2007) 72, S36–S42

High glucose

- Induction of hypertrophy
- Increased production of collagen a1(IV), a3(IV), and a5(IV) Activation of p38 MAPK pathway
- Increased production of VEGF and angiotensin II
- Reduced expression of P-cadherin
- Reduced expression of integrin a3 subunit
- Increased C-type NP-induced production of cGMP Enhancement of mechanical stress-induced glucose uptake

Angiotensin II

- Induction of hypertrophy
- Increased production of collagen a3(IV)
- Modulation of the expression of SD complex and induction of proteinuria
- Induction of apoptosis
- Increased excretion of podocytes in urine
- Increased intracellular calcium activity and induction of depolarization
- Release of various growth factors (?)

TGF-β

- Modulation of CTGF expression
- Increased production of collagen a3(IV) Involvement of Ang II-me diated collagen a3(IV) production
- Decreased production of collagen a1(IV) and a5(IV)
- Increased activities of MMP-2 and -9
- Enhanced secretion of cystatin C
- Induction of apoptosis
- Increased production of VEGF

Mechanical stress

- Increased glucose uptake
- Induction of hypertrophy
- Reduced proliferation
- Activation of intracellular renin-angiotensin system
- Increased osteopontin expression
- Induction of reversible reorganization of the actin cytoskeleton
- Reduced cGMP response to ANP and to C-type NP
- Increased COX-2 and PG EP4 receptor expression

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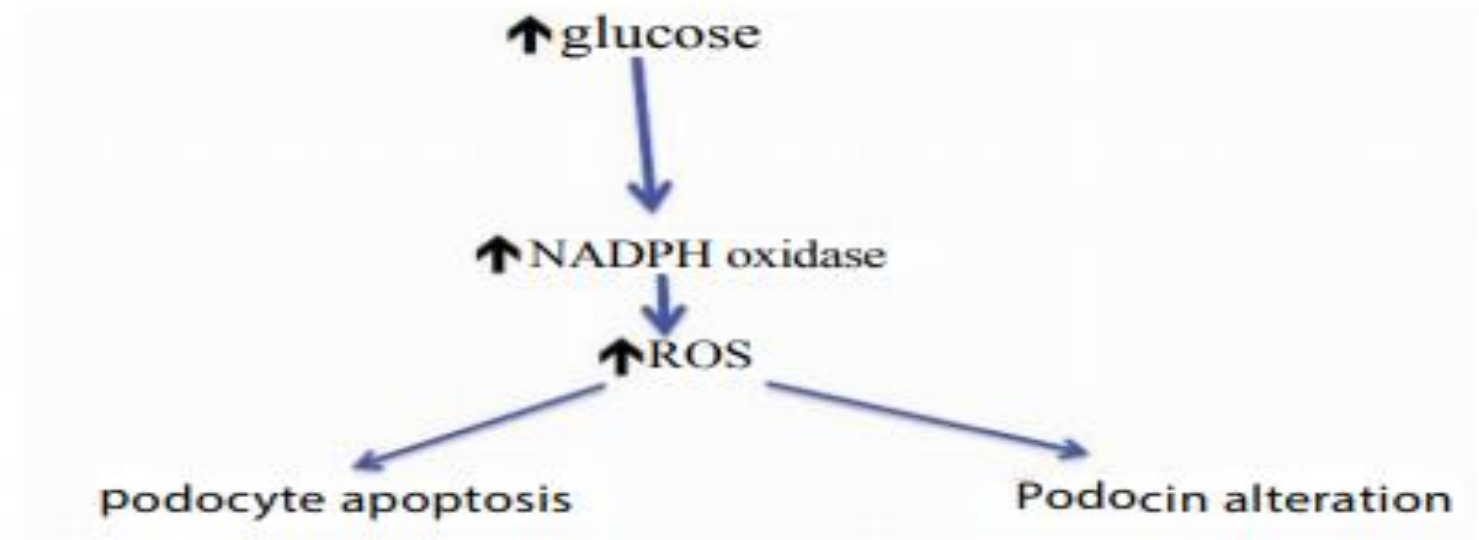
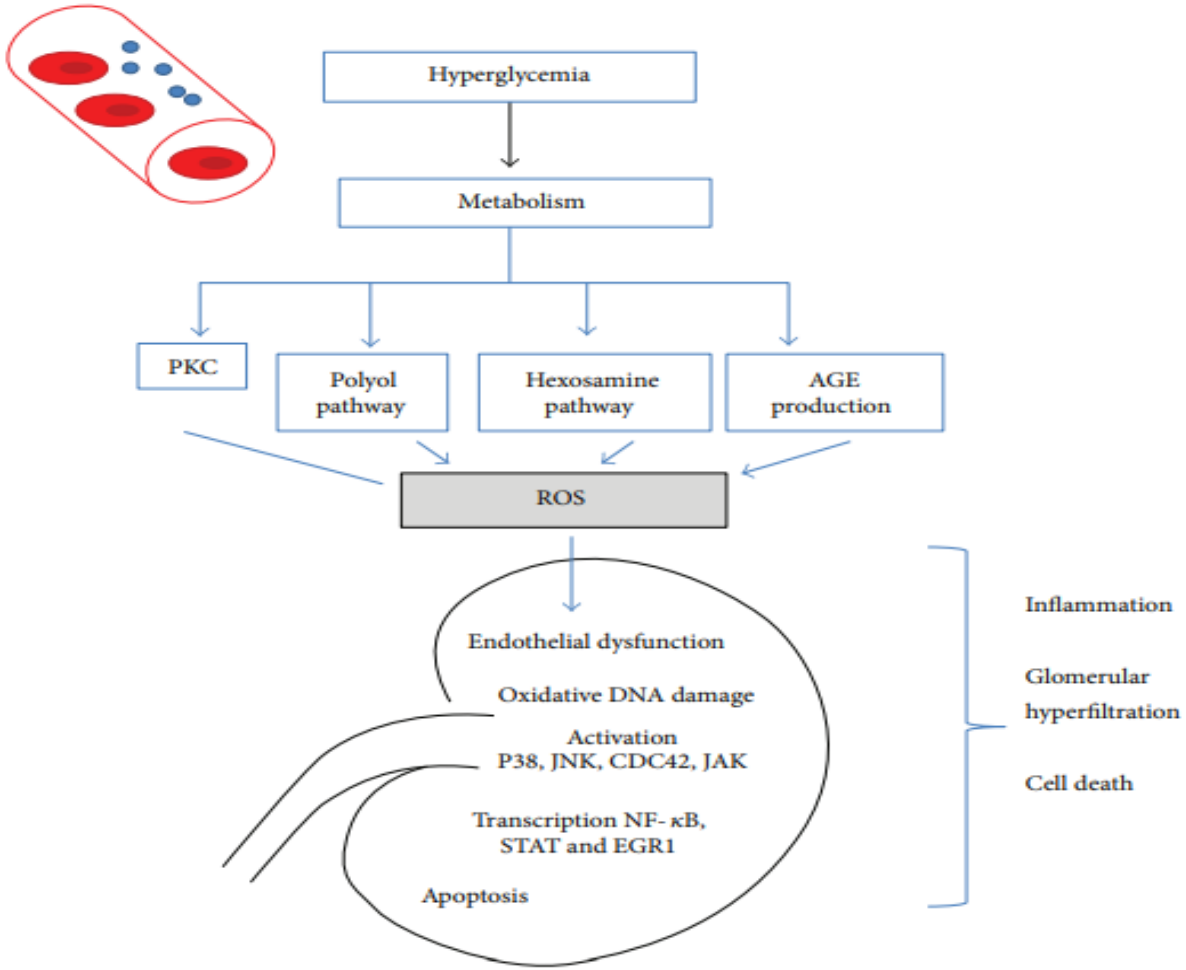
- Reactive oxygen species mediated podocyte injury and podocin protein alteration

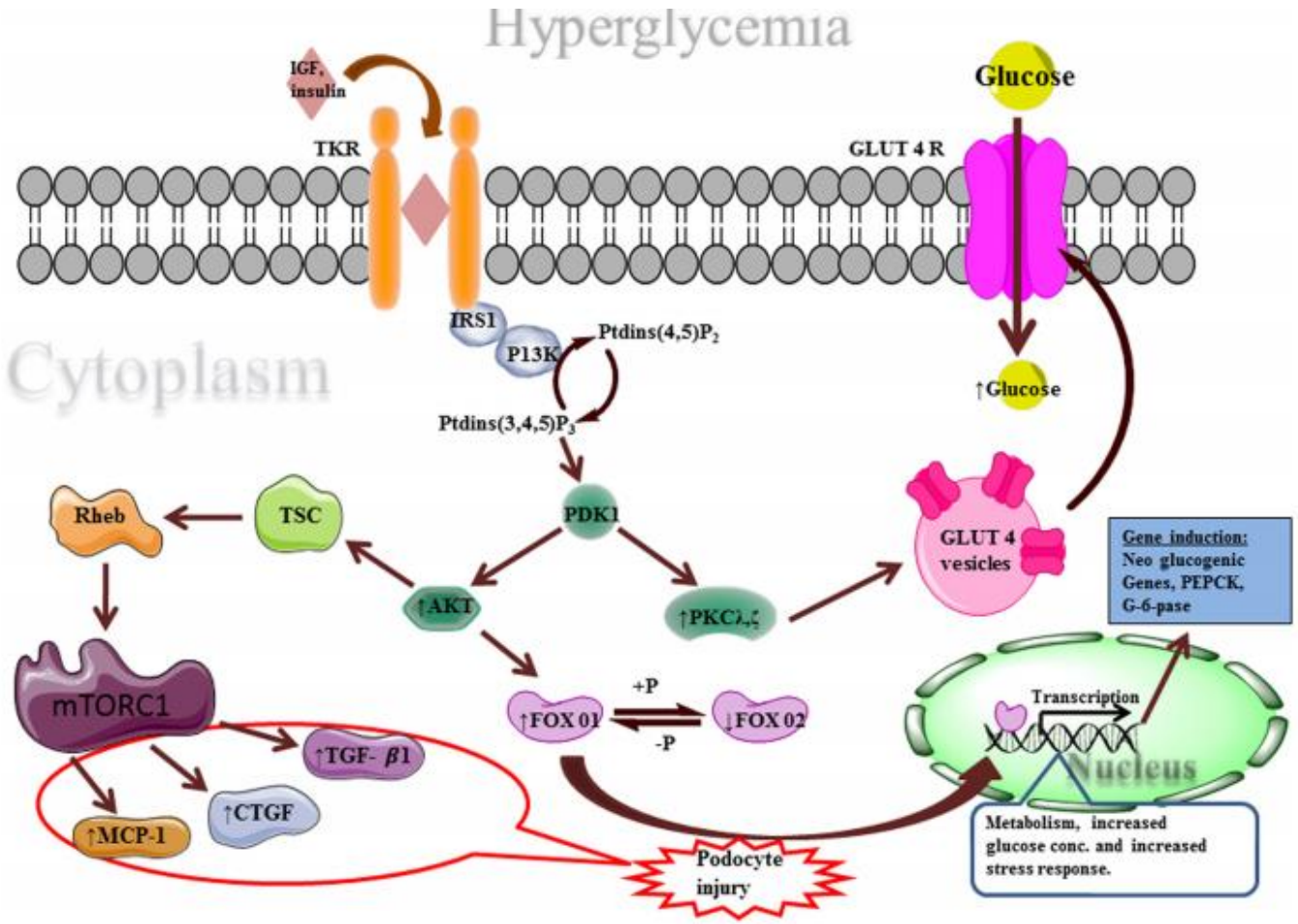


Hypothetical drawing of the apoptotic process in DN from hyperglycemia



International Journal of Endocrinology Volume 2018, Article ID 1875870, 13 pages

Schematic diagram represents role of mTORC1 pathway in podocyte injury



N. Bhattacharjee et al. / European Journal of Pharmacology 791 (2016) 8–24

Journal of Clinical & Experimental Nephrology
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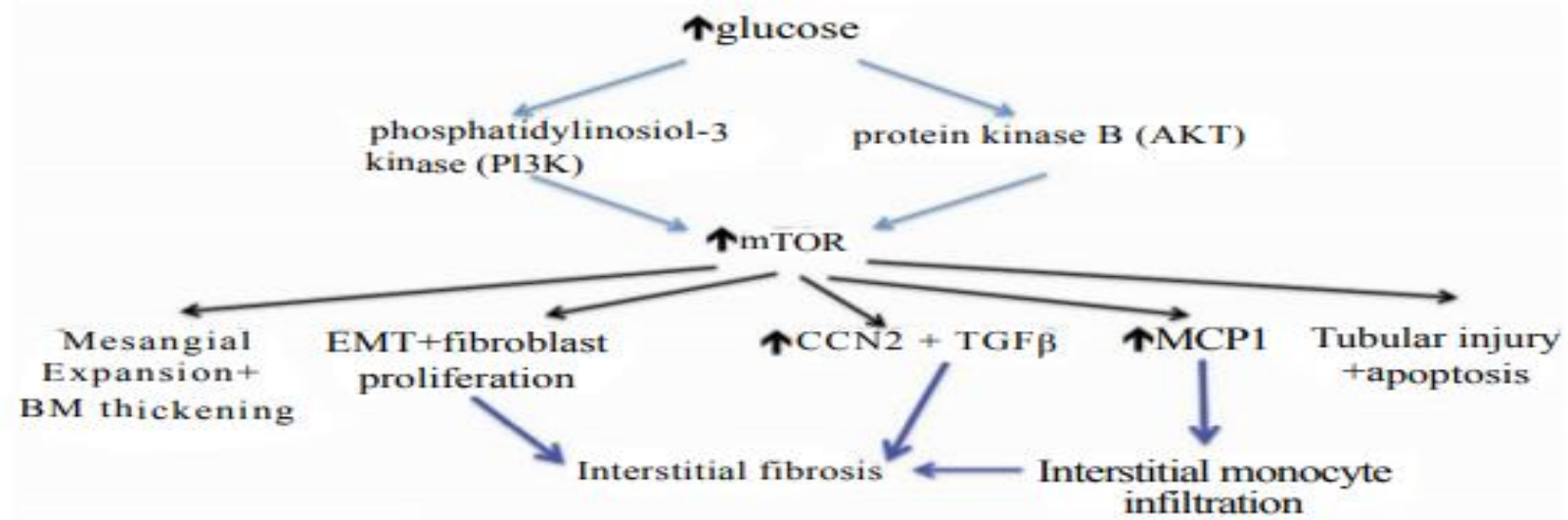
- Consequences of mTOR activation induced by hyperglycemia

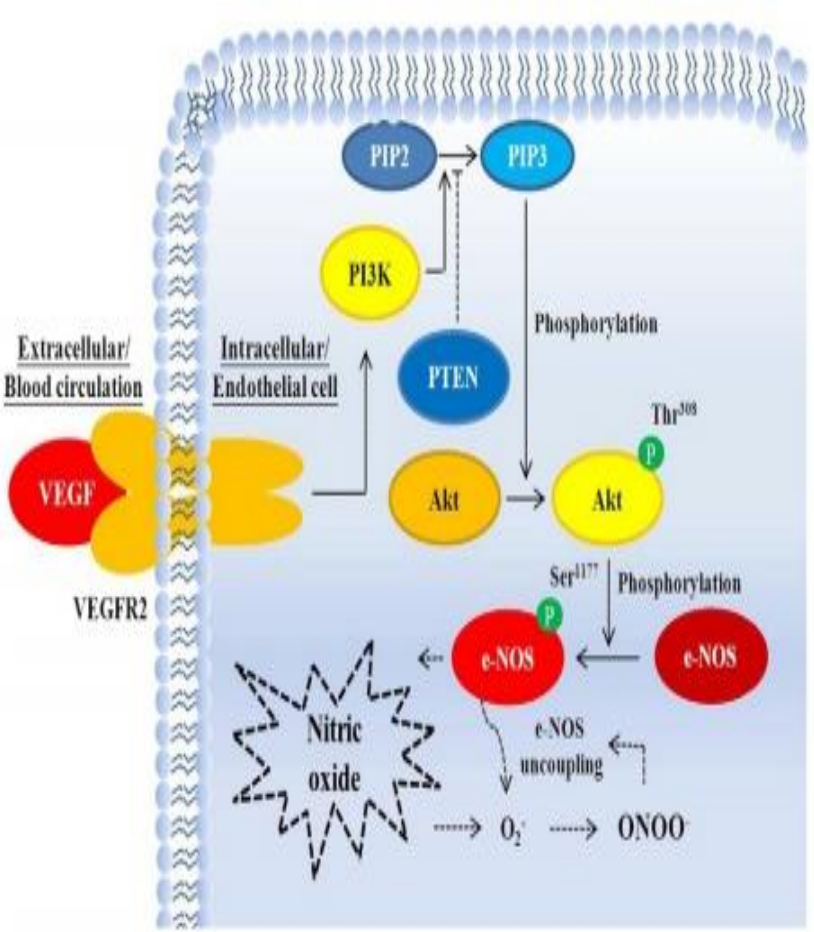


Abnormalities in the glomerular endothelium cause proteinuria in diabetes

- Endothelial cell injury
- Diminished endothelial glycocalyx
- Altered VEGF signaling

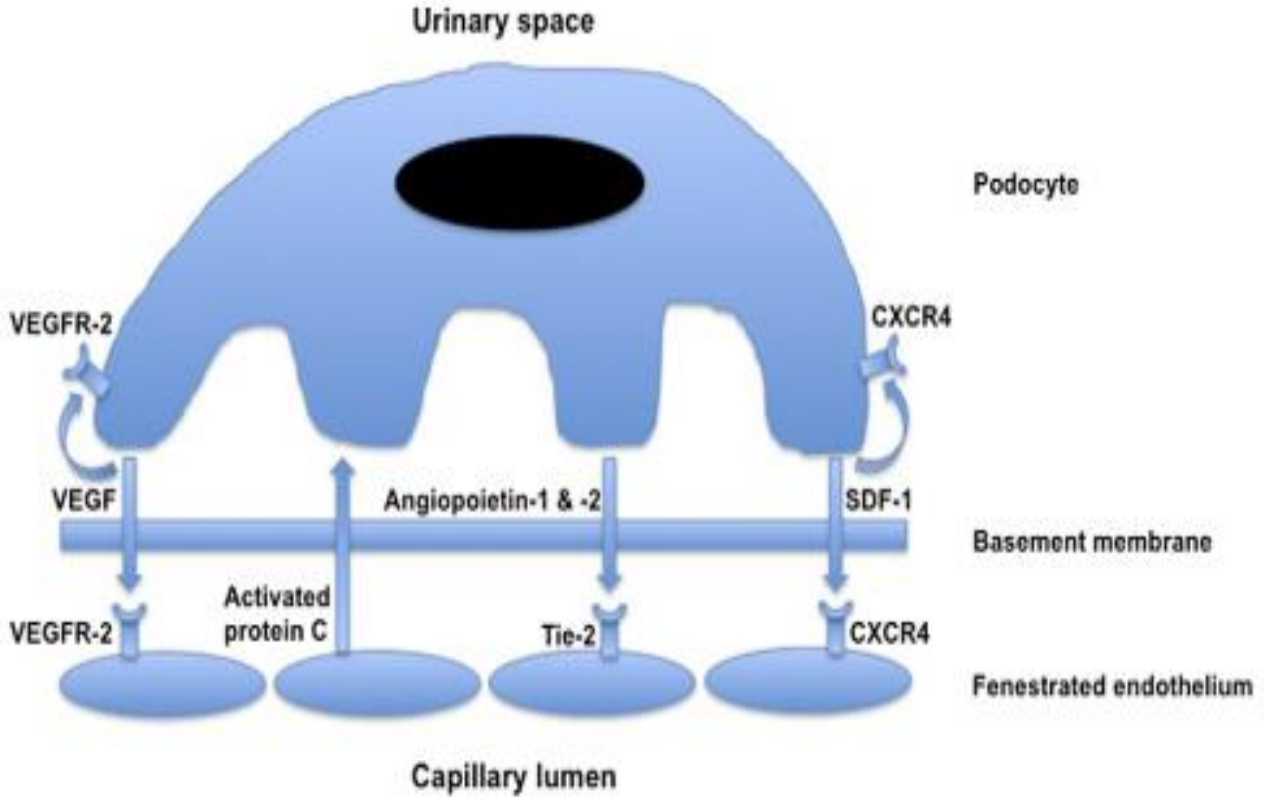
High blood glucose-induced endothelial dysfunction

- Activated VEGF signaling
- Increased NO
- Induced ROS overproduction
- Form, ONOO peroxynitrite molecules



W.K.C. Leung et al. / Life Sciences 166 (2016) 121–130

Podocyte and endothelial cell cross-talk in diabetes



Seminars in Nephrology, Vol 32, No 2, March 2012, pp 199-207

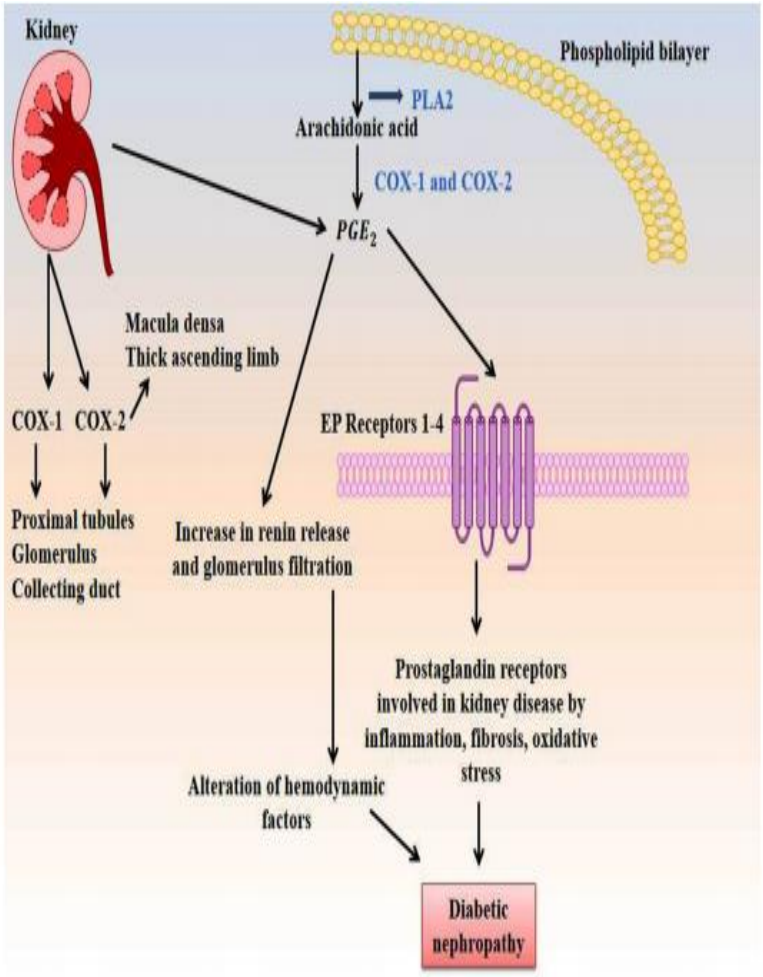
New insights into established in novel molecular targets

- Role of COX and PGE2 in diabetic nephropathy
- Nuclear factor-kappa b (NF-kb) signaling in diabetic nephropathy
- Role of protein kinase C in s in diabetic nephropathy
- Wnt signaling and stress in diabetic nephropathy
- MicroRNAs and diabetic nephropathy
- Epigenetical mechanisms involved in pathogenesis and progression of diabetic nephropathy

Diabetic research and clinical practice 128 (2017) 91 – 108

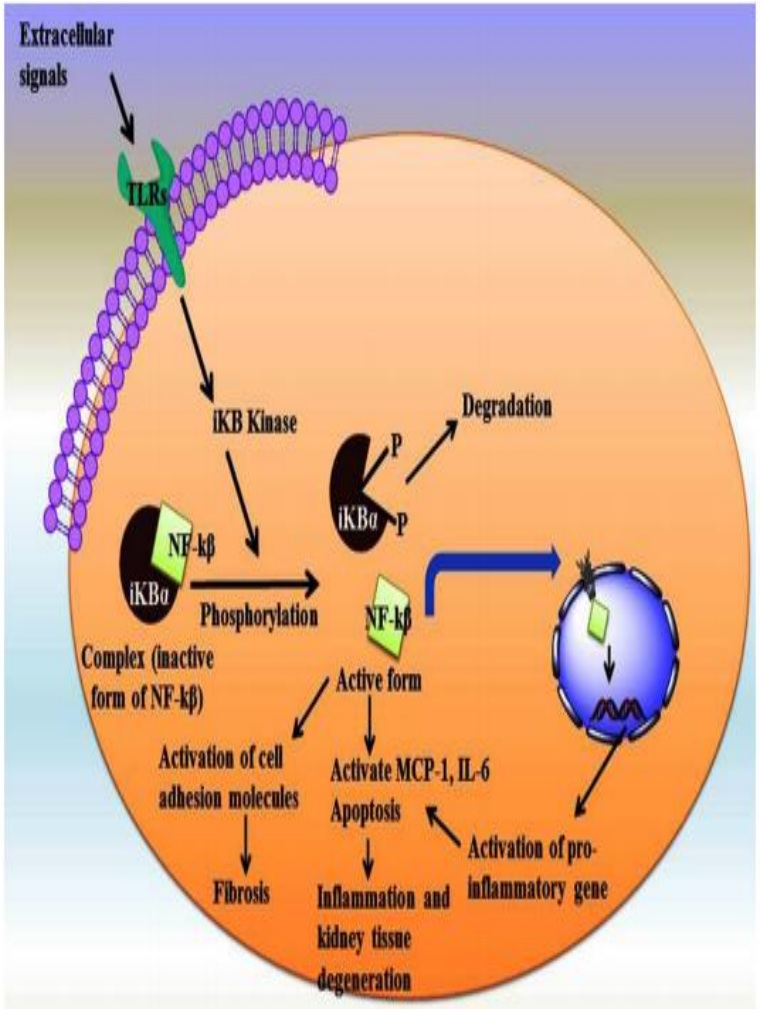
Diabetes research and clinical practice 128 (2017) 91 – 108

- Role of COX and PGE2 in diabetic nephropathy. Production of prostaglandin is initiated by COX enzymes which lead to progression of diabetic nephropathy by inducing inflammation, fibrosis and alterations of hemodynamic factors

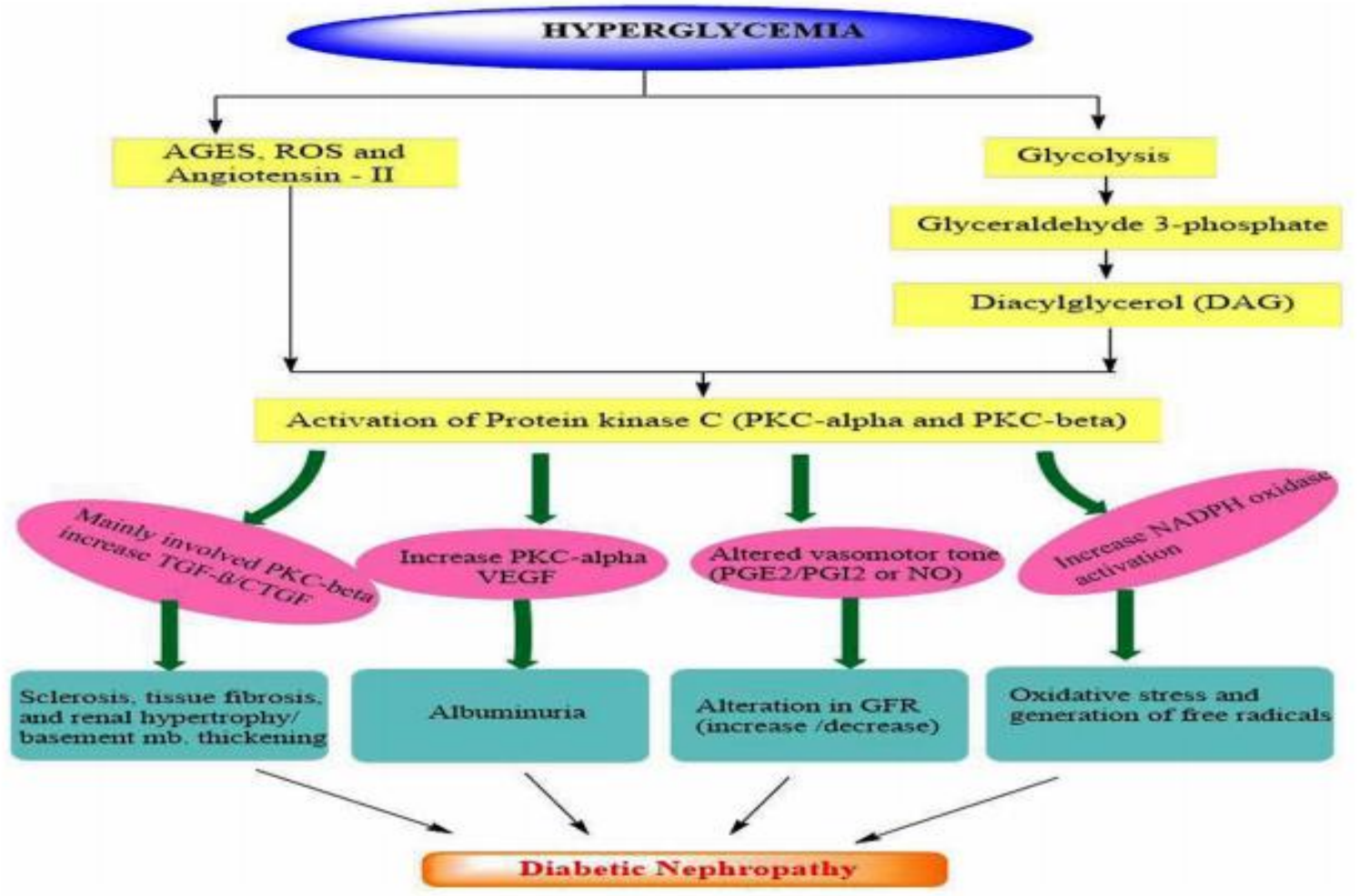


Diabetes research and clinical practice 128 (2017) 91 – 108

- Hyperglycemia induced activation of NF-kb signaling. Extracellular signals like hyperglycemia activate iKB kinase via TLRs and converts inactive form of NF-kb to active form. Activated NF-kb leads to generation of pro-inflammatory genes and cytokines causing renal apoptosis. TLRs: Toll-like receptors; MCP-1: Monocyte-chemoattractant protein-1; IL-6: Interleukin-6; NF-kb: Nuclear factor-kb.

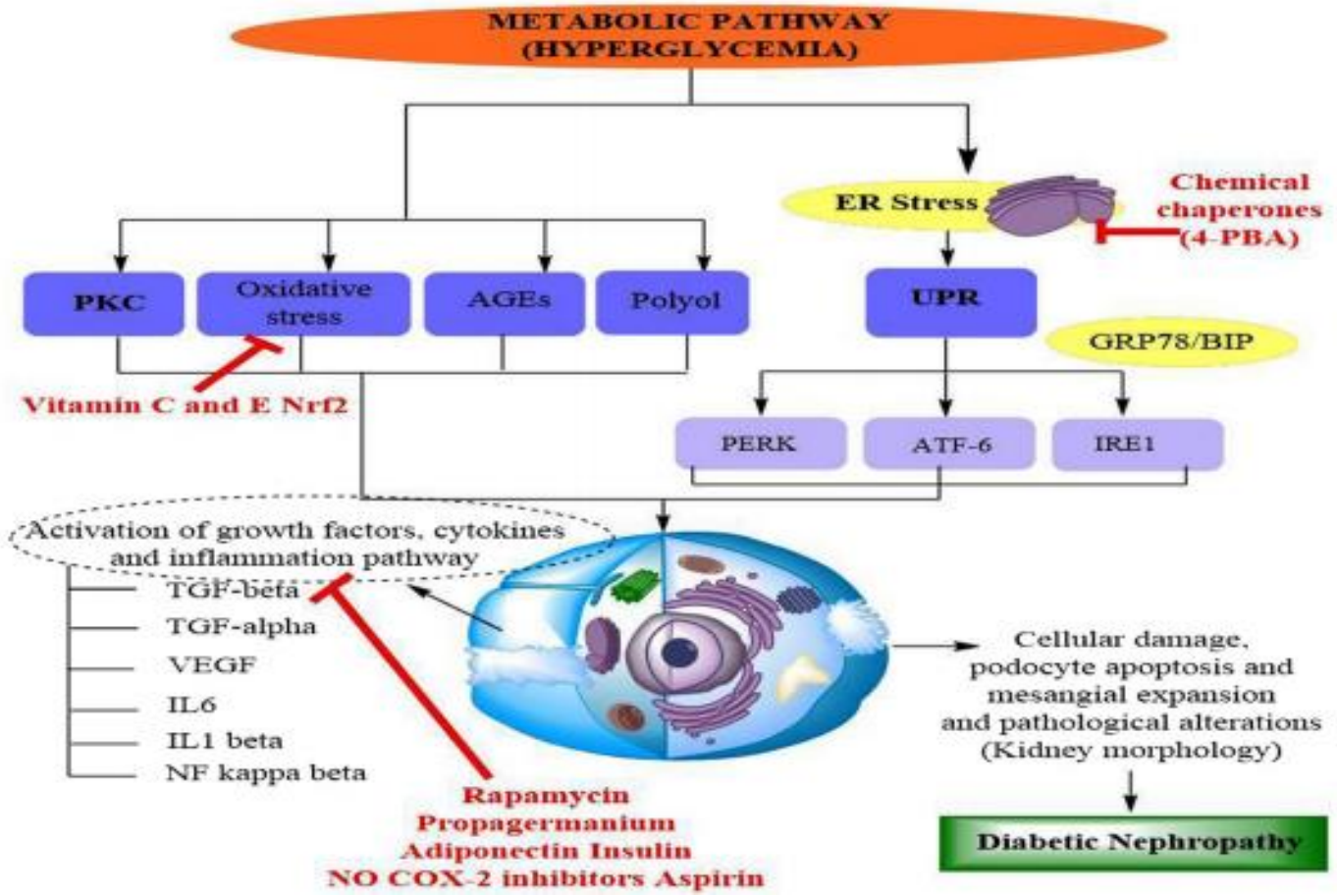


Role of protein kinase C in hyperglycemia-induced diabetic nephropathy



Diabetes research and clinical practice 128 (2017) 91 – 108

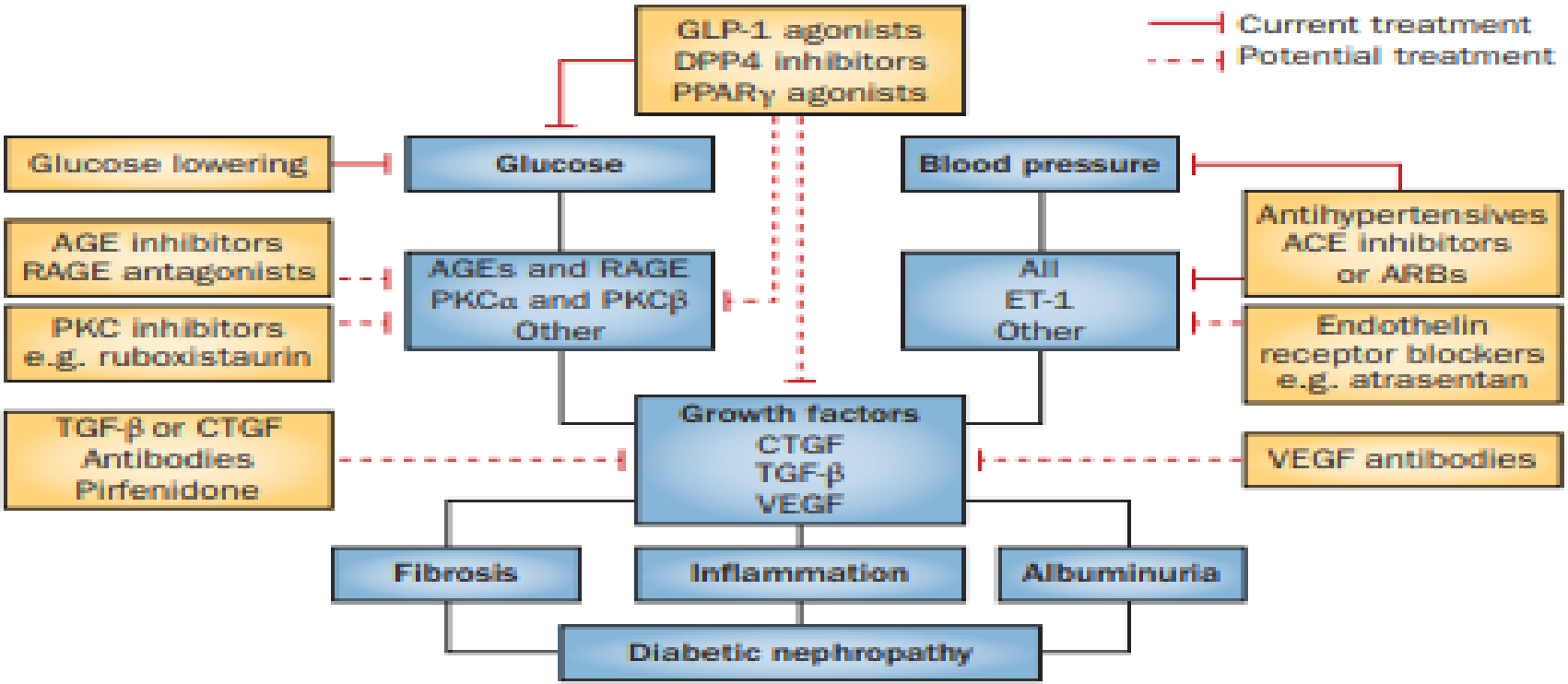
Metabolic pathways associated with diabetic nephropathy along with potential sites for therapeutic targeting.



Diabetes research and clinical practice 128 (2017) 91 – 108

Diabetic nephropathy: diagnosis and treatment

Daniel Fineberg, Karin A. M. Jandeleit-Dahm and Mark E. Cooper



Fineberg, D. et al. Nat. Rev. Endocrinol. 9, 713–723 (2013)

Conclusions

- Multiple mechanisms are operative in diabetes that are related to injury to the kidney and, in susceptible individuals, contribute to nephropathy development
- After a long time of inertia, many novel agents were introduced as potential additions to the standard of care treatment of DN