Diabetes & the Kidneys

Nephropathy & beyond

Amir A. Nassiri, MD, DIU

SBUMS

Tehran, 2025 Oct 10th

Conflict of Interest

Outlines

- Why DM is important for the Nephrologists ?
- Spectrum of renal disease in DM (renal disease in DM is very heterogenous)
- Trajectory of DN (Natural Hx of DN) & Histo-pathological correlation
- NADKD

THE LANCET
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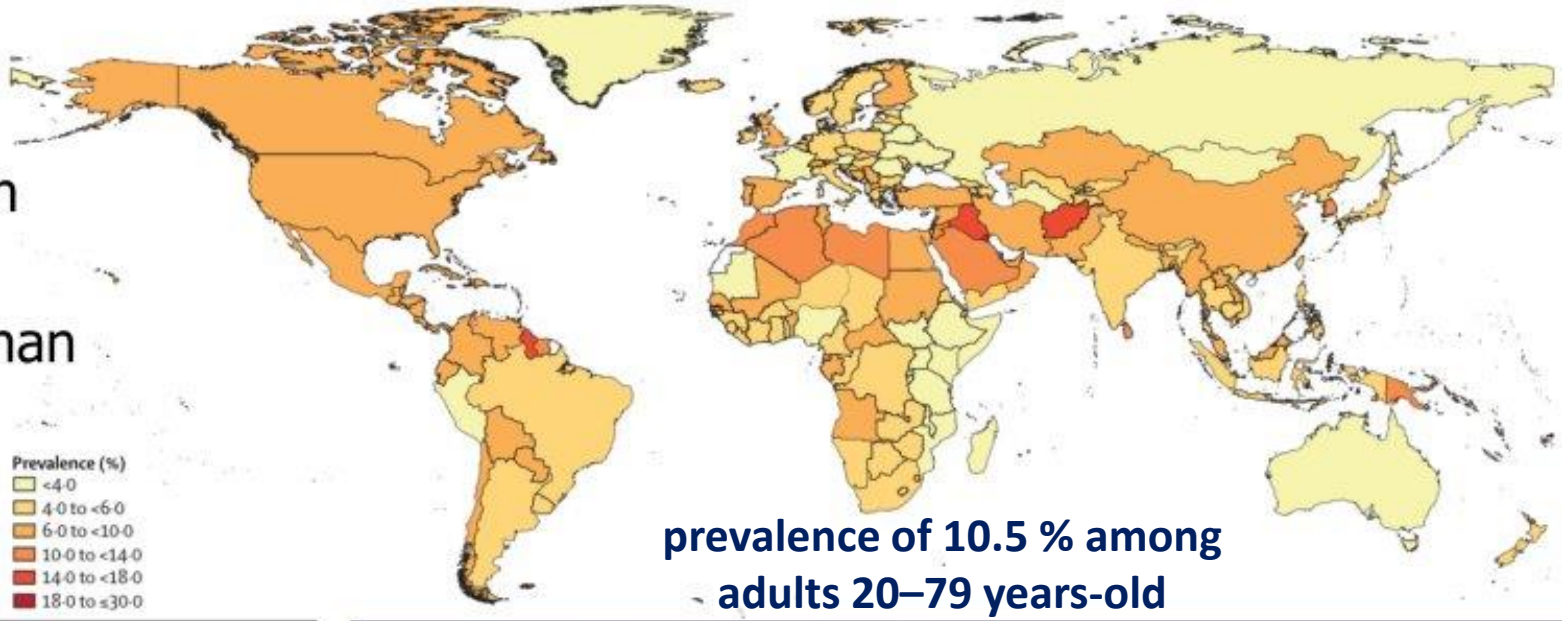
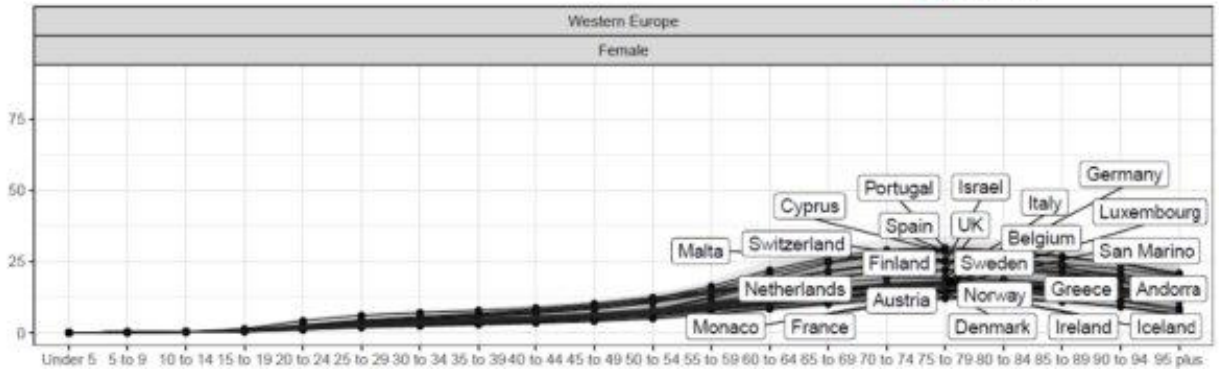
p. 203-234, July 15, 2023

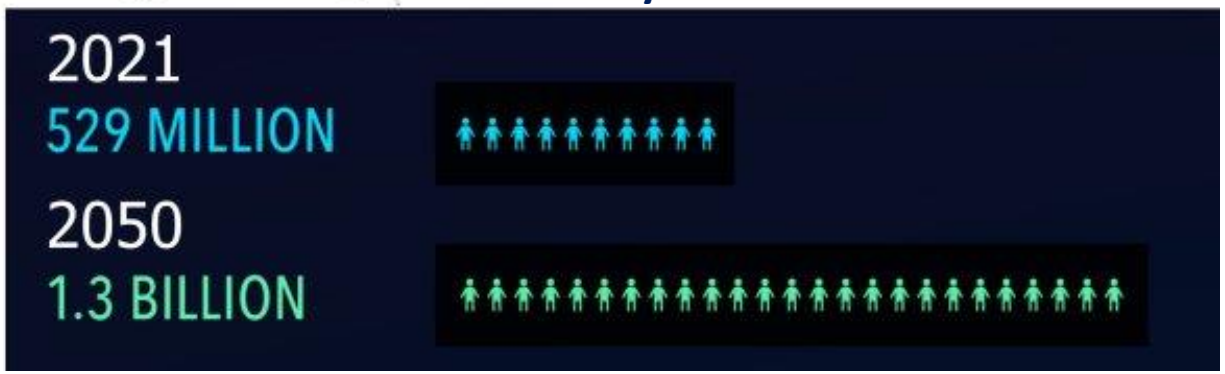
Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021

" More than half a billion people are living with diabetes worldwide, affecting men, women, and children of all ages in every country, and that number is projected to more than double to 1.3 billion people in the next 30 years, with every country seeing an increase."

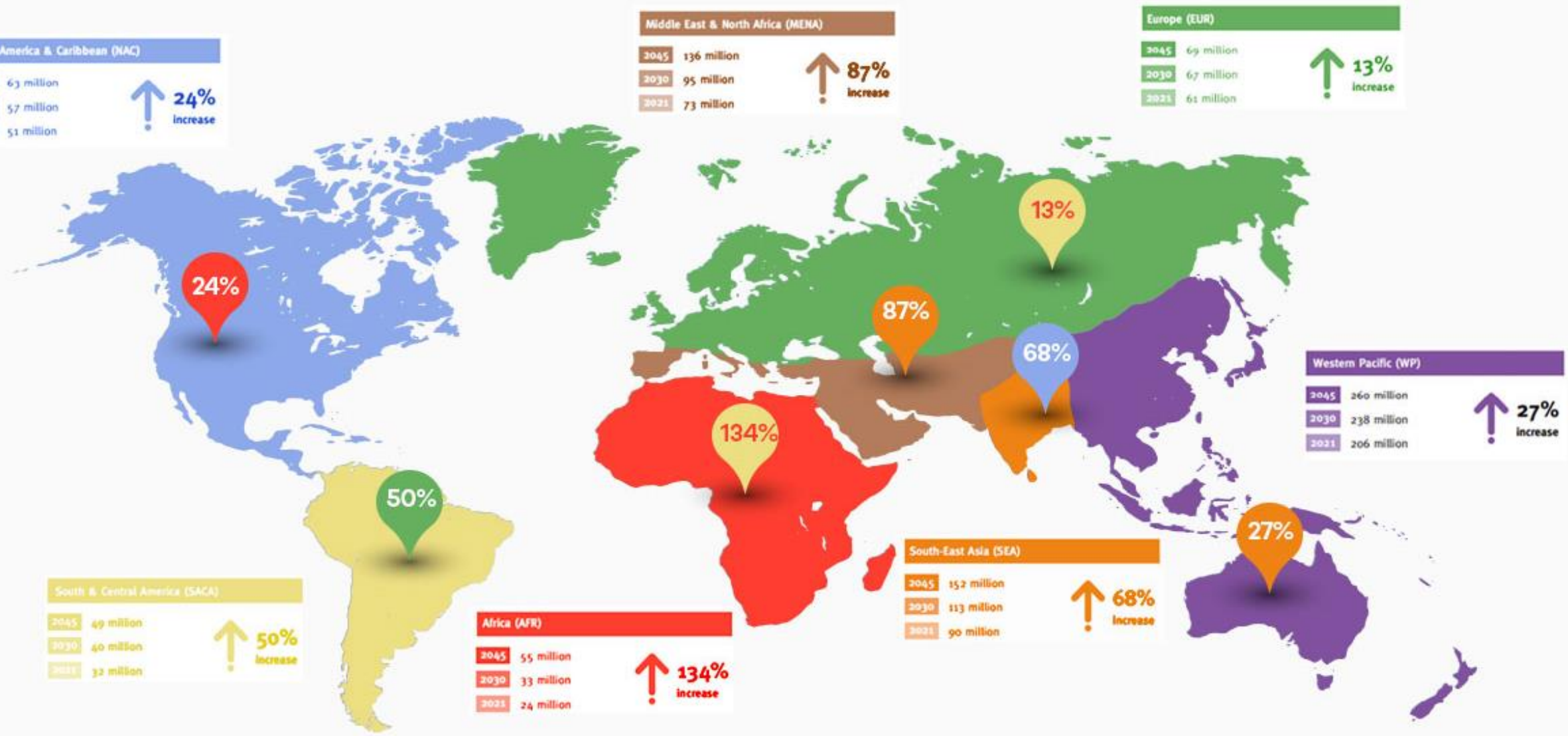


prevalence of 10.5 % among adults 20–79 years-old

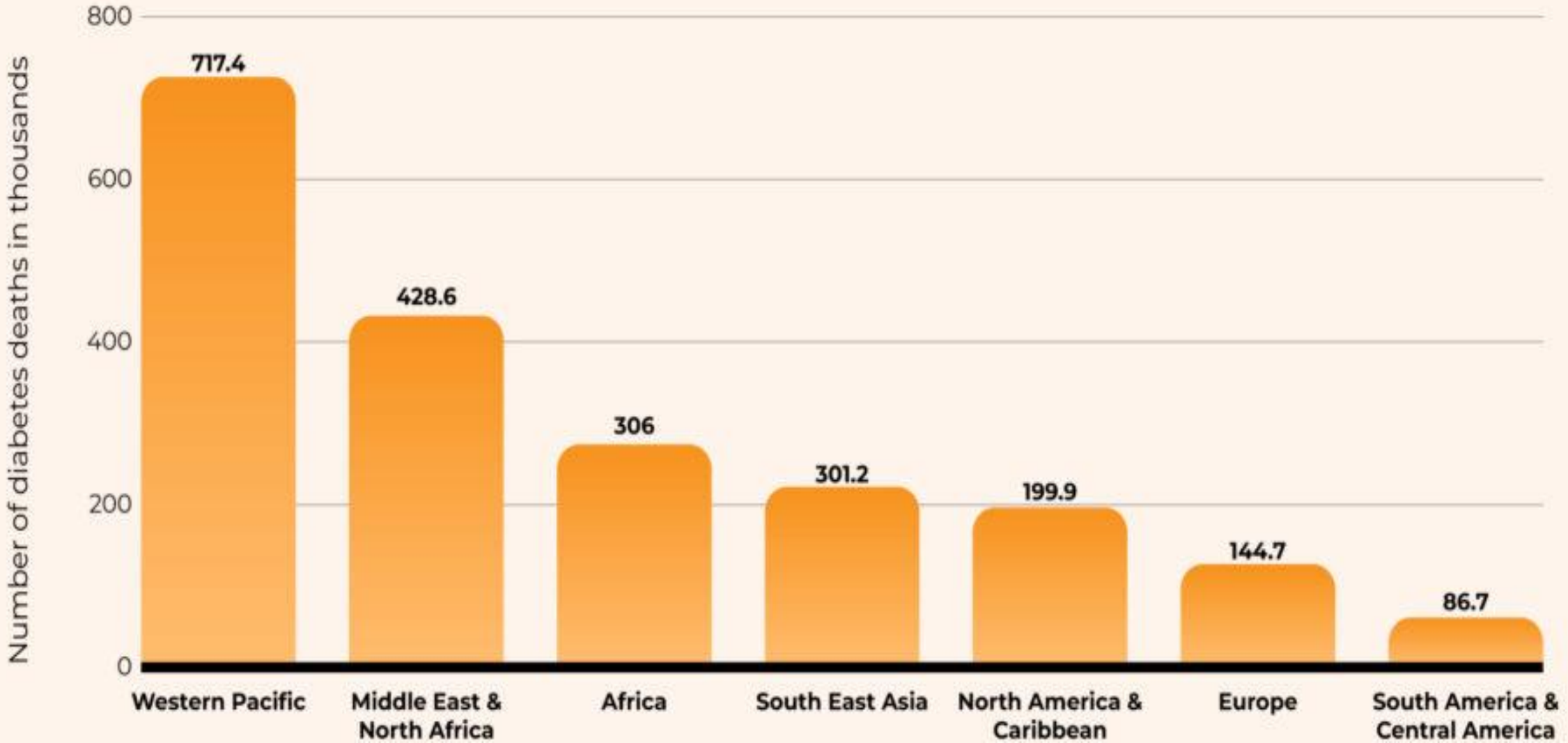




GLOBAL ANTICIPATIONS FOR DIABETES. 2021-45



DIABETES-RELATED DEATHS BEFORE AGE 60 WORLDWIDE IN 2021, BY REGION (IN THOUSANDS)



Epidemiology of chronic kidney disease: an update 2022

kidney INTERNATIONAL supplements

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Extremely common

843,6 Million in 2017

Approximately 1 in 10

Increasing death rate

+41.5% 1990 to 2017

Rank in cause of death

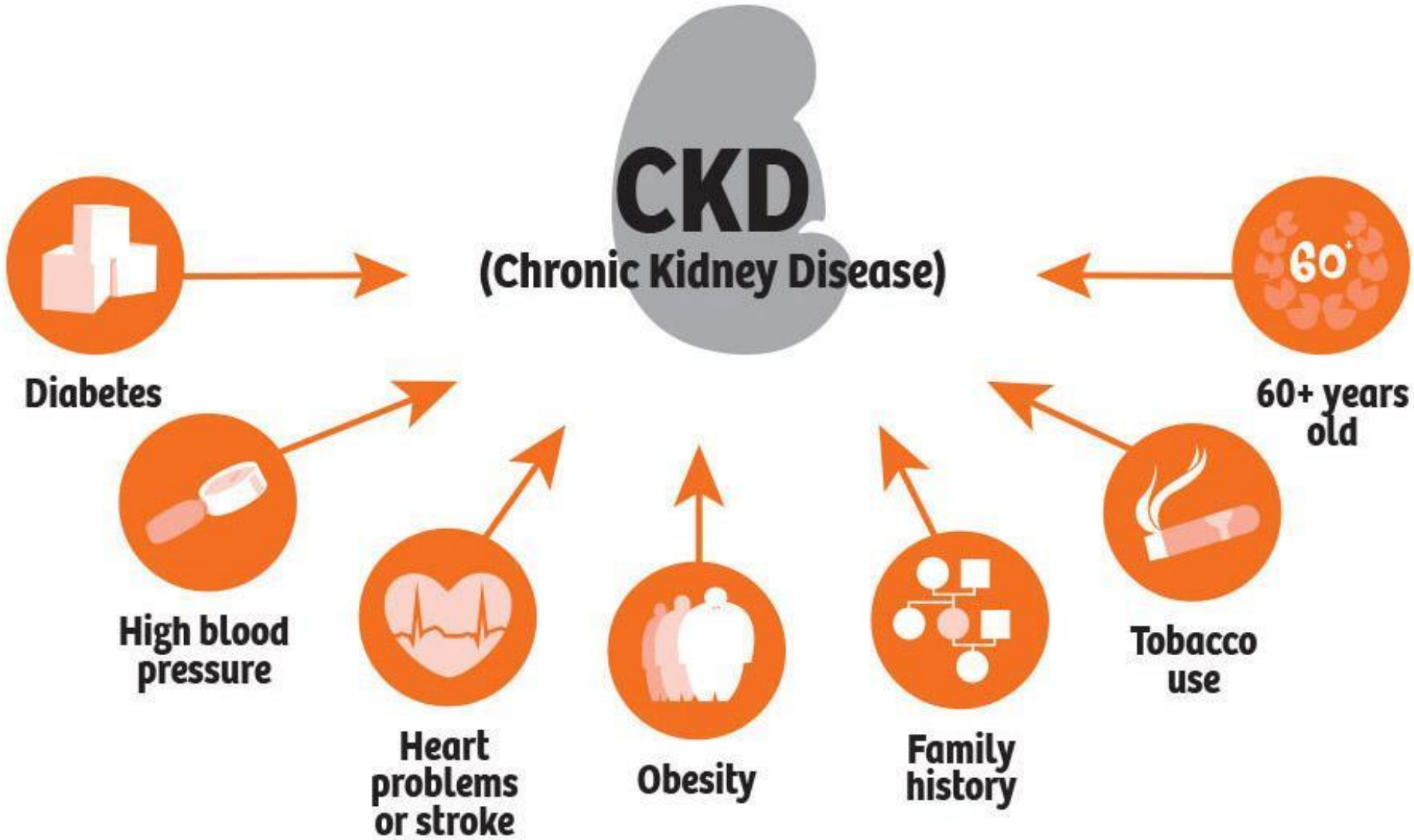
Large burden in low- and middle-income countries

Among the **top 10 causes** of death in Singapore, Greece, and Israel

Kovesdy, 2022

CONCLUSION

Chronic kidney disease (CKD) occurs frequently and has devastating consequences. This should prompt major efforts to develop preventative and therapeutic measures that are effective. The aim of these measures should be lowering the incidence of CKD and slowing its progression.

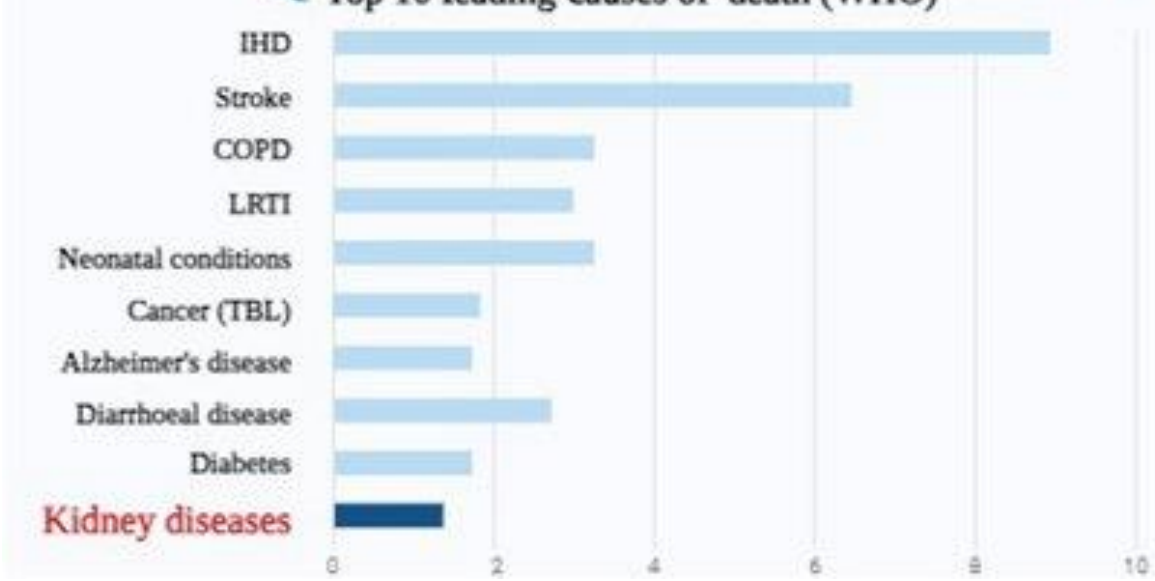

CKD
(Chronic Kidney Disease)
Diabetes
60+
60+ years old
High blood pressure
Heart problems or stroke
Obesity
Family history
Tobacco use

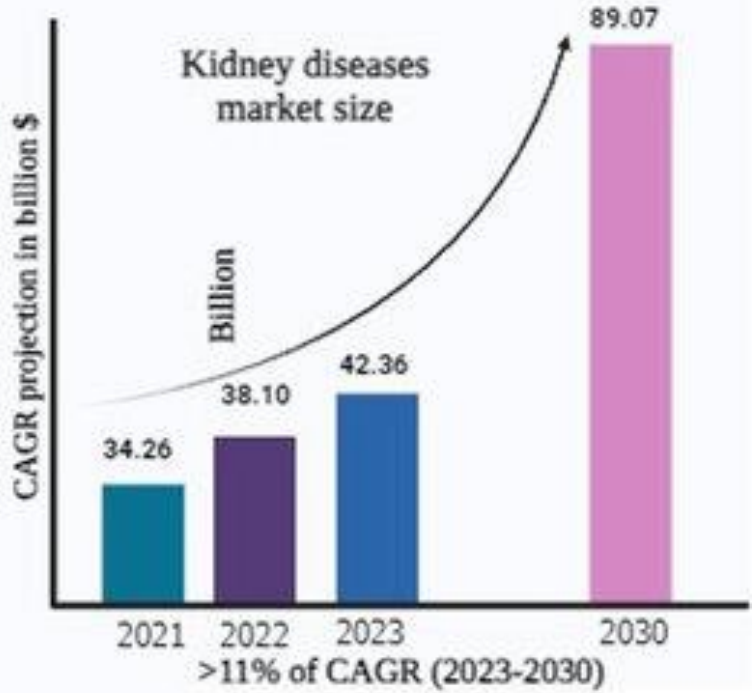
Kidney diseases
are leading cause of death

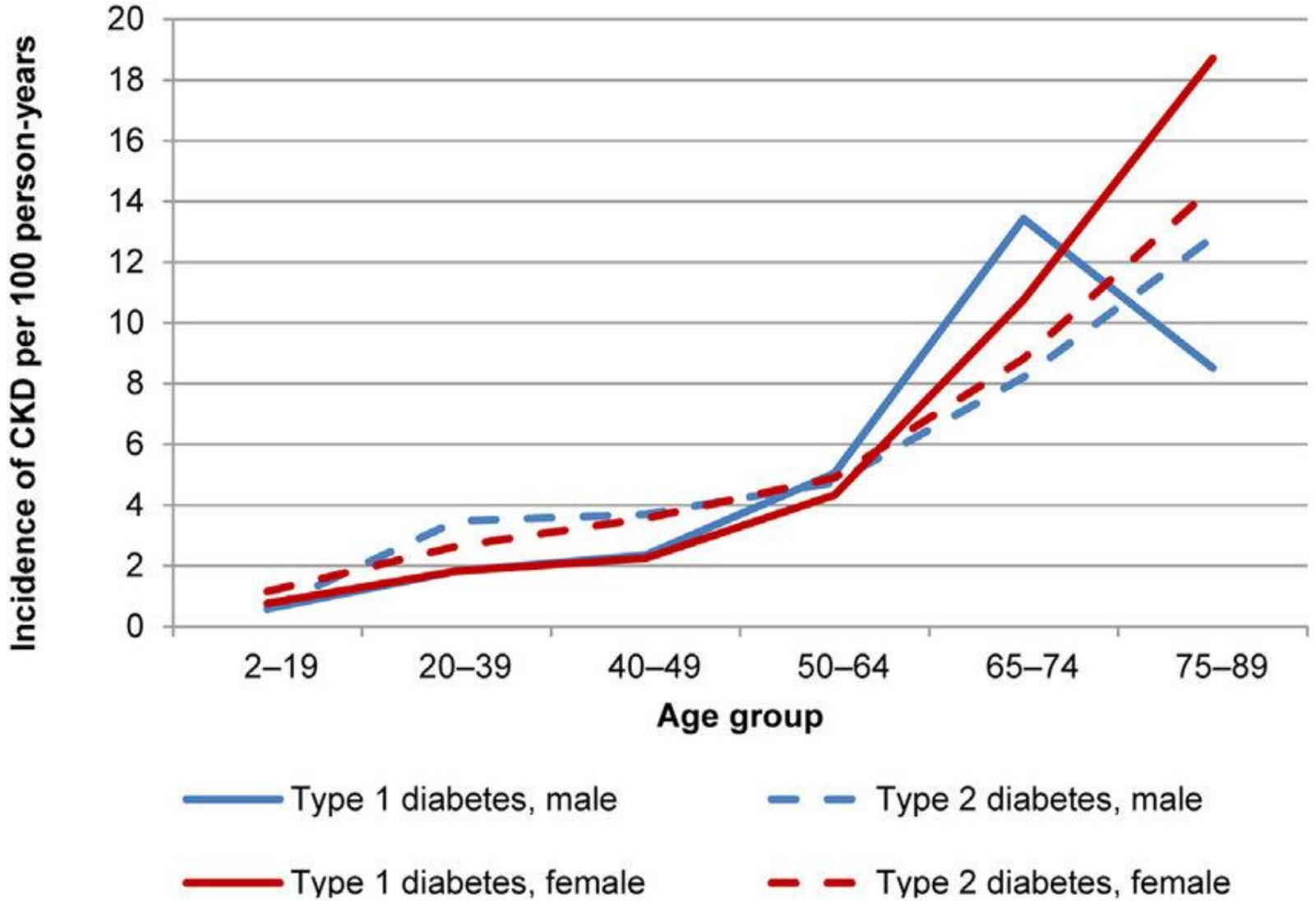
Ranked **10**

> 800
Million cases

DM-CKD **2501.2k** cases in 2019
The global ASIR hypertension-related CKD were **19.45%**
Approx. **7.6%** of all CVD deaths attributed to impaired kidney function



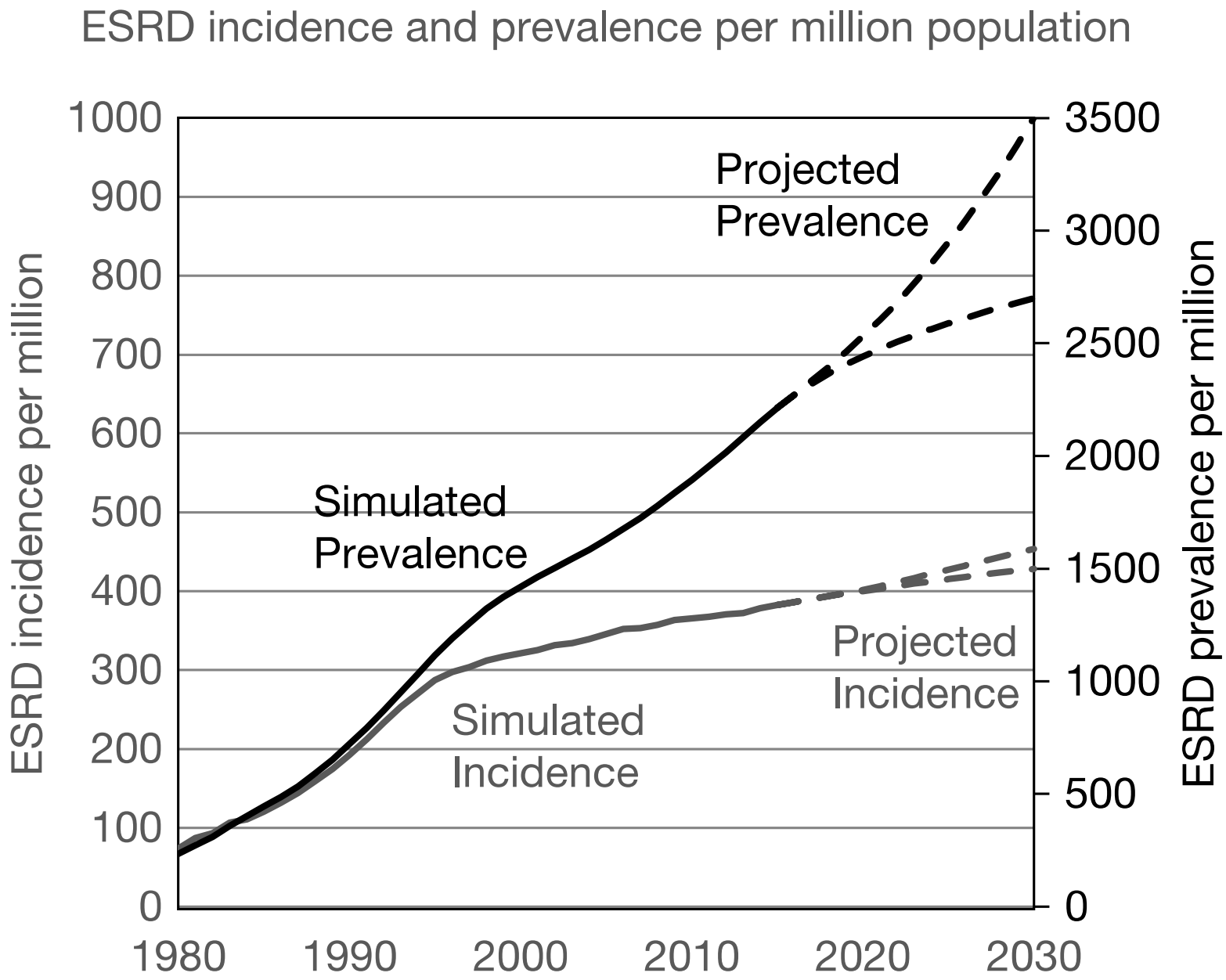



Incidence of CKD per 100 person-years
20
18
16
14
12
10
8
6
4
2
0
2–19
20–39
40–49
50–64
65–74
75–89
Age group
Type 1 diabetes, male
Type 2 diabetes, male
Type 1 diabetes, female
Type 2 diabetes, female

Dangerous Duo

Why it is important to Dx CKD in DM pts ?

In nephrology, our “conventional focus” is on the progression to ESRD


ESRD incidence and prevalence per million population
ESRD incidence per million
ESRD prevalence per million
1000
900
800
700
600
500
400
300
200
100
0
3500
3000
2500
2000
1500
1000
500
0
1980
1990
2000
2010
2020
2030
Projected Prevalence
Simulated Prevalence
Projected Incidence
Simulated Incidence

Kidney related issues in DM

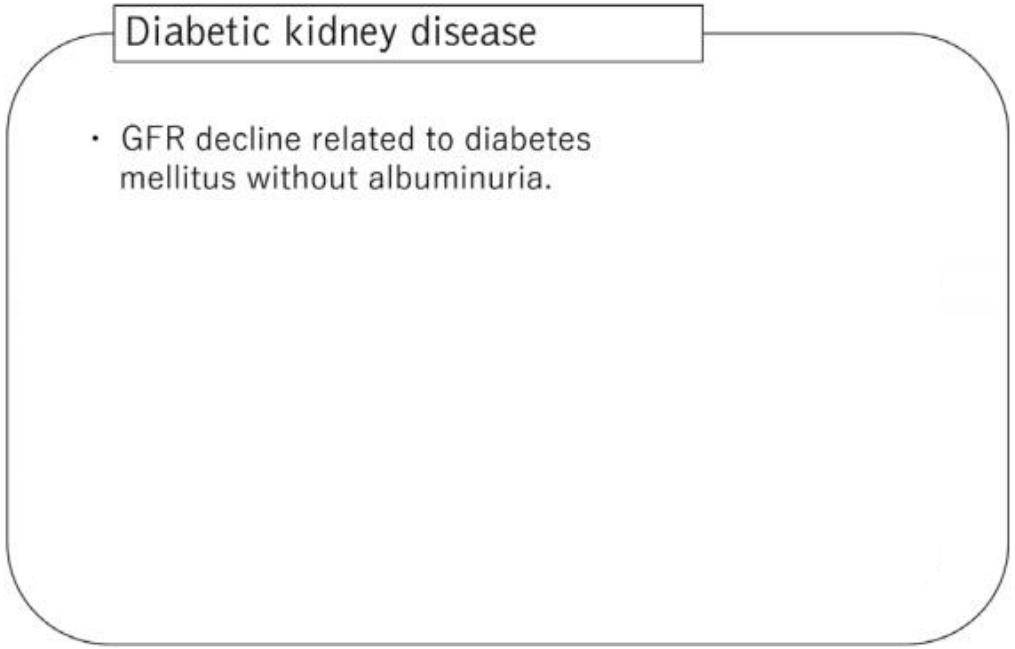
- DKD/DN
- Atherosclerotic Reno-Vascular disease
- UTI
- Papillary necrosis
- Drug associated complications
- Obstructive uro-pathy
- Multiple electrolyte imbalances
- GN
- …

DKD, DN, and CKD with diabetes

- **“Diabetic kidney disease (DKD)”** is a **concept** that widely recognizes the pathophysiological change induced by diabetes as the onset and progressive factor of **renal injury and renal function decline**, **regardless of the level of albuminuria**.

DKD may contain multiple renal pathologies, including **nephrosclerosis** due to **hypertension**, renal changes associated with **atherosclerosis**, **obesity**-related **glomerulopathy** and **gouty nephropathy.**

DKD: the pathophysiological **change induced by diabetes (persistent hyperglycemia)**



DKD, DN, and CKD with diabetes

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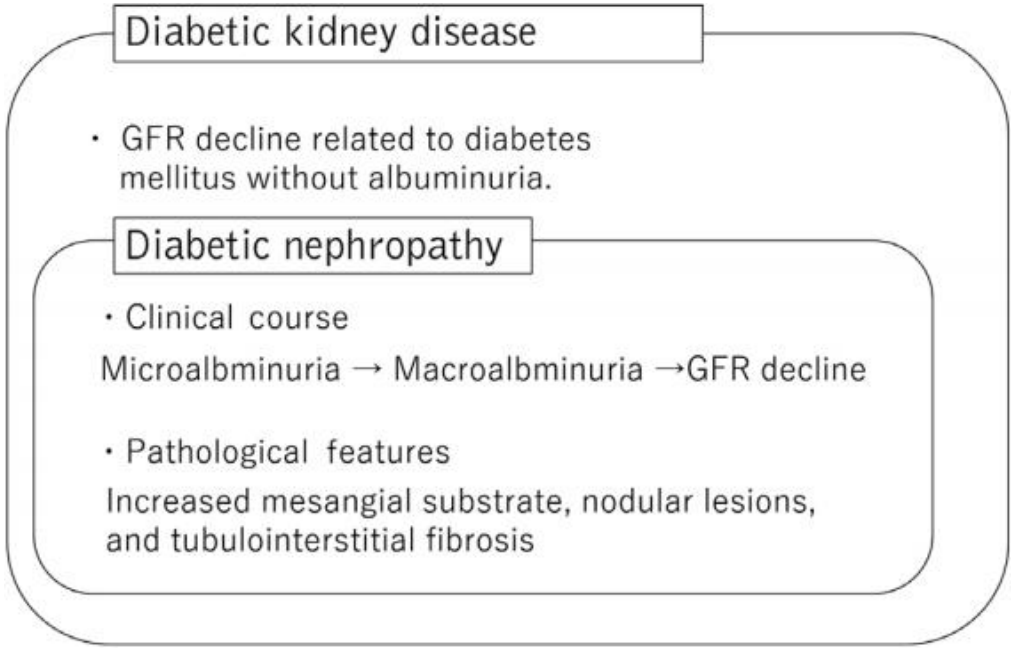
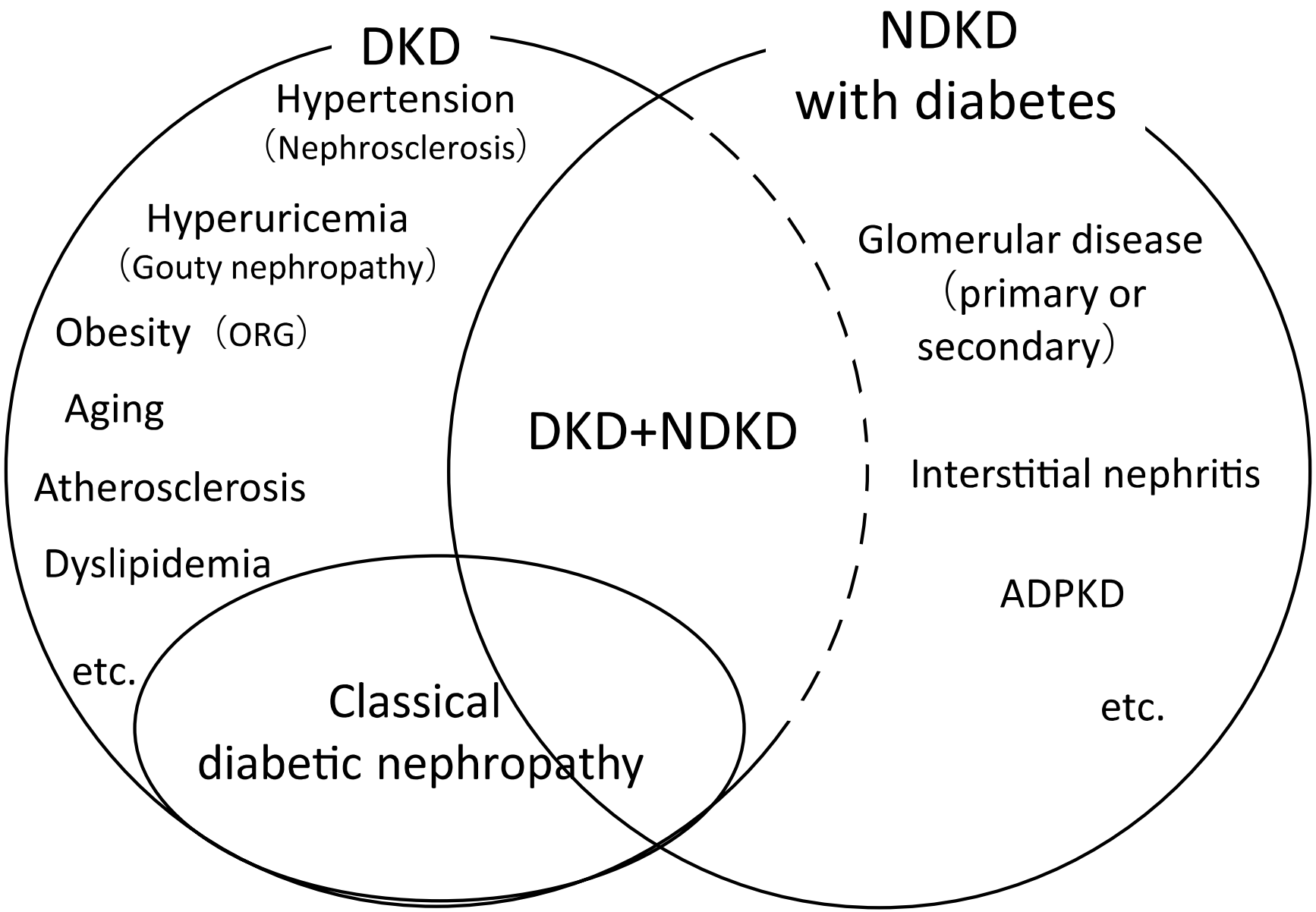


DN relates to a specific pathological phenotype

DKD is not DN!


DKD
Hypertension
（Nephrosclerosis）
Hyperuricemia
（Gouty nephropathy）
Obesity（ORG）
Aging
Atherosclerosis
Dyslipidemia
etc.
NDKD
with diabetes
Glomerular disease
（primary or
secondary）
Interstitial nephritis
ADPKD
etc.
DKD+NDKD
Classical
diabetic nephropathy

Elevated levels of albumin in the urine

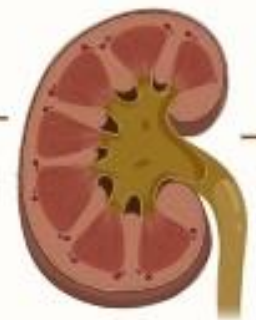
Elevated urinary excretion of albumin, known as microalbuminuria (30-300 mg/g) or macroalbuminuria (> 300 mg/g), is a significant risk factor for renal damage in individuals with diabetes, indicating a higher amount of albumin in urine.

Dyslipidemia

Dyslipidemia, an abnormal distribution of lipids in the blood, is a significant factor in diabetic kidney disease (DKD), leading to increased extracellular matrix formation, macrophage infiltration, and podocyte death. It is positively correlated with DKD prevalence.

Hypertension

Diabetes-related nephropathy, a common condition in children with chronic kidney disease, is linked to hypertension, with effective hypertension management potentially reducing end-stage renal failure by 23%



Hyperglycemia

Hyperglycemia, disrupted by the antioxidant system and advanced glycation end products, is a major contributor to Diabetes Kidney Disease (DKD) due to its negative impact on renal function, with strict glucose control potentially reversing albuminuria in type 2 diabetes.

Risk factors of DKD

Obesity

Obesity is a significant risk factor for diabetic kidney disease (DKD), with studies suggesting weight reduction could slow its progression in obese individuals, despite the exact cause remaining uncertain.

Smoking

Smoking increases diabetic nephropathy risk in diabetes patients, influenced by factors like oxidative stress, elevated blood lipids, and renal filtering unit scarring, with smoking quantity directly correlated with kidney damage.

Adults with Diabetes, Hypertension, older than 60, or a family history of kidney disease

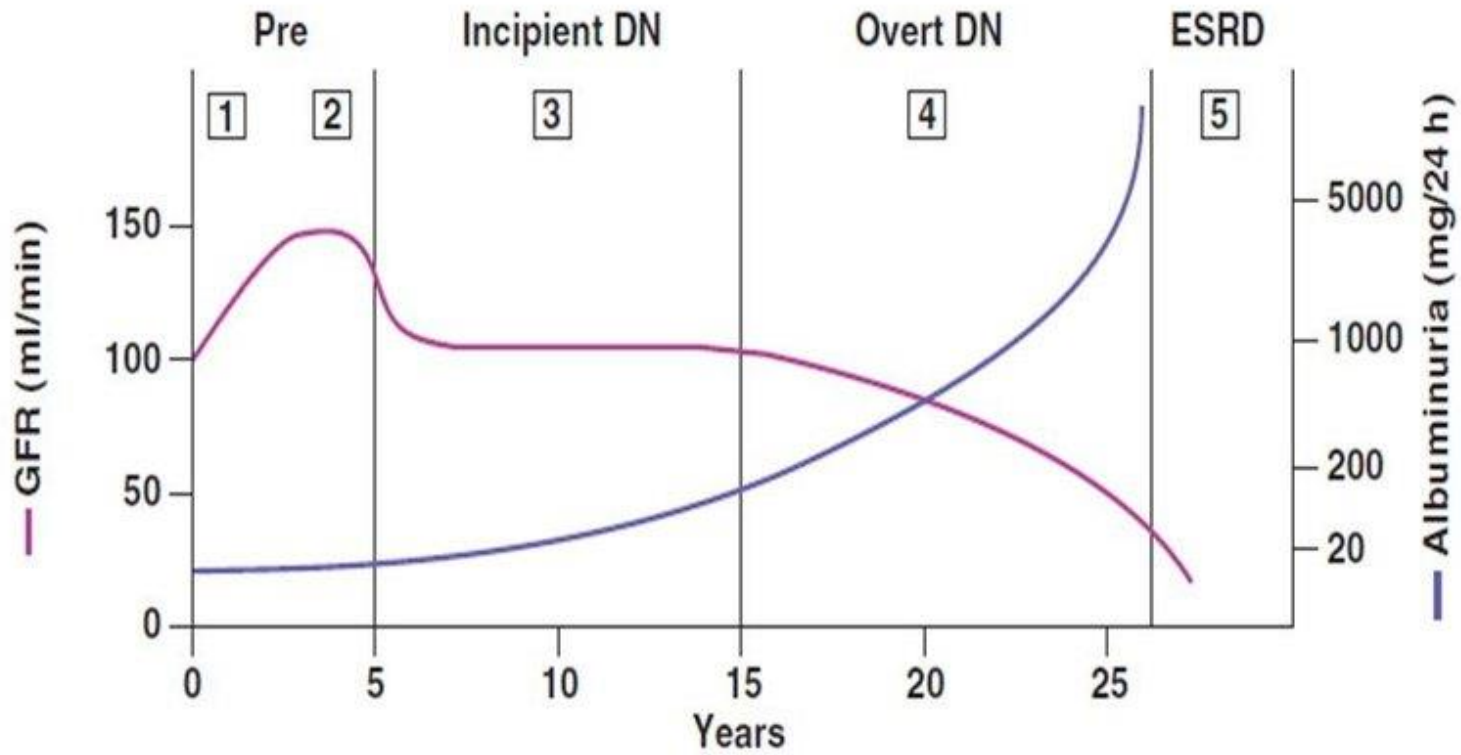
→ Request Kidney Profile (eGFR & ACR)

UACR urine test	eGFR blood test
 Checks for protein in the urine, which is one of the earliest indicators of CKD or **kidney damage**	 Measures the amount of **kidney function** remaining

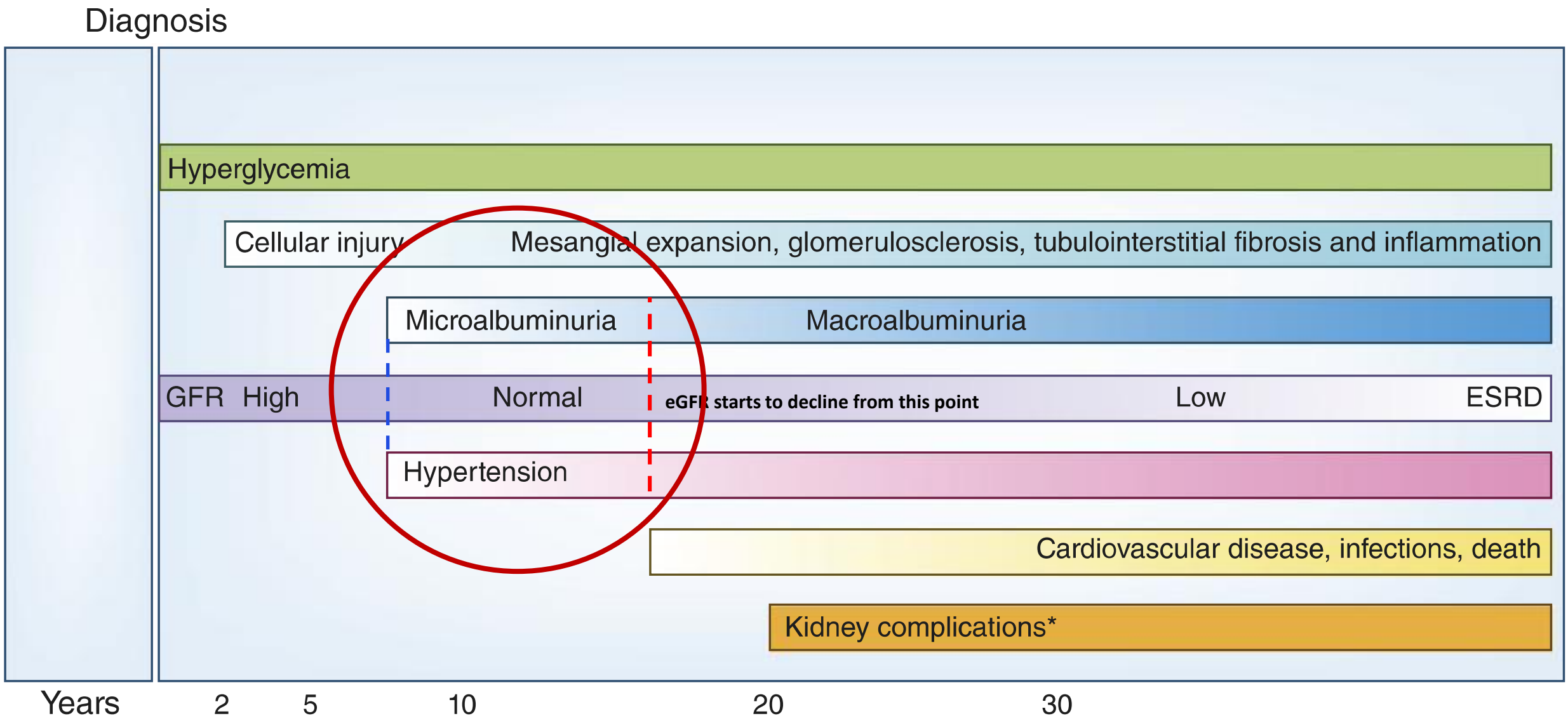
GFR categories (mL/min/1.73m²) Description and range				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severly increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	1	1	2
	G2	Mildly decreased	60-89	1	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	2	3	3
	G4	Severely decreased	15-29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

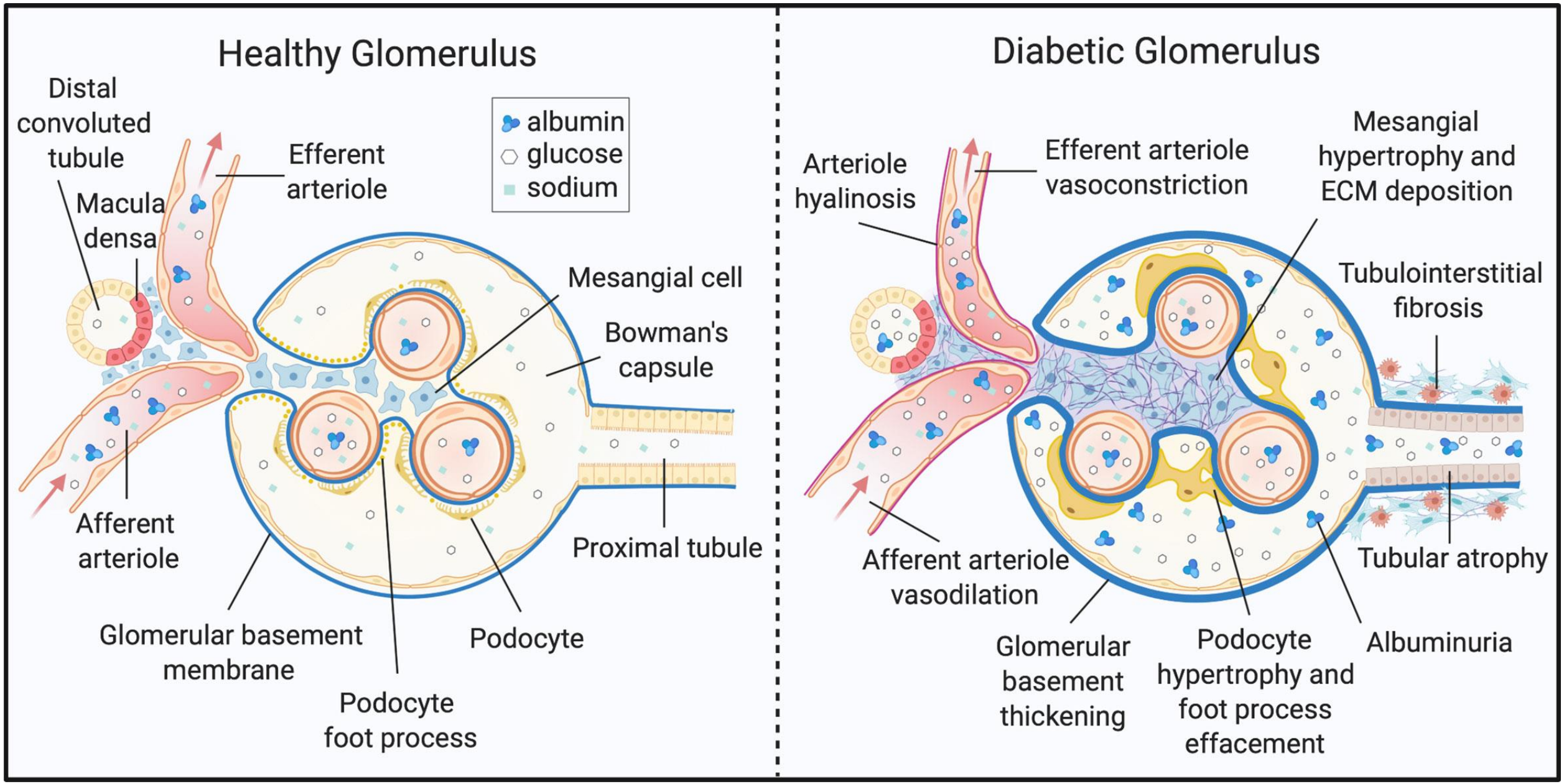

ACR
eGFR

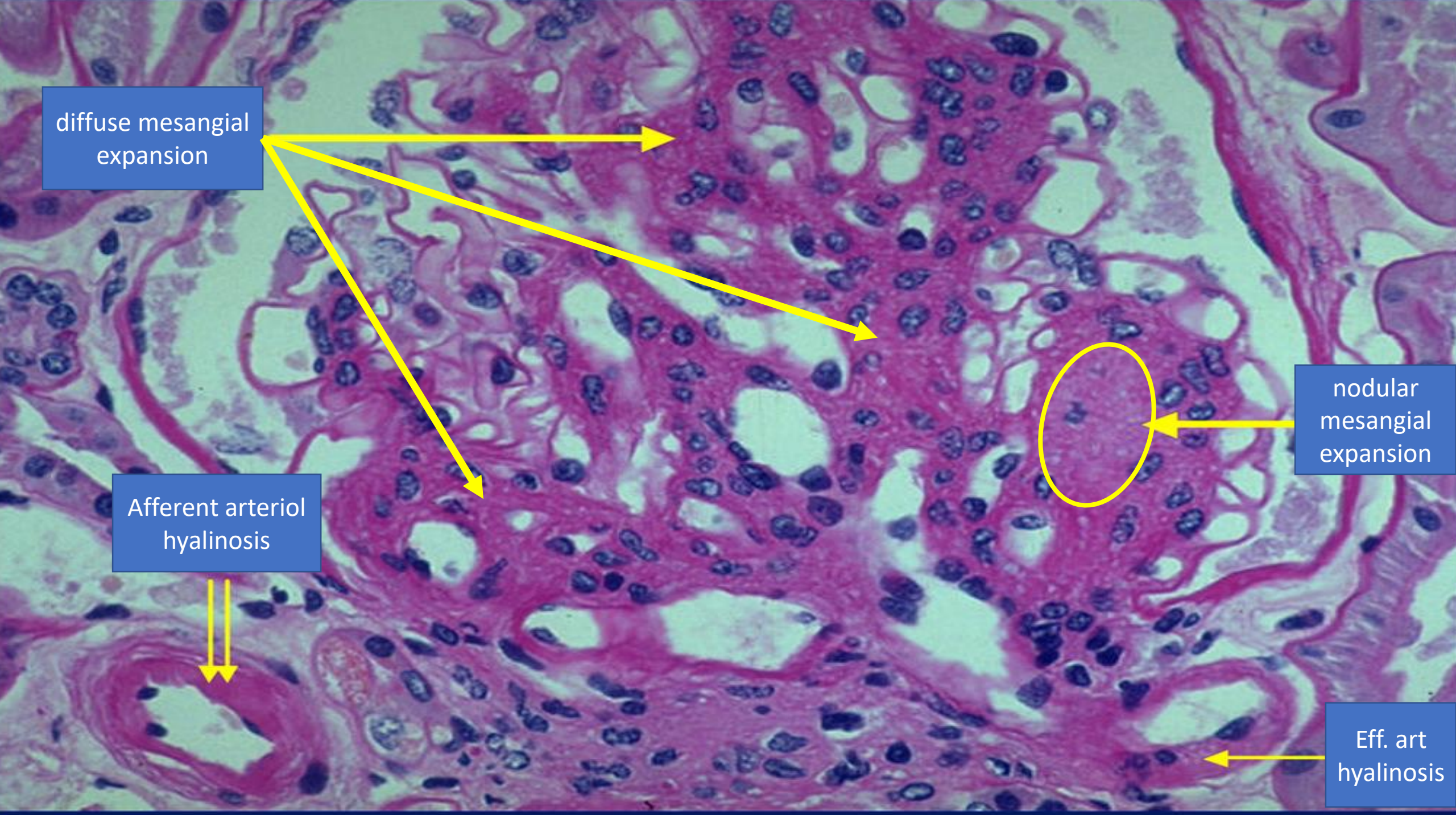
Natural History of Type 1 Diabetic Nephropathy

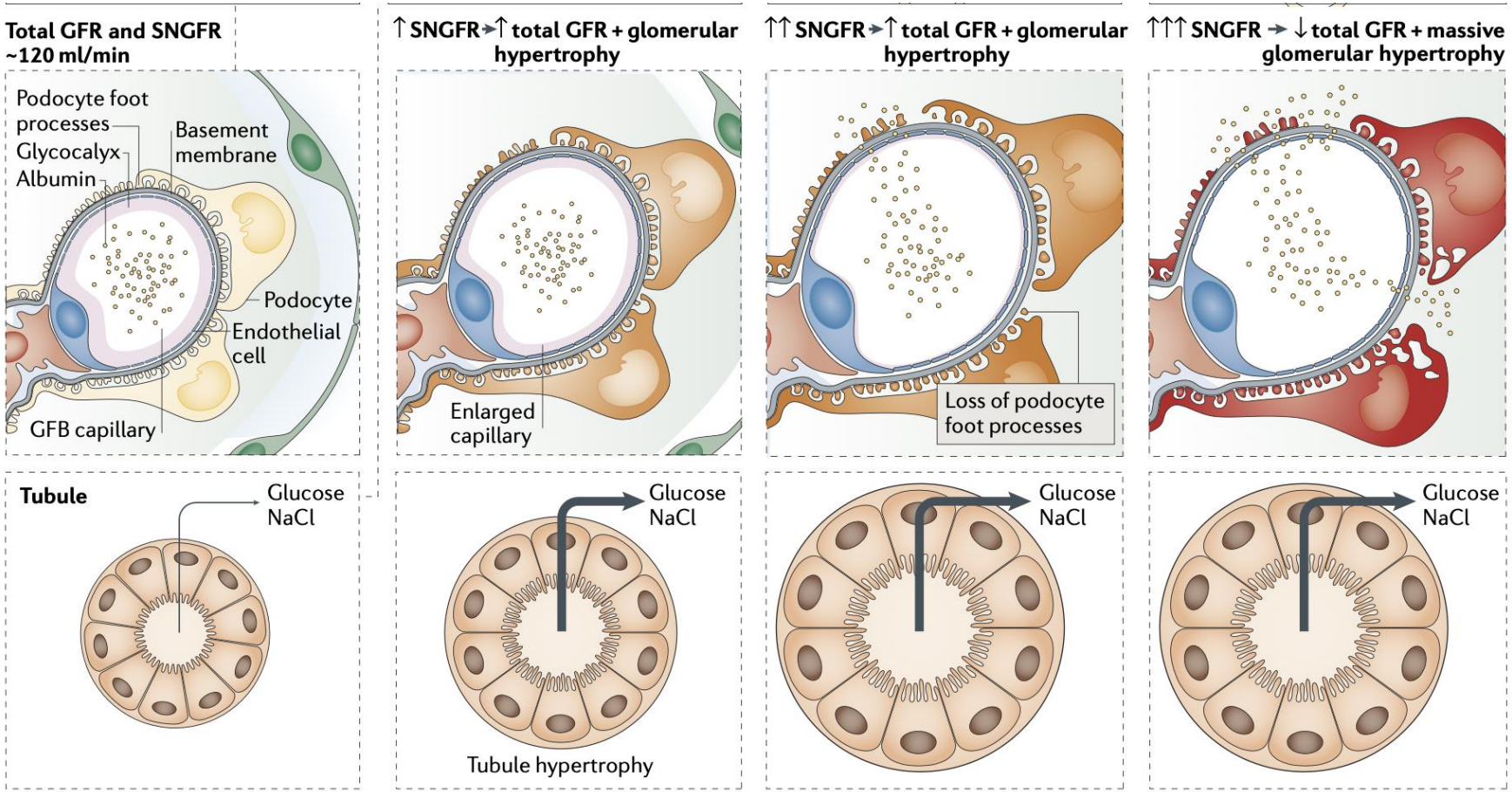


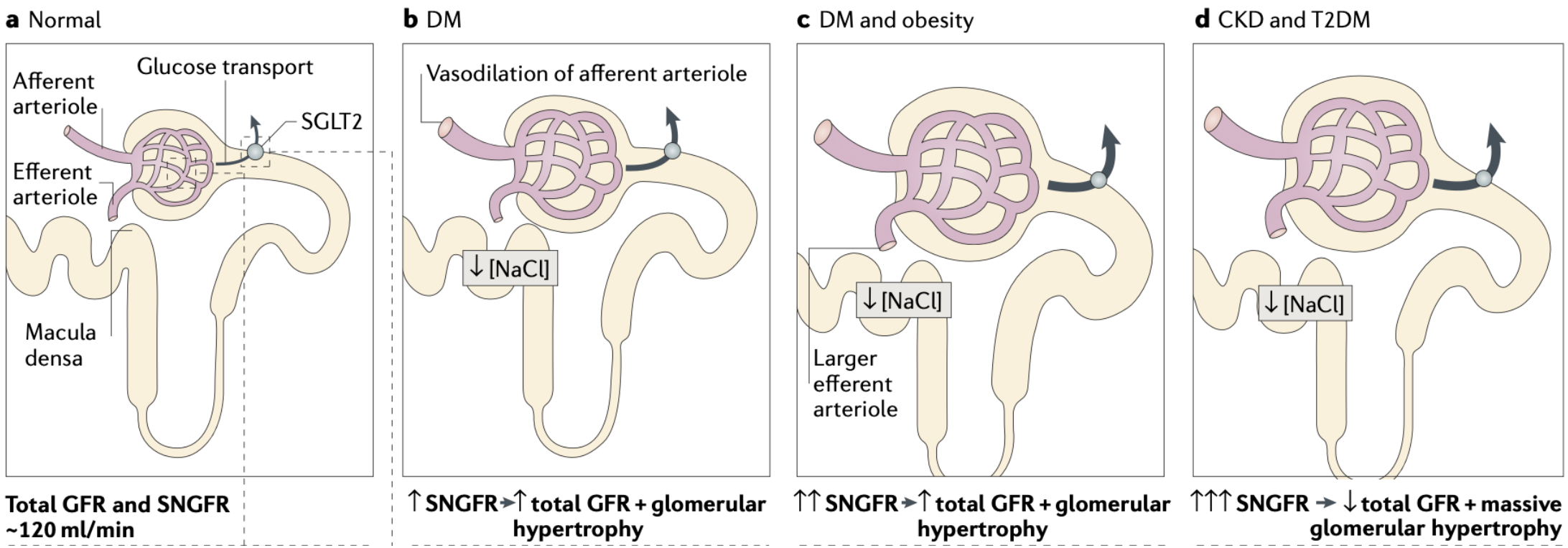
Stage	Pre	Incipient	Overt
Functional	GFR ↑ (25%–50%)	Microalbuminuria, hypertension	Proteinuria, nephrotic syndrome, GFR ↓
Structural	Renal hypertrophy	Mesangial expansion, GBM thickening, arteriolar hyalinosis	Mesangial nodules (Kimmelstiel-Wilson lesions) Tubulointerstitial fibrosis

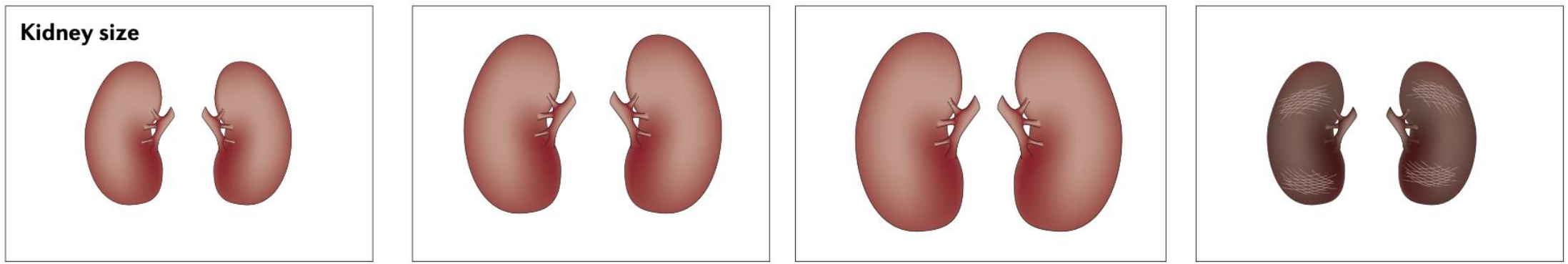

Diagnosis
Hyperglycemia
Cellular injury
Mesangial expansion, glomerulosclerosis, tubulointerstitial fibrosis and inflammation
Microalbuminuria
Macroalbuminuria
GFR High
Normal
eGFR starts to decline from this point
Low
ESRD
Hypertension
Cardiovascular disease, infections, death
Kidney complications*
Years
2
5
10
20
30


Healthy Glomerulus
Distal convoluted tubule
Macula densa
Efferent arteriole
albumin
glucose
sodium
Mesangial cell
Bowman's capsule
Afferent arteriole
Proximal tubule
Glomerular basement membrane
Podocyte
Podocyte foot process
Diabetic Glomerulus
Arteriole hyalinosis
Efferent arteriole vasoconstriction
Mesangial hypertrophy and ECM deposition
Tubulointerstitial fibrosis
Afferent arteriole vasodilation
Tubular atrophy
Glomerular basement thickening
Podocyte hypertrophy and foot process effacement
Albuminuria

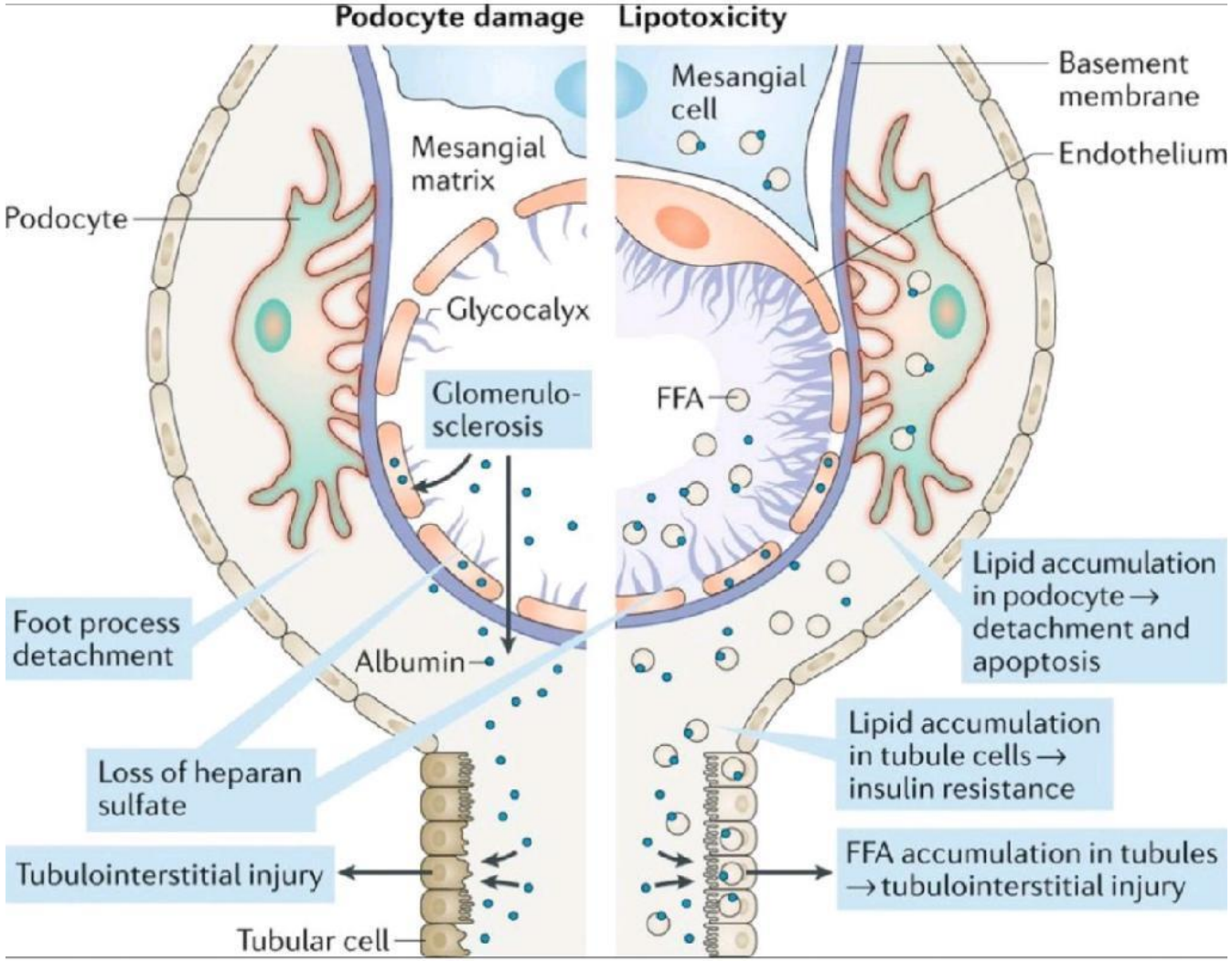

diffuse mesangial expansion
nodular mesangial expansion
Afferent arteriol hyalinosis
Eff. art hyalinosis


Total GFR and SNGFR
~120 ml/min
Podocyte foot processes
Glycocalyx
Albumin
Basement membrane
Podocyte
Endothelial cell
GFB capillary
↑ SNGFR → ↑ total GFR + glomerular hypertrophy
Enlarged capillary
↑↑ SNGFR → ↑ total GFR + glomerular hypertrophy
Loss of podocyte foot processes
↑↑↑ SNGFR → ↓ total GFR + massive glomerular hypertrophy
Tubule
Glucose
NaCl
Glucose
NaCl
Tubule hypertrophy
Glucose
NaCl
Glucose
NaCl

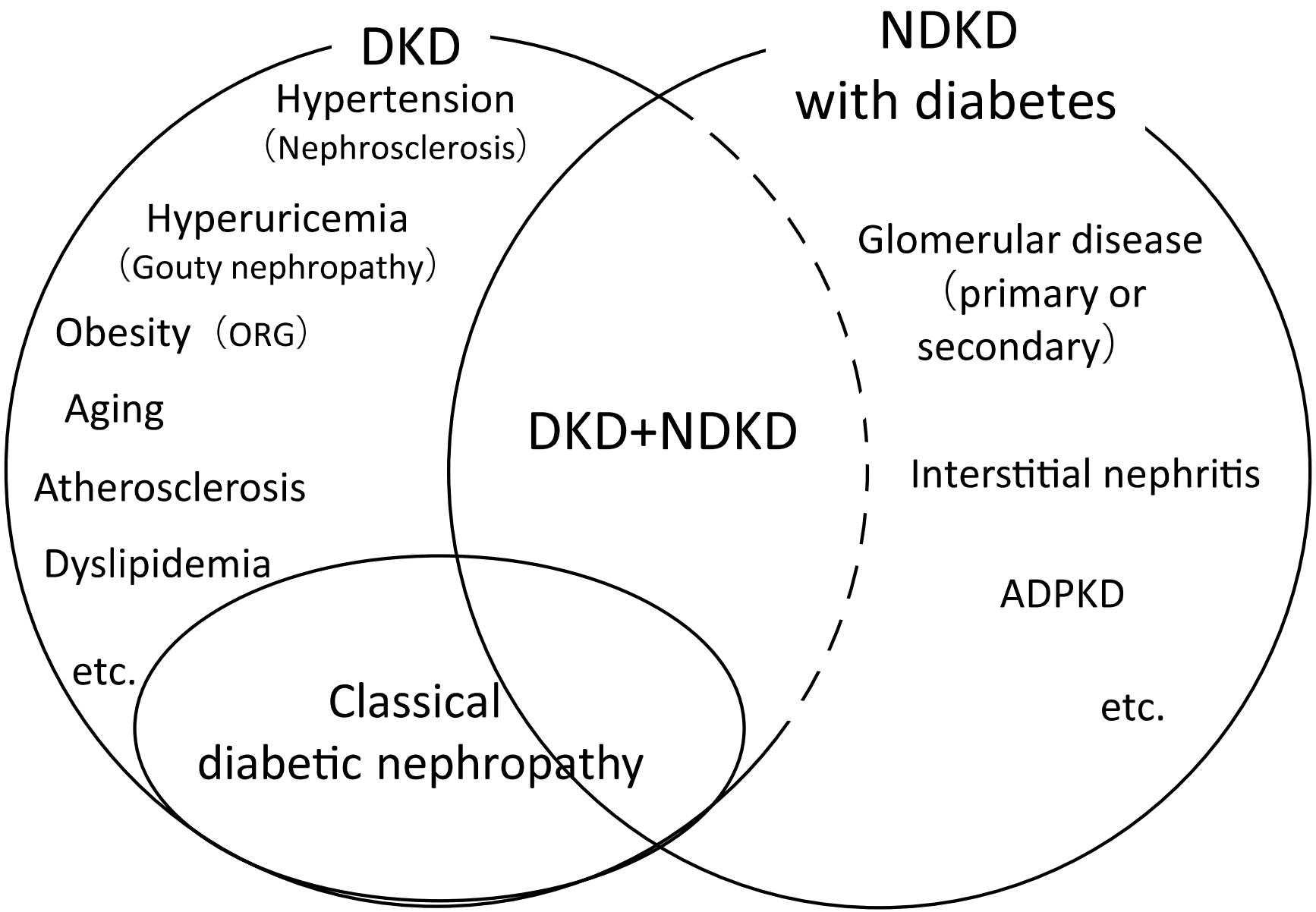

a Normal
Afferent arteriole
Glucose transport
SGLT2
Efferent arteriole
Macula densa
Total GFR and SNGFR ~120 ml/min
b DM
Vasodilation of afferent arteriole
↓ [NaCl]
↑ SNGFR → ↑ total GFR + glomerular hypertrophy
c DM and obesity
↓ [NaCl]
Larger efferent arteriole
↑↑ SNGFR → ↑ total GFR + glomerular hypertrophy
d CKD and T2DM
↓ [NaCl]
↑↑↑ SNGFR → ↓ total GFR + massive glomerular hypertrophy


Kidney size

Podocyte injury in Diabetic Kidney disease (Nature Reviews Nephrology)



Not all cases of CKD in patients with DM are DKD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Hypertension
（Nephrosclerosis）
Hyperuricemia
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Aging
Atherosclerosis
Dyslipidemia
etc.
NDKD
with diabetes
Glomerular disease
（primary or
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Interstitial nephritis
ADPKD
etc.
DKD+NDKD
Classical
diabetic nephropathy

NDRD in DM

Glomerular diseases other than DN

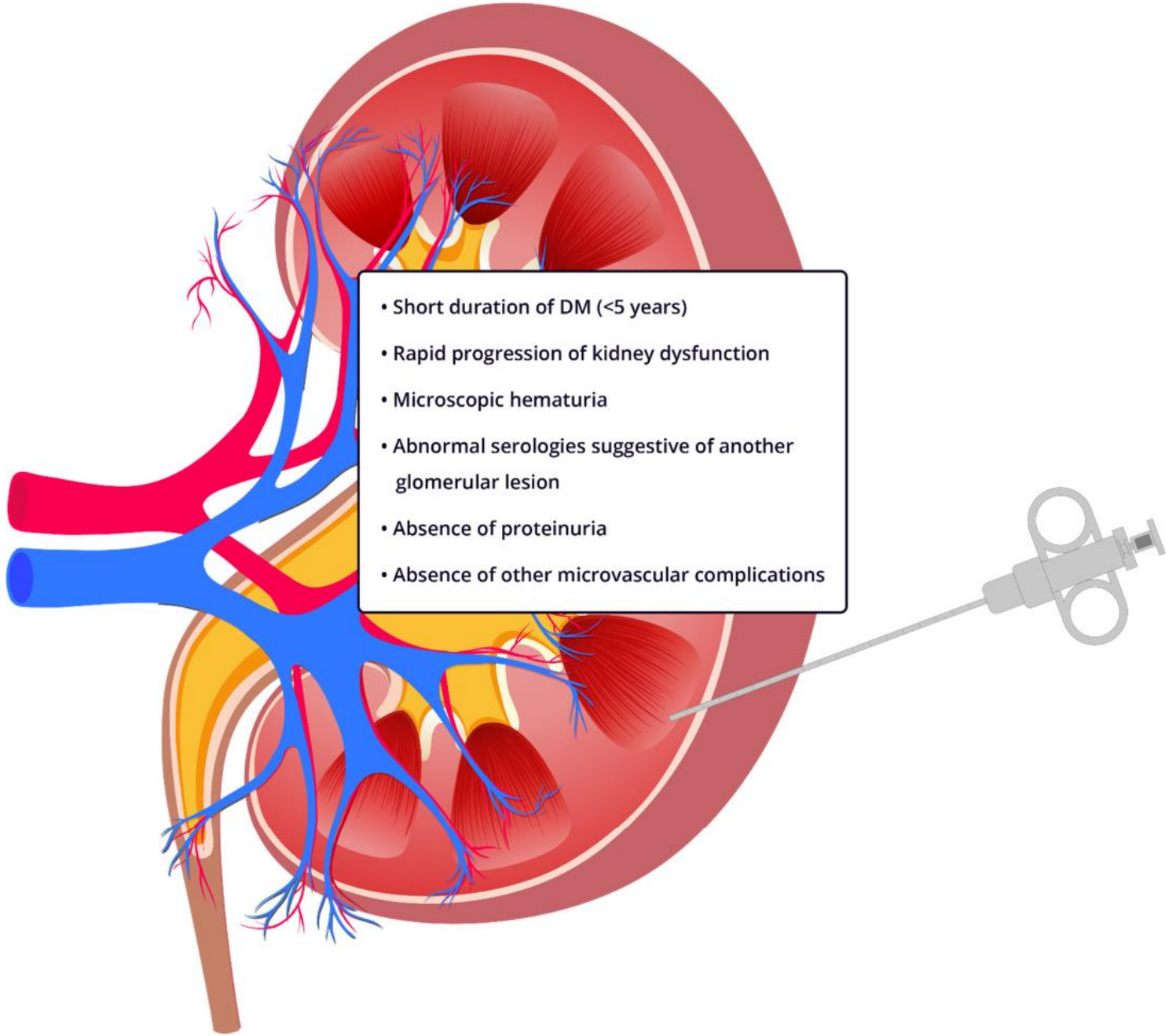
- IgA N
- FSGS
- MGN
- MPGN
- Post-infectious GN
- Pauci- immune GN
- SLE
- …

Non-glomerular renal disease

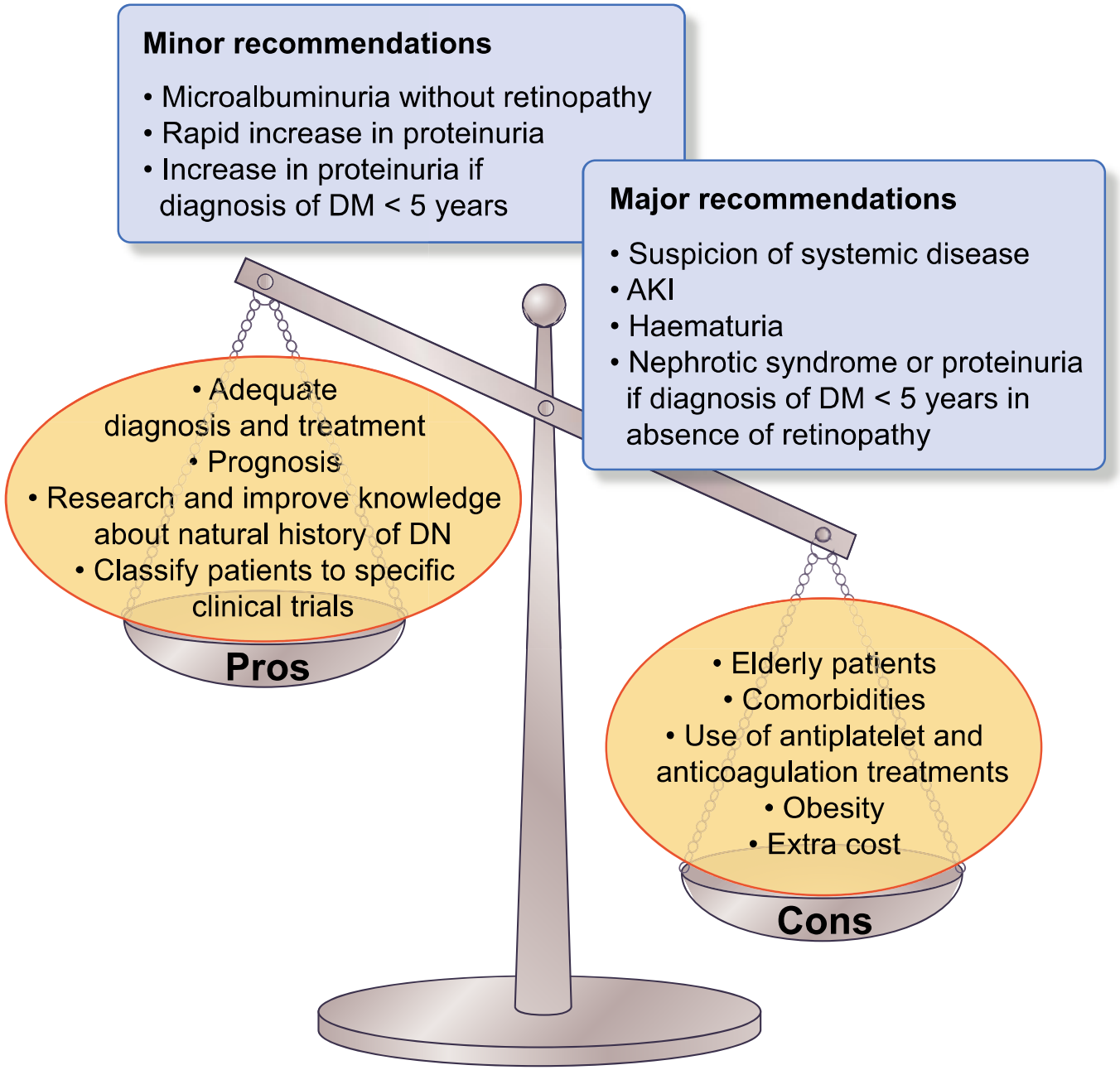
- Macrovascular (RV)
- AKI/ C-AKI, ACEi induced AKI
- CKD (Ischemic nephropathy, chronic Pyleo,…)
- Electrolyte abn (Hypo-Na, Hyper-K [RTA-4]
- UTI (cystitis, acute pyelo, chronic pyleo, PN, Bladder dysfunction)
- Obstructive uropathy (neuro bladder, PN,…)

DM-independent factors
cause CKD, even in patients with DM

- 1- Genetic kidney disorders,
- 2- Immunoglobulin A (IgA) nephropathy,
- 3- Infection-related glomerulopathies,
- 4- Secondary focal segmental glomerulosclerosis and minimal change disease,
- 5- Cholesterol embolism, and
- 6- All types of AKI
    - >>> can **cause precedent, concomitant, or subsequent kidney injury in patients with DM**


• Short duration of DM (<5 years)
• Rapid progression of kidney dysfunction
• Microscopic hematuria
• Abnormal serologies suggestive of another glomerular lesion
• Absence of proteinuria
• Absence of other microvascular complications

Renal biopsy is the only way to determine whether CKD in a patient with DM is in fact a direct ***consequence of the diabetic environment***


Minor recommendations
• Microalbuminuria without retinopathy
• Rapid increase in proteinuria
• Increase in proteinuria if diagnosis of DM < 5 years
Major recommendations
• Suspicion of systemic disease
• AKI
• Haematuria
• Nephrotic syndrome or proteinuria if diagnosis of DM < 5 years in absence of retinopathy
• Adequate diagnosis and treatment
• Prognosis
• Research and improve knowledge about natural history of DN
• Classify patients to specific clinical trials
Pros
• Elderly patients
• Comorbidities
• Use of antiplatelet and anticoagulation treatments
• Obesity
• Extra cost
Cons

Clinical and laboratory parameters associated with the spectrum of kidney histopathologic features in patients with diabetes

Kidney360

Retrospective analysis

UNIVERSITY of WASHINGTON

2014 – 2016

Diabetes

Kidney biopsy

n = 399
Kidney biopsies

48%
n = 192
Diabetic nephropathy
Primary diagnosis
(26 had an additional diagnosis)

52%
n = 207
Non-diabetic kidney disease
Primary diagnosis
(67 also had diabetic nephropathy)

Associations with diabetic nephropathy

Retinopathy
OR 27.1
(95% CI 6.8,107.7)
Sensitivity 0.86
Specificity 0.81

Higher levels of proteinuria
7.6 g/d v. 4.1 g/d
p-value = 0.004

Lower risk of diabetic nephropathy

Physician description of AKI
OR 0.13
(95% CI 0.04, 0.38)

4 most prevalent diagnoses in participants with NDKD

n = 39
FSGS

n = 29
Nephrosclerosis

n = 27
IgA Nephropathy

n = 21
Acute Tubular Injury

Conclusions Among patients with diabetes who undergo kidney biopsy in the Pacific Northwest, approximately half have DN and half have NDKD. Retinopathy and more severe proteinuria were associated with DN, and AKI was a more common descriptor in NDKD.

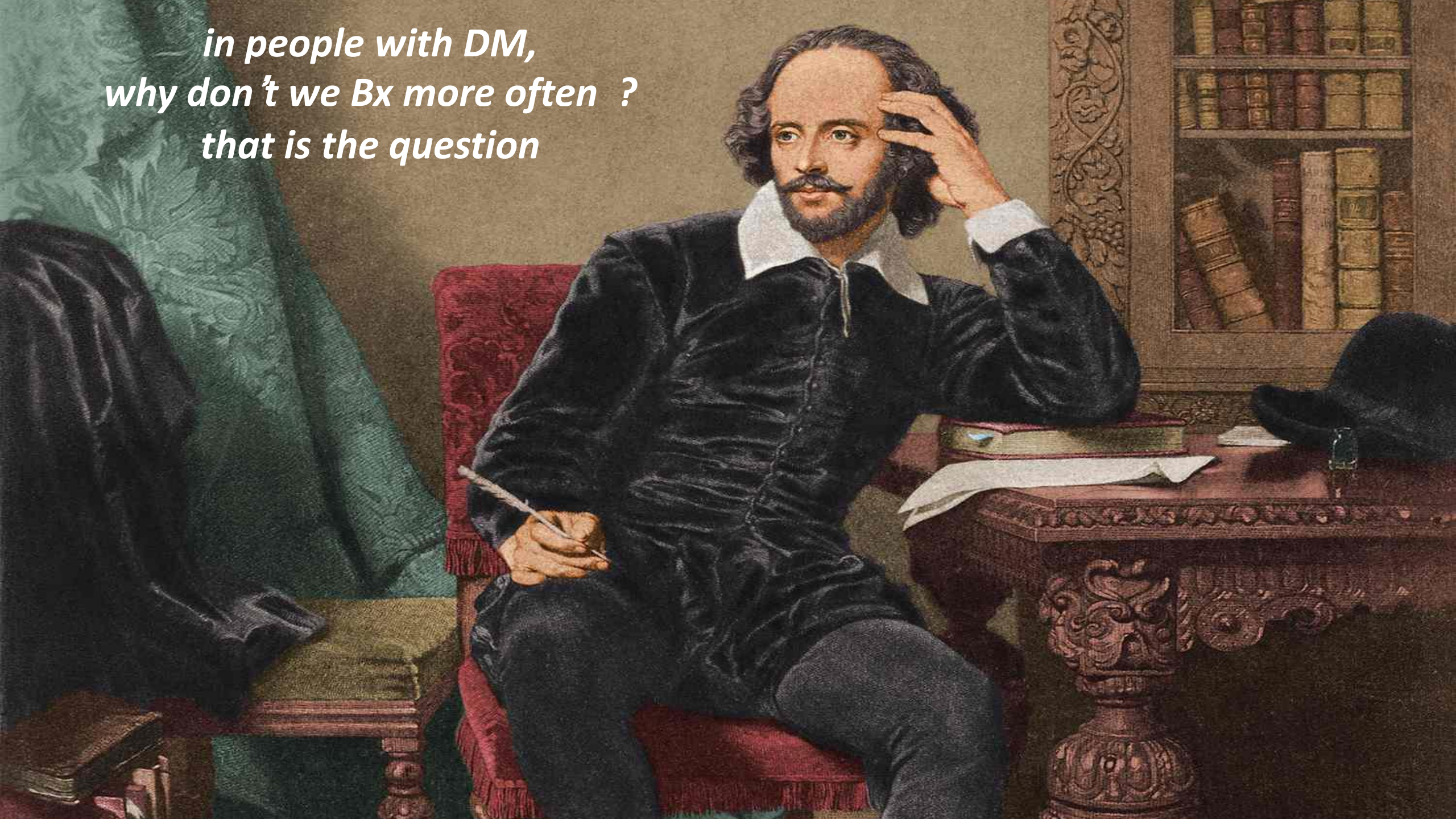
Sarah F. Sanghavi, Travis Roark, Leila R. Zelnick, et al. ***Histopathologic and Clinical Features in Patients with Diabetes and Kidney Disease.*** *Kidney360*. doi: 10.34067/KID
Visual Abstract by Edgar Le

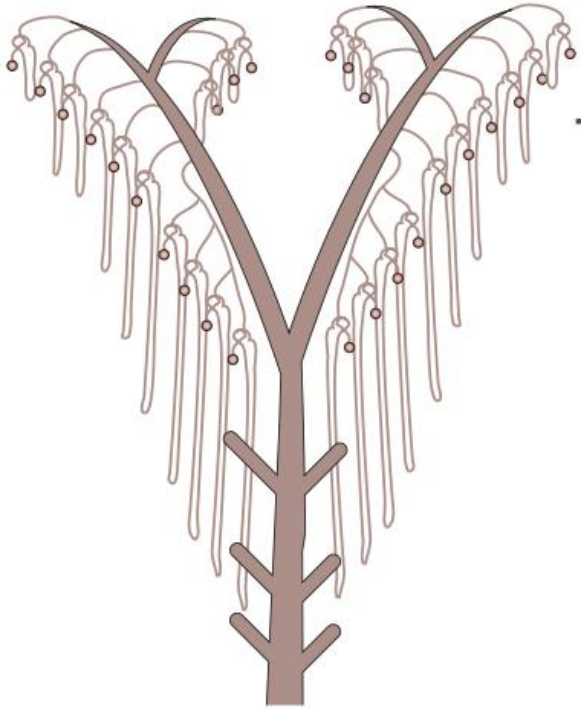
treatable Dx in 20% overall
(40% non-DKD)

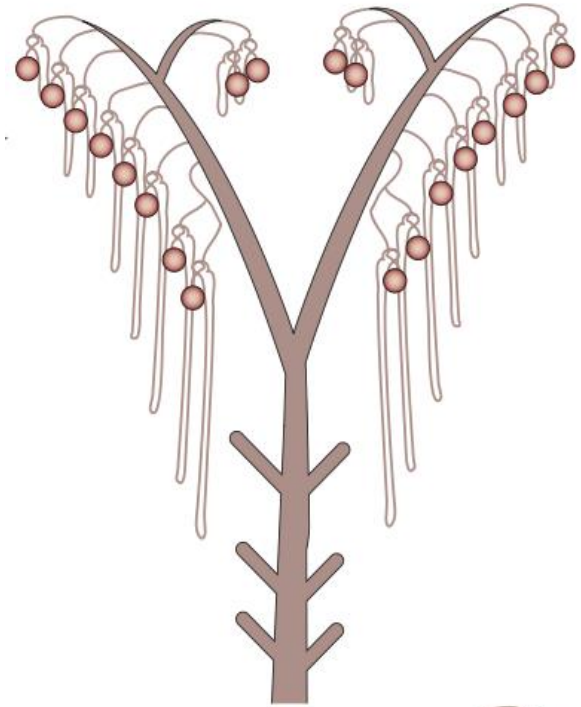
DM pts more prone to MGN, or IgA N, or FSGS ?

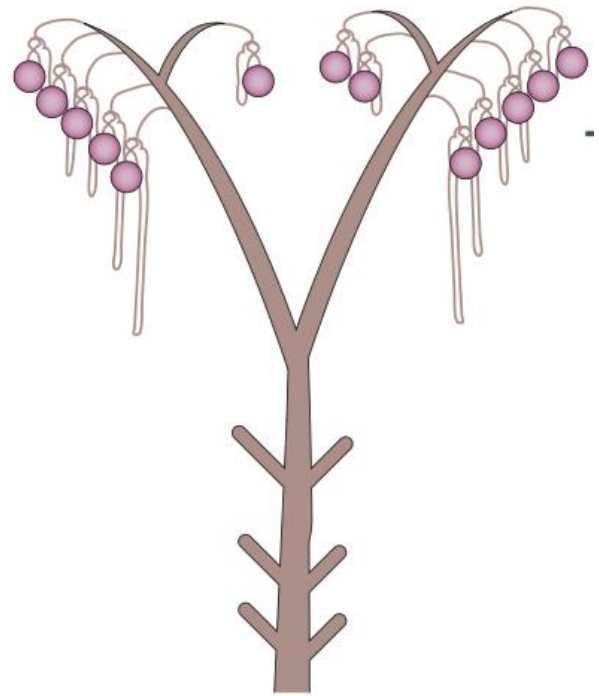
Diagnoses	18–59 years; $N = 621$ (%)	≥60 years; $N = 43$ (%)
IgA nephropathy	33.3	10.3
MsPGN	34.5	23.1
MCD	4.2	5.1
MGN	8.8	17.9
FSGS	3.5	12.8
MPGN	7.9	5.1
Crescentic GN	0.9	10.3
Chronic GN	3.1	10.3
Minor change	4.2	5.1

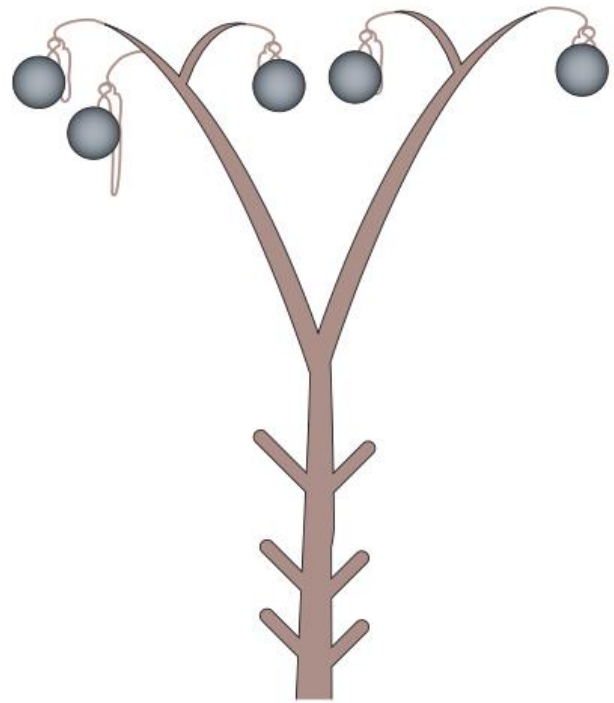
FSGS: focal segmental glomerulosclerosis; GN: Glomerulonephritis; MCD: minimal change disease; MGN: membranous glomerulonephritis; MPGN: membranoproliferative glomerulonephritis; MsPGN: mesangial proliferative glomerulonephritis.


in people with DM,
why don't we Bx more often ?
that is the question

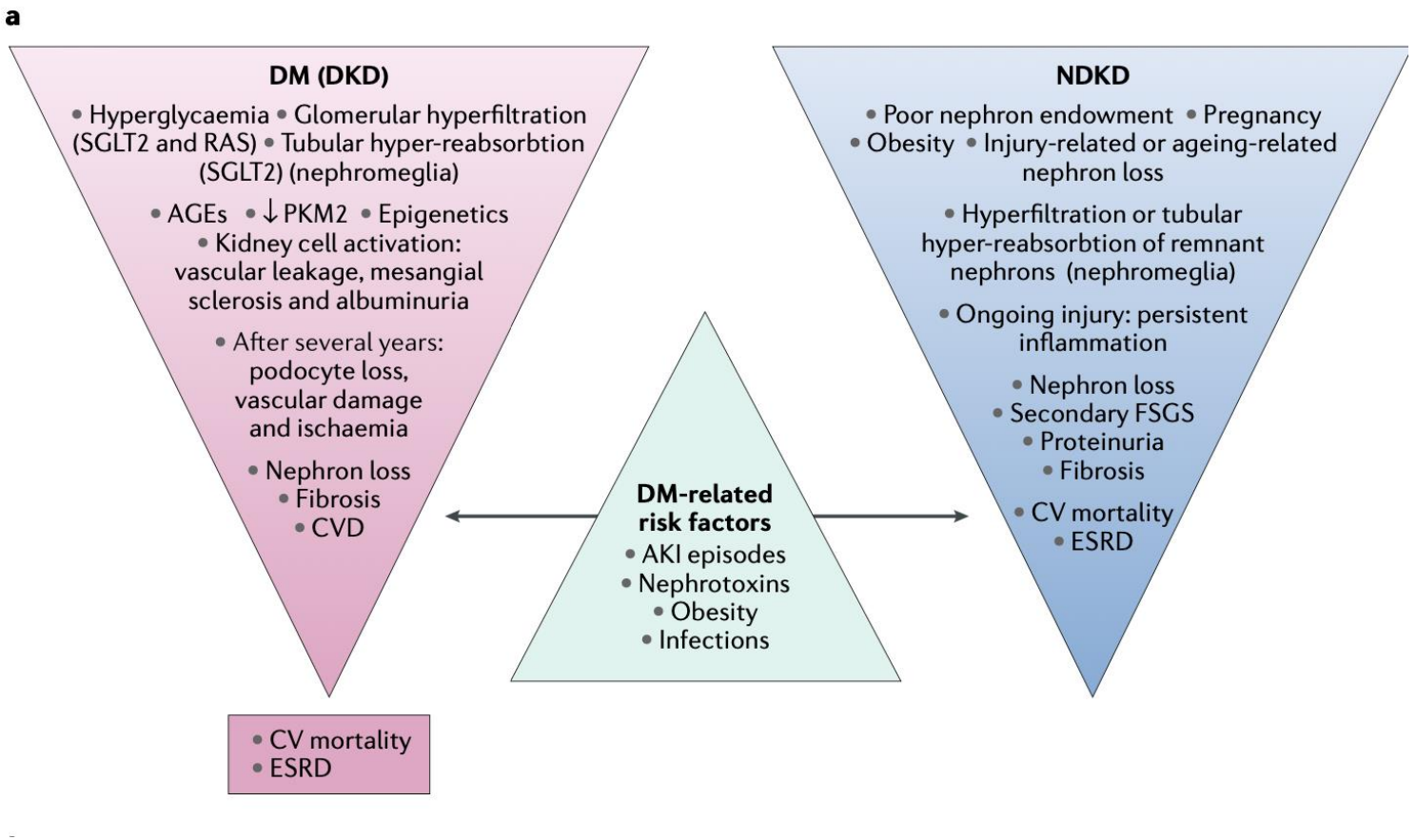




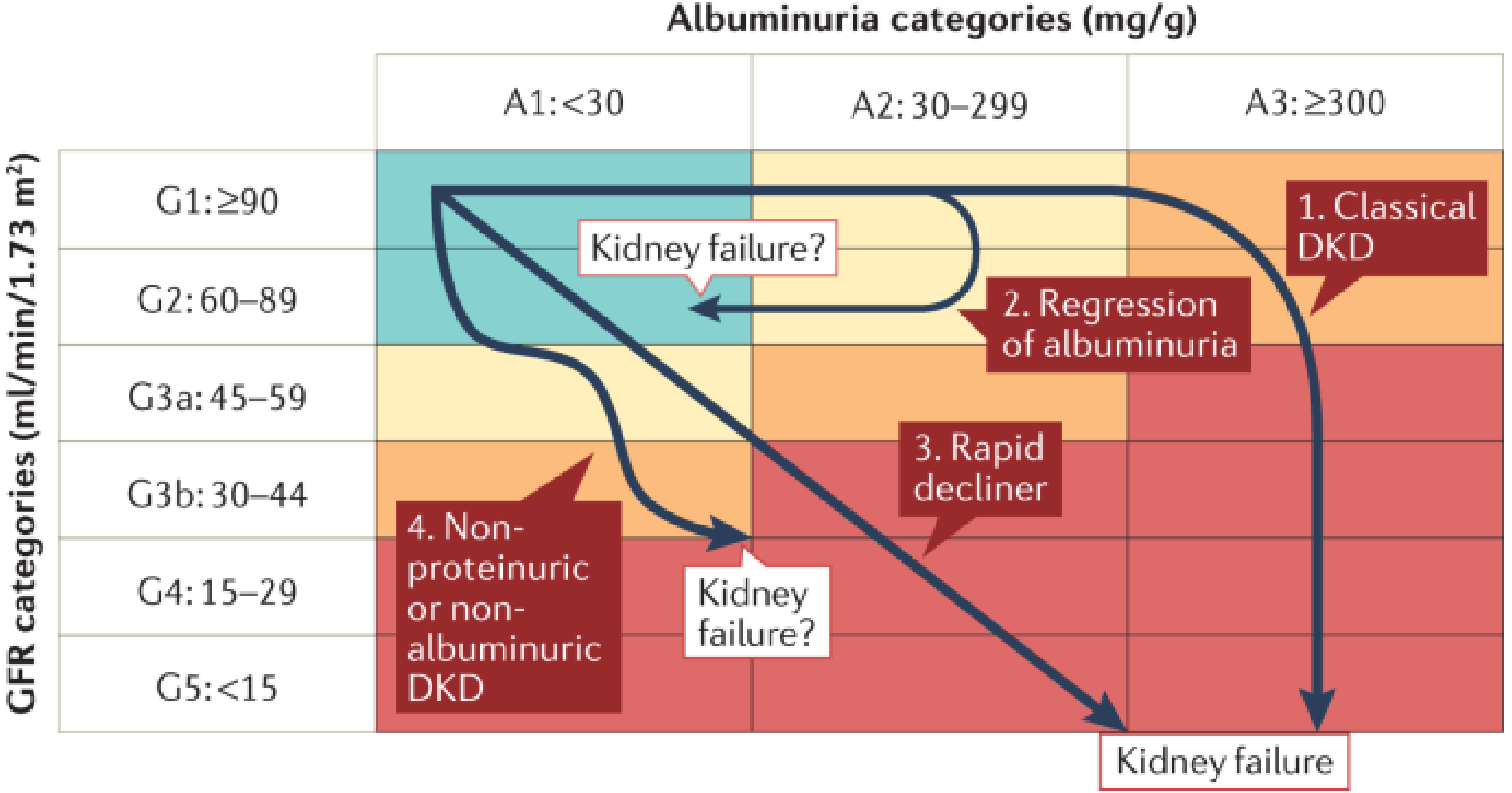


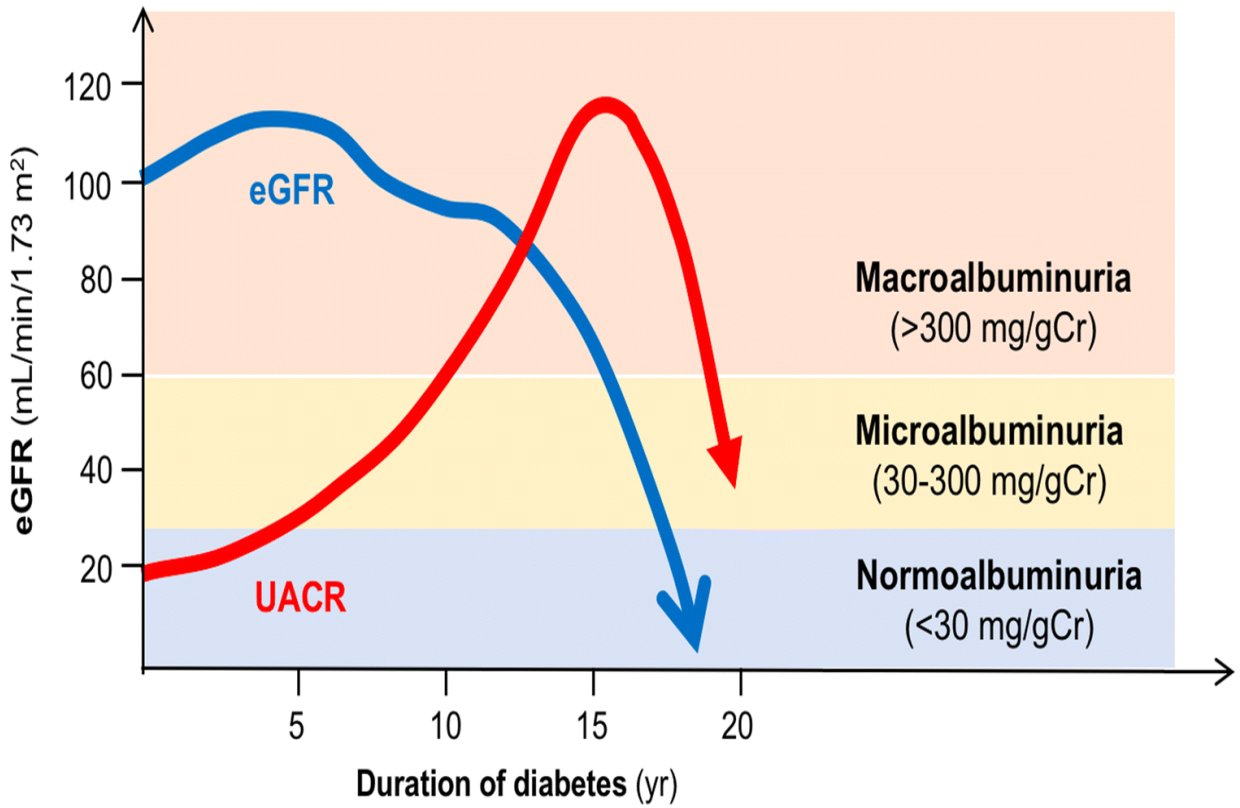


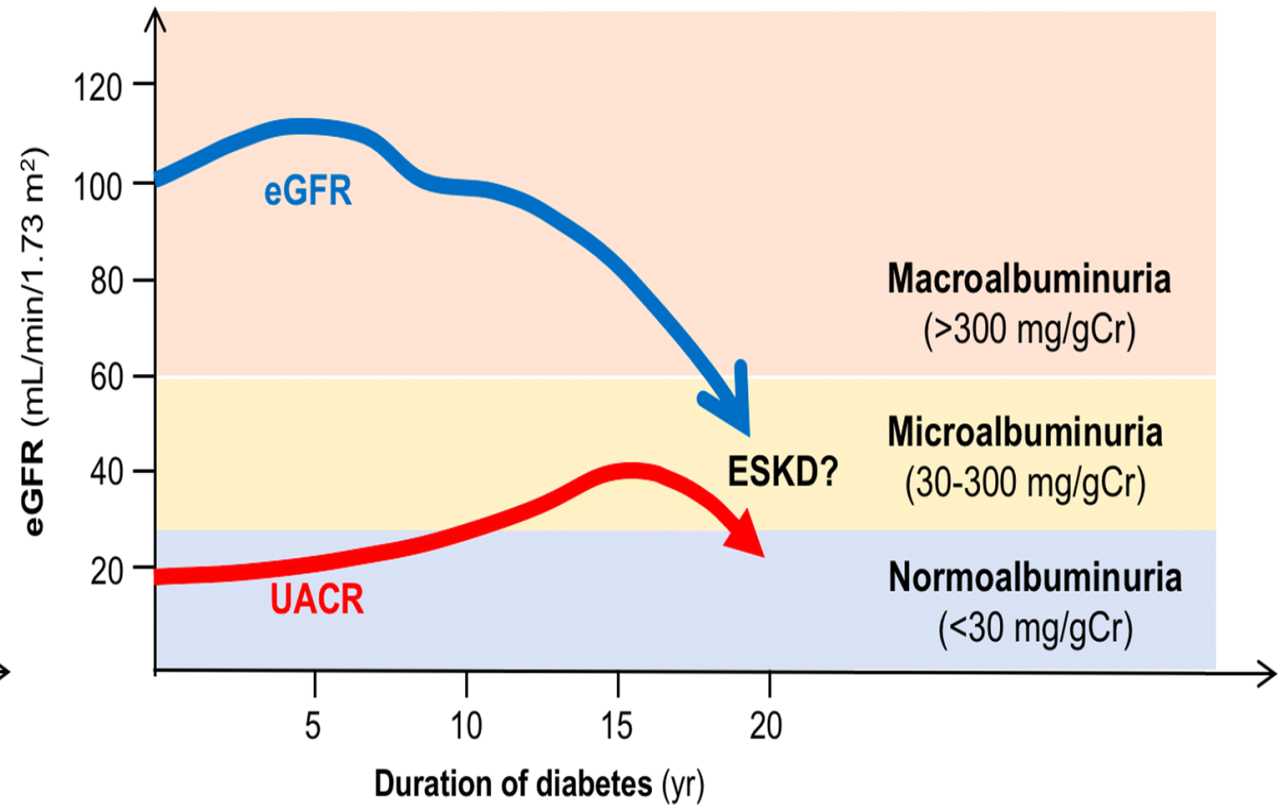
Hierarchy of pathomechanisms and temporal associations of diabetes mellitus and NDKD



Modern evolution of the natural history of DKD


Albuminuria categories (mg/g)
A1: <30
A2: 30–299
A3: ≥300
GFR categories (ml/min/1.73 m²)
G1: ≥90
G2: 60–89
G3a: 45–59
G3b: 30–44
G4: 15–29
G5: <15
Kidney failure?
1. Classical DKD
2. Regression of albuminuria
3. Rapid decliner
4. Non-proteinuric or non-albuminuric DKD
Kidney failure?
Kidney failure


120
100
80
60
40
20
eGFR (mL/min/1.73 m²)
eGFR
UACR
Macroalbuminuria
(>300 mg/gCr)
Microalbuminuria
(30-300 mg/gCr)
Normoalbuminuria
(<30 mg/gCr)
5
10
15
20
Duration of diabetes (yr)

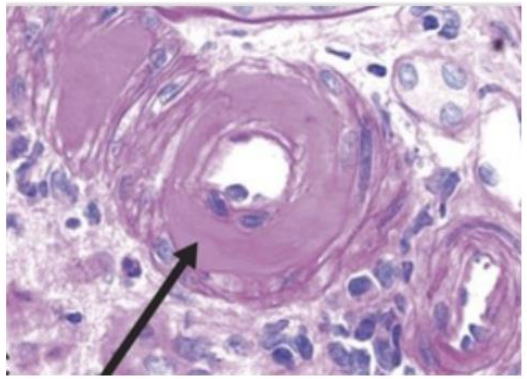

120
100
80
60
40
20
eGFR (mL/min/1.73 m²)
eGFR
UACR
ESKD?
Macroalbuminuria
(>300 mg/gCr)
Microalbuminuria
(30-300 mg/gCr)
Normoalbuminuria
(<30 mg/gCr)
5
10
15
20
Duration of diabetes (yr)

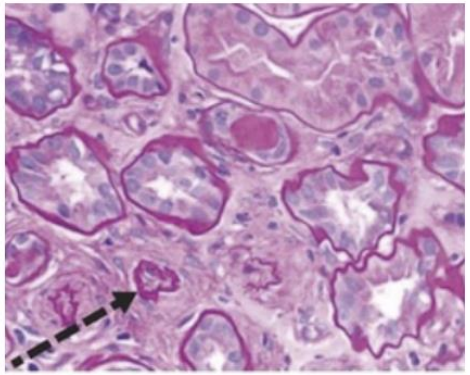
Clinical characteristics of patients with NADKD vs. those with classical DKD (reduced eGFR + albuminuria)

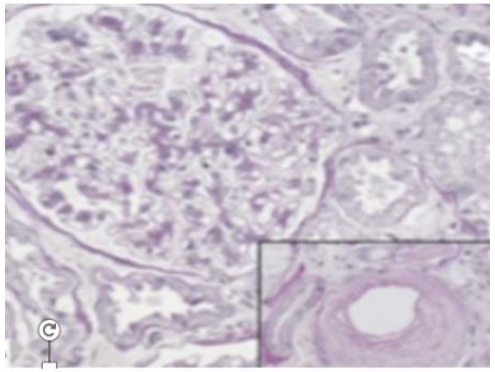
- Older age
- Shorter duration of diabetes
- Lower levels of Hgb A1C
- Lower levels of blood pressure
- Higher proportion in females
- Lower prevalence of cardiovascular disease
- Lower frequency of diabetic retinopathy
- Lower rate of using RAAS inhibitors

Clinical characteristics of patients with NADKD vs. diabetics with normal GFR and normal albumin excretion

- Older age
- **Longer duration of diabetes**
- **Higher systolic blood pressure**
- Lower diastolic pressure
- **Higher TG**
- Higher proportion in females
- **Higher prevalence cardiovascular disease**
- **Higher rate of retinopathy**
- **More probability of using RAAS inhibitors**



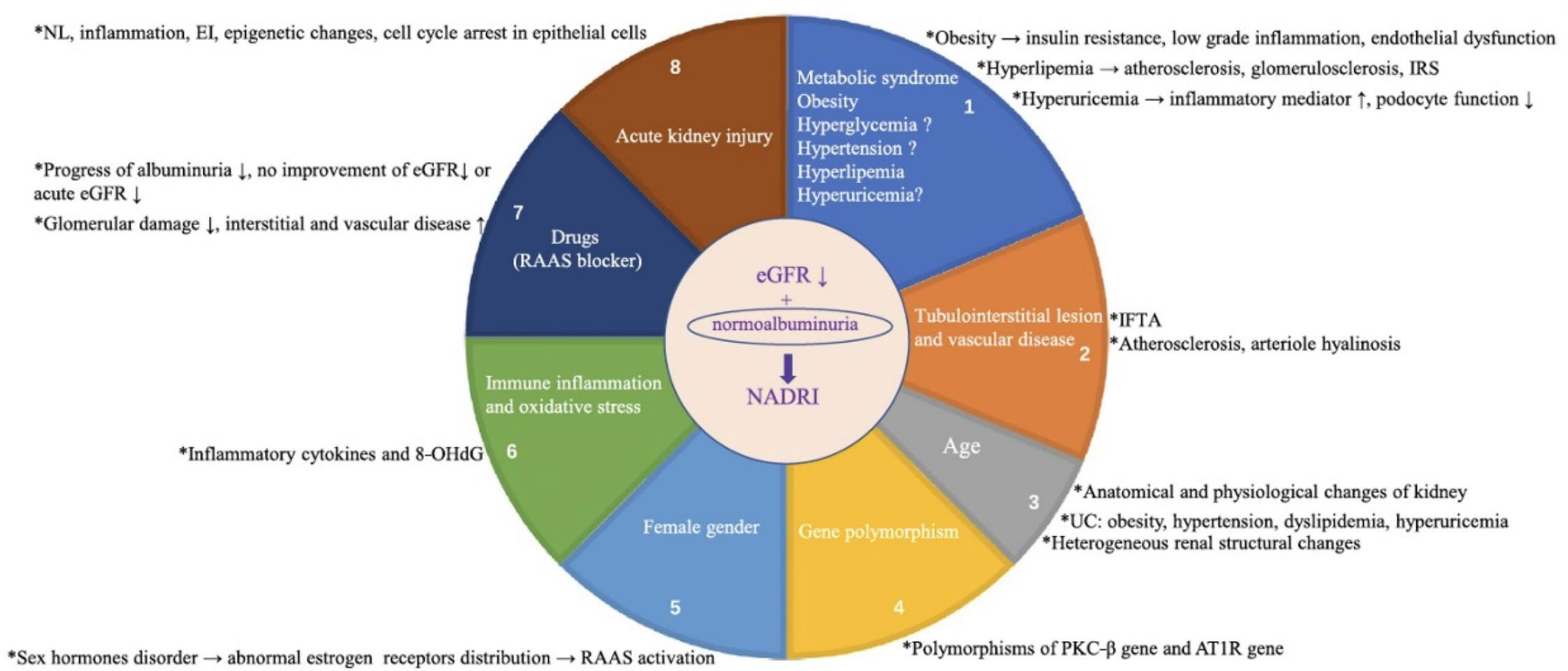




Non-albuminuric DKD phenotype: a breakthrough in DKD classic conception

Albuminuric DKD		Non-albuminuric DKD
UACR > 30 mg/g	 	eGFR < 60 ml/min/1.73m^2 and UACR < 30 mg/g
Microangiopathy	 	Macroangiopathy
Correlation with retinopathy	 	No correlation with retinopathy
Glomerulosclerosis	 	Tubular and vascolar damage
Male sex		Female sex 
Correlation with Hb1Ac		No correlation with Hb1Ac 

NADKD
pathogenesis



Concluding Thoughts

- CKD in DM is common & is a growing public health priority
- Identification & assessment of the cause of CKD (DKD,NDKD)
- Try & idnetify NDKD , they are treatable
- KBx can identify disease subtype, with distinct prognosis & response to a different specific treatment
- DM has heterogeneous implications for clinical, pathological & molecular signatures.
- NADKD demonstrate an increasing rate (esp T2DM)
- We can improve care of DKD pts

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