UCLA Health

DIABETES AND YOUR KIDNEYS

OR AS WE CALL IT "DIABETIC NEPHROPATHY"

The latest guidelines to keep you safe, healthy, fit, and out of danger from needing dialysis

A UCLA HEALTH EDUCATIONAL SEMINAR

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THE NUMBERS

- Chronic kidney disease (CKD) is a worldwide public health problem affecting more than 50 million people, and more than 1 million of them are receiving kidney replacement therapy.[1,2] The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative™ (NKF-KDOQI™) Clinical Practice Guidelines (CPGs) on CKD estimate that CKD affects 11% of the US population,[3] and those affected are at increased risk of cardiovascular disease (CVD) and kidney failure. Kidney failure represents about 1% of the prevalent cases of CKD in the United States,[3] and the prevalence of kidney failure treated by dialysis or transplantation is projected to increase from 453,000 in 2003 to 651,000 in 2010.[3,4]

http://www2.kidney.org/professionals/kdoqi/guideline_diabetes/background.htm

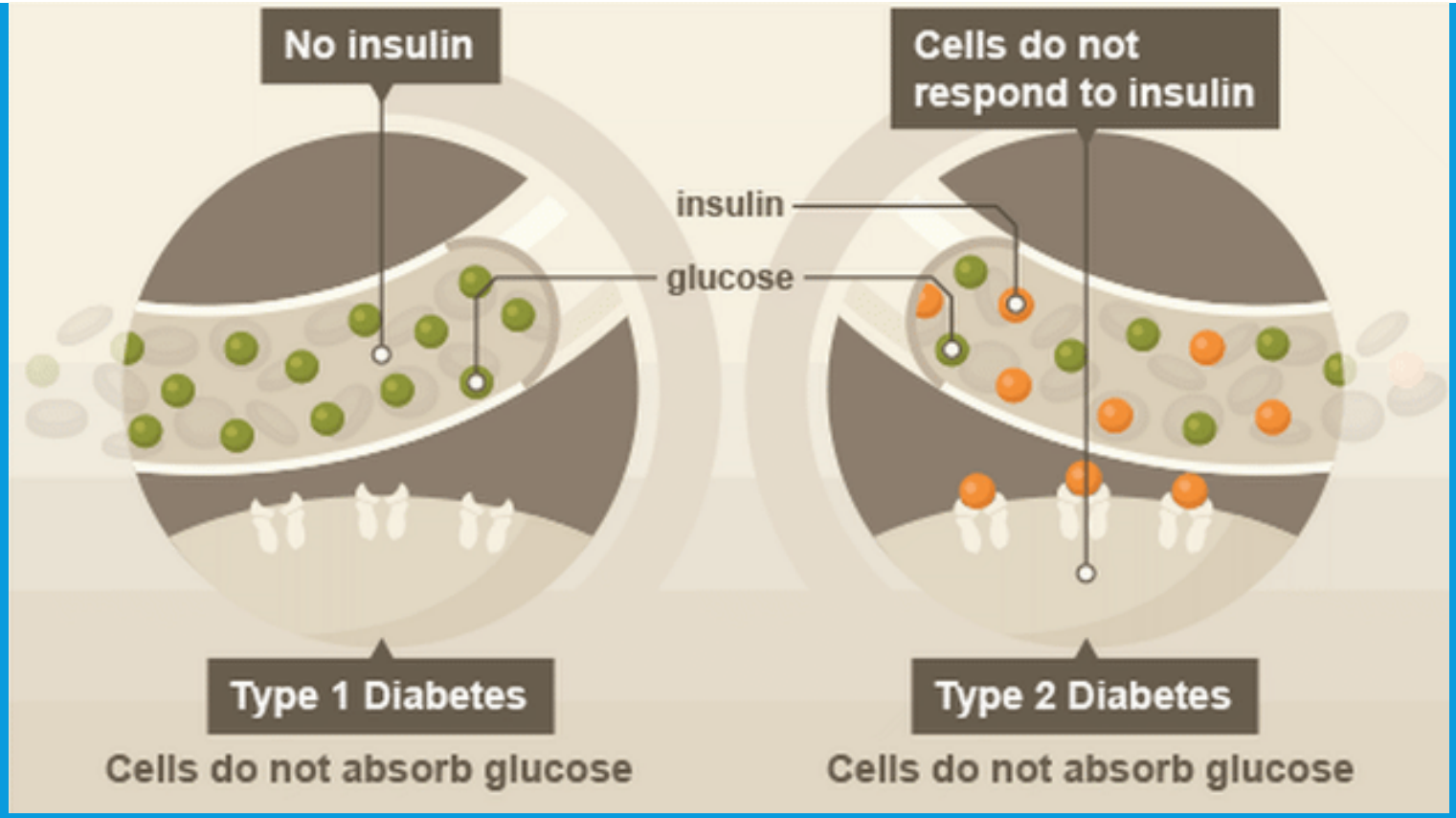
CLASSIFICATION OF DIABETES TYPES

Classification of Diabetes

I	Type 1 diabetes	
	1A	Immune-mediated
	1B	Idiopathic
II	Type 2 diabetes	
III	Other specific types (Secondary diabetes)	
IV	Gestational Diabetes Mellitus	

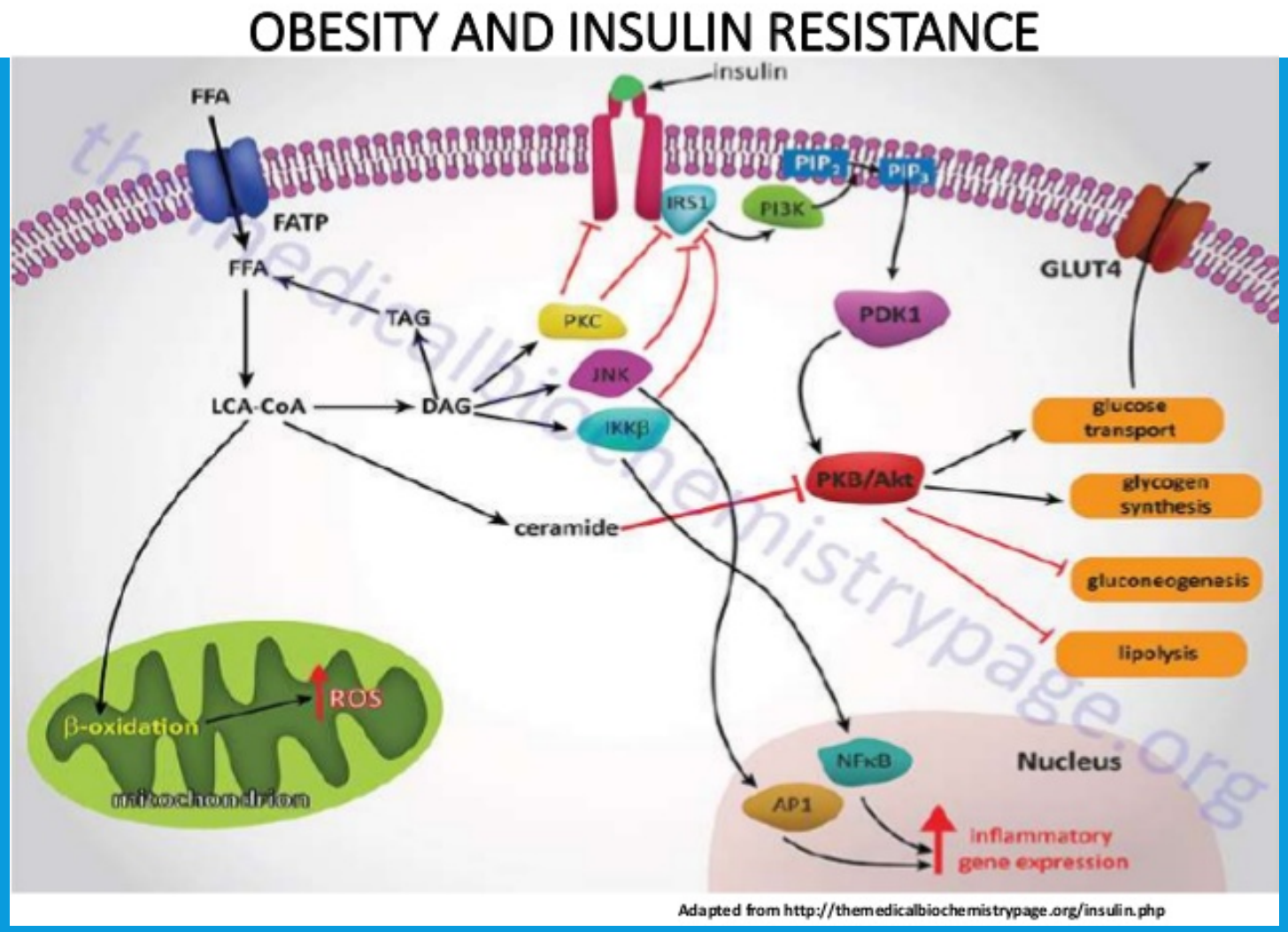
WHO Consultation 1999

HOW DIABETES HAPPENS

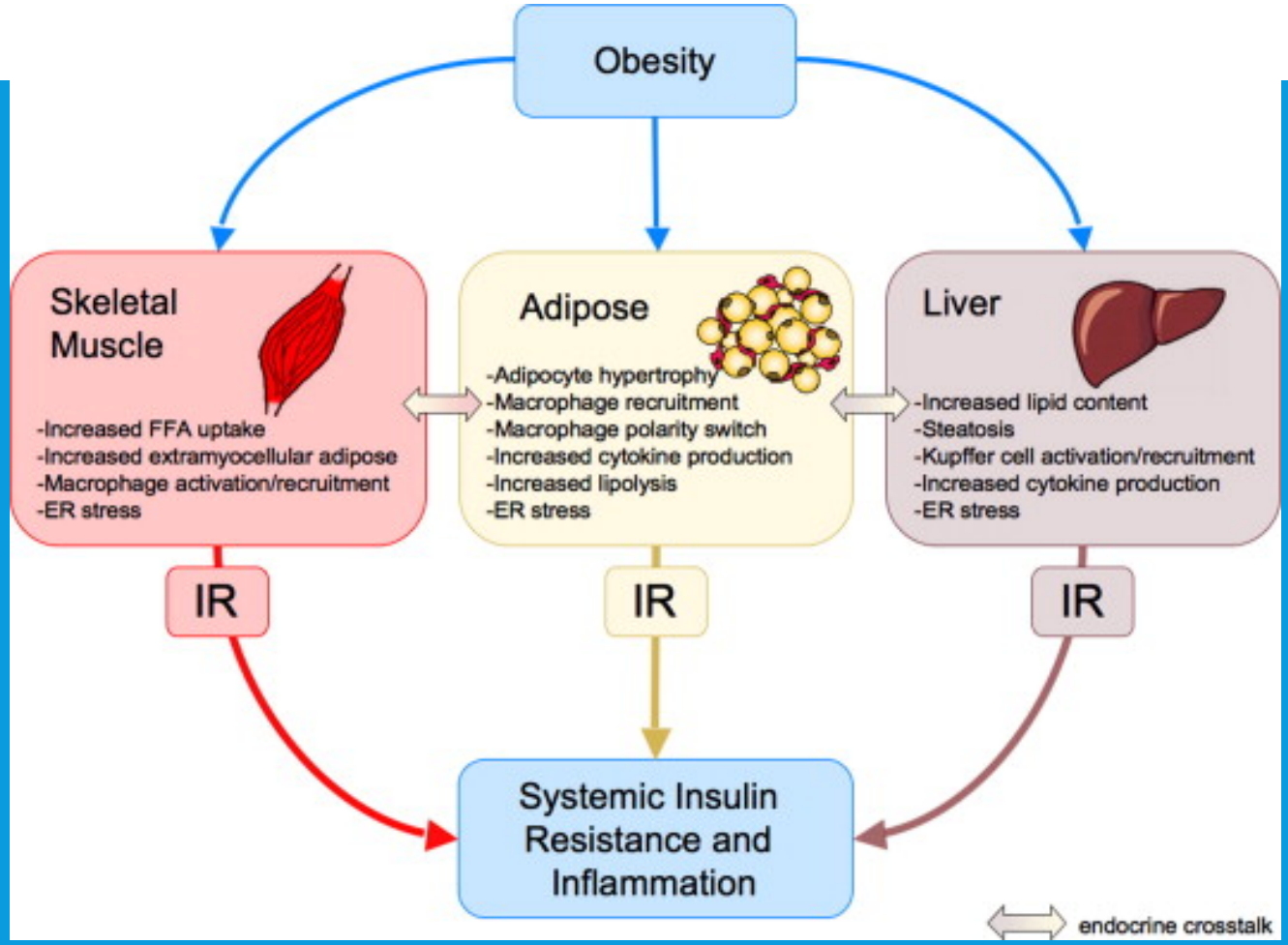


http://www.bbc.co.uk/science/o/21704103

INSULIN RESISTANCE-FOR THE BIOCHEMIST



INSULIN RESISTANCE-FOR THE REST OF US



https://www.sciencedirect.com/science/article/pii/S0014579307012082

KIDNEY DISEASE-KDOQI OLDER (NKF, US) -KIDNEY DISEASE OUTCOMES QUALITY INITIATIVE

Table 10. Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

National Kidney Foundation®

http://www2.kidney.org/professionals/kdoqi/guideline_diabetes/background.htm

THE NEW WAY OF LOOKING AT KIDNEY DISEASE KDIGO-NEWER (GLOBAL) KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES

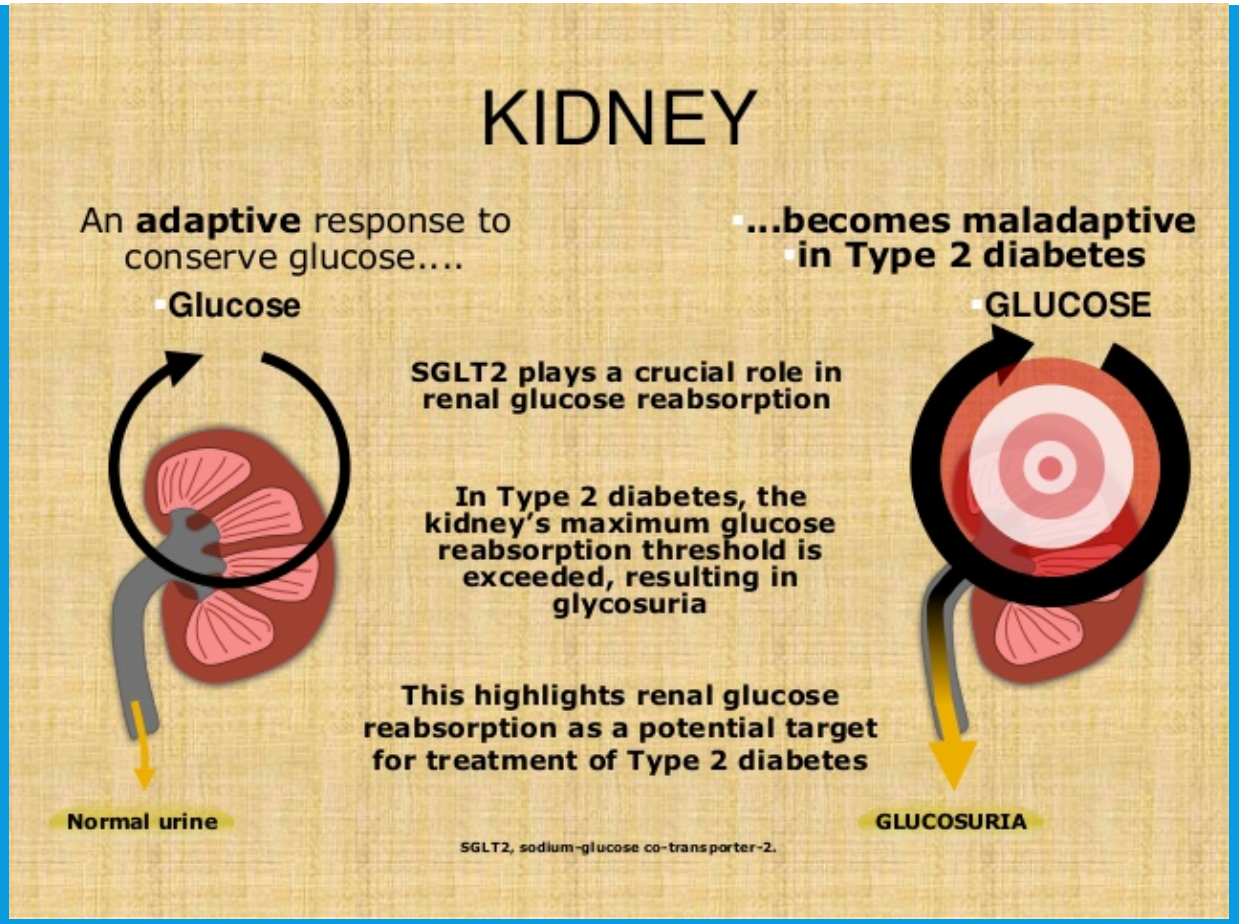
Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

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

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

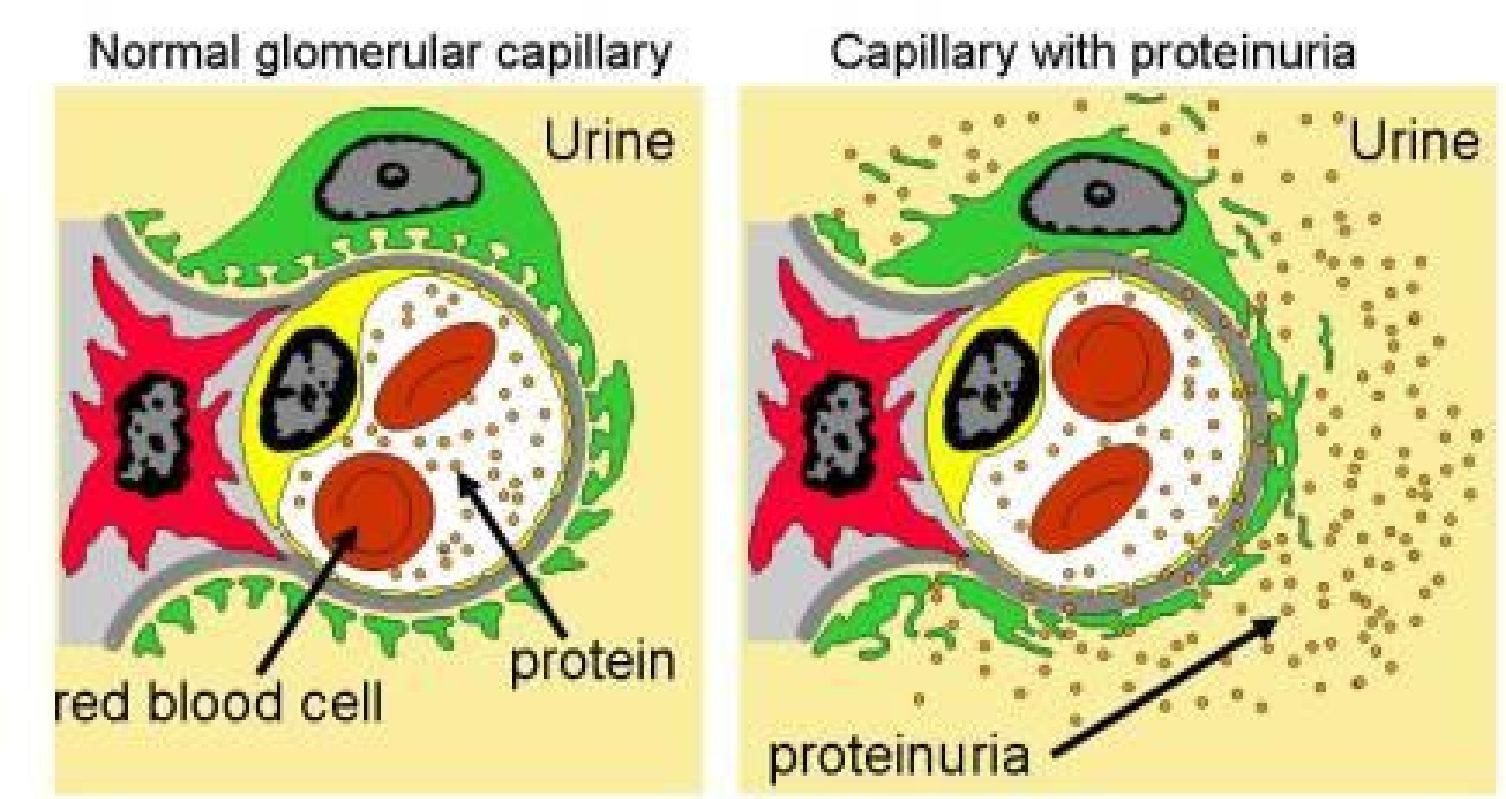
https://www.slideshare.net/SumaneePrakobsuk/kdigo-ckd-2012

WHY DO KIDNEYS LEAK GLUCOSE INTO URINE IN DIABETES?



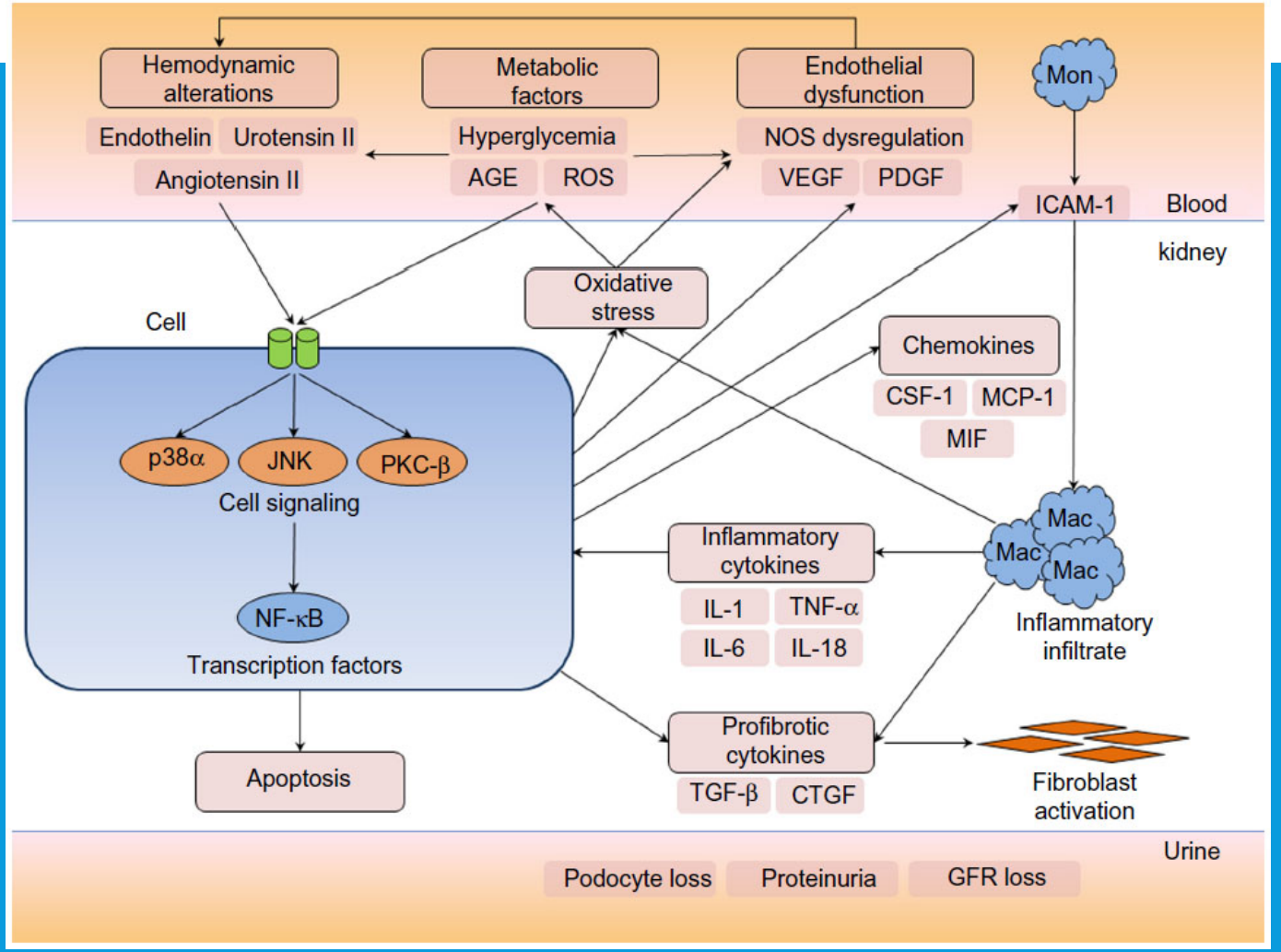
https://www.slideshare.net/shahjadaselimg/pathophysiology-of-diabetes-by-dr-shahjada-selim

WHY DO KIDNEYS LEAK PROTEIN IN DIABETES

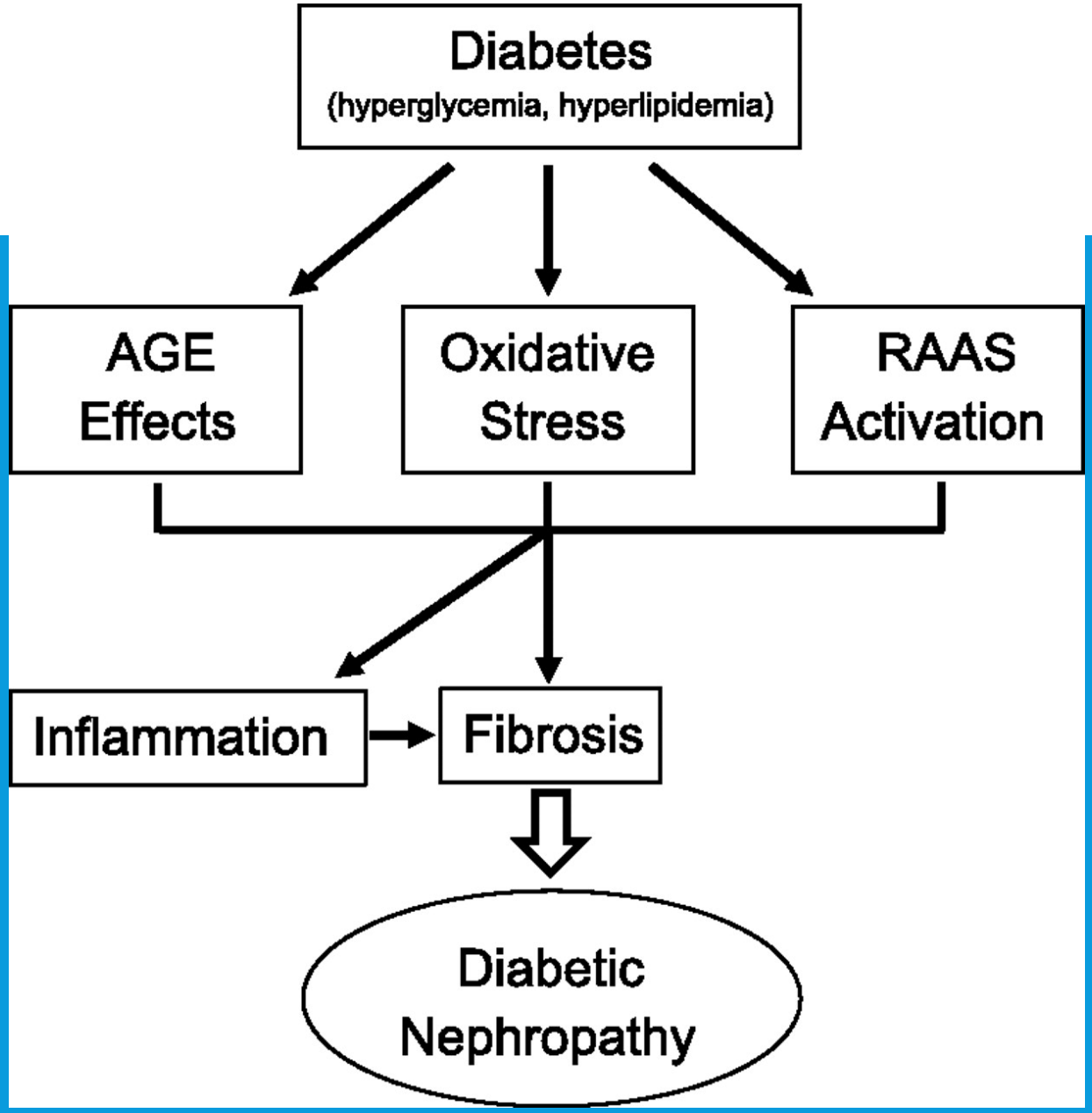


https://proteinpower.com/drmike/2009/04/19/thiamin-and-diabetic-nephropathy/

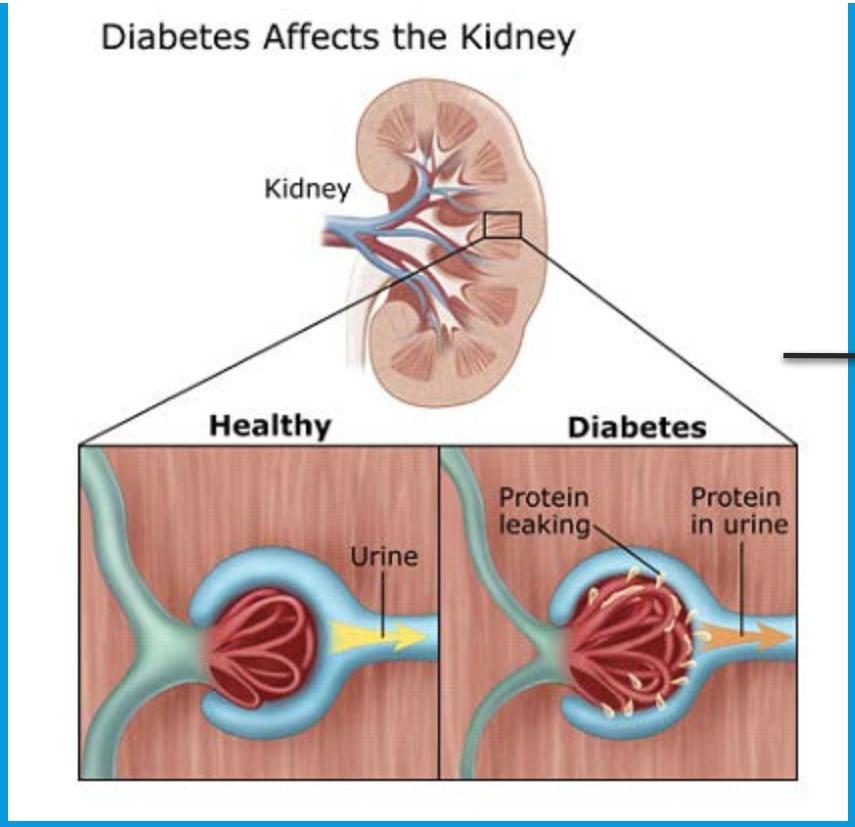
IT'S NOT REALLY ALL THAT SIMPLE

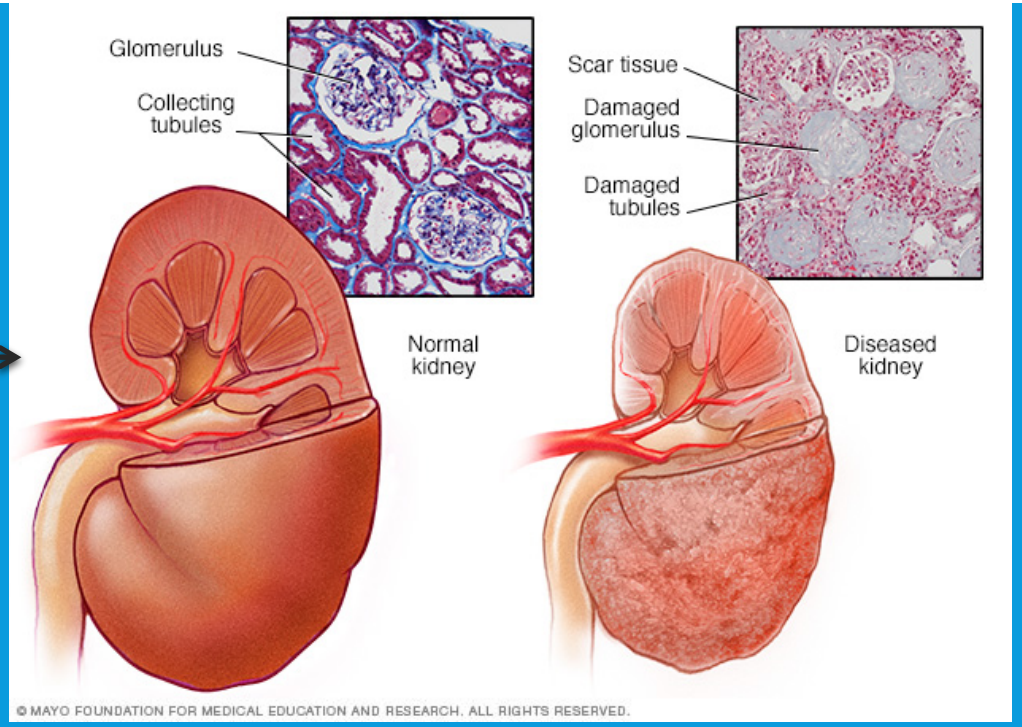


https://www.dovepress.com/diabetic-nephropathy-ndash-complications-and-treatment-peer-reviewed-fulltext-article-IJNRD


Diabetes
(hyperglycemia, hyperlipidemia)
AGE
Effects
Oxidative
Stress
RAAS
Activation
Inflammation
Fibrosis
Diabetic
Nephropathy

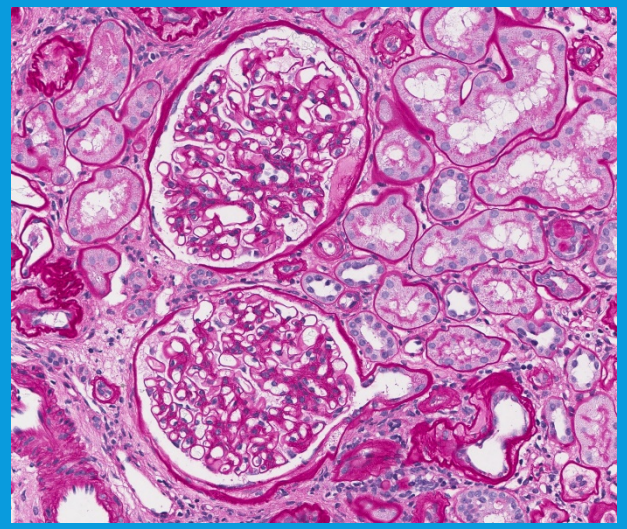
SIMPLY STATED: HOW DIABETES CAUSES KIDNEY DISEASE

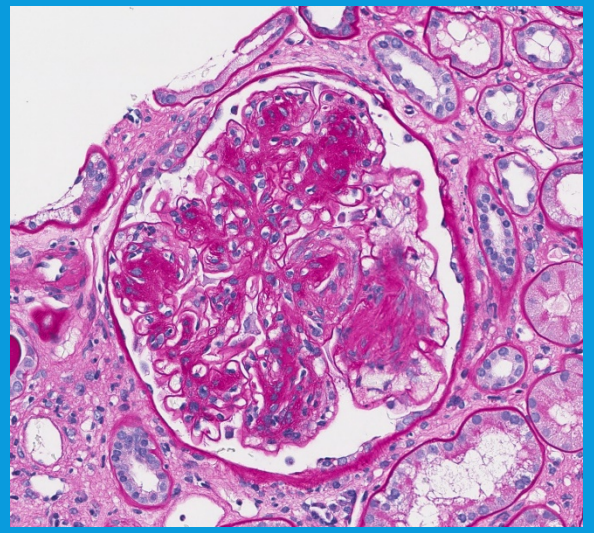


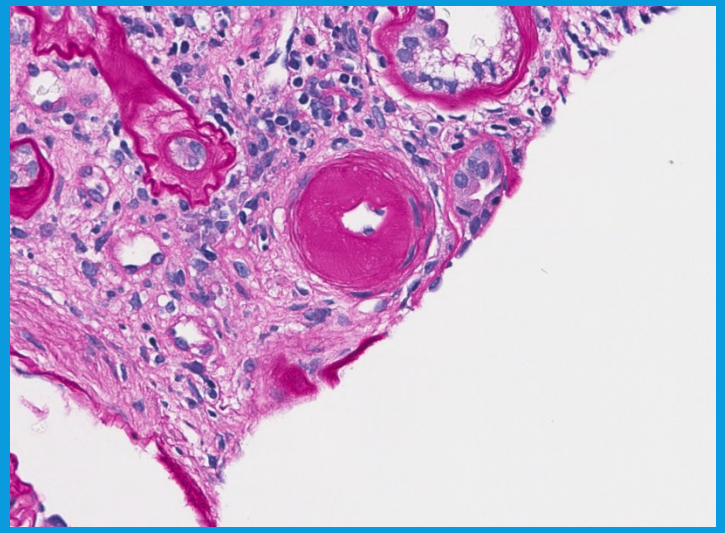


https://www.mayoclinic.org/diseases-conditions/diabetic-nephropathy/symptoms-causes/syc-20354556

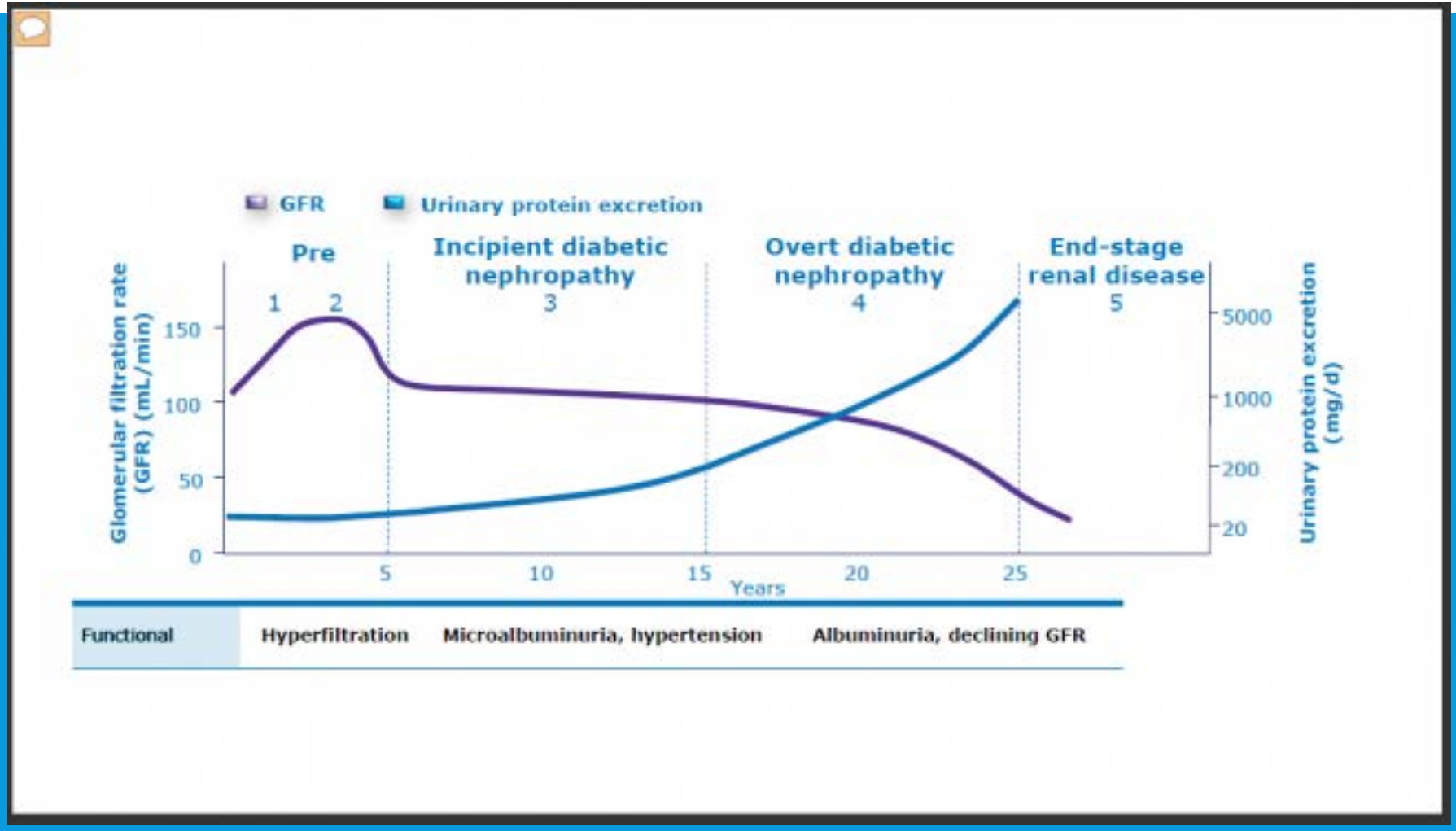
WHAT DOES DIABETES IN MY KIDNEY LOOK LIKE?

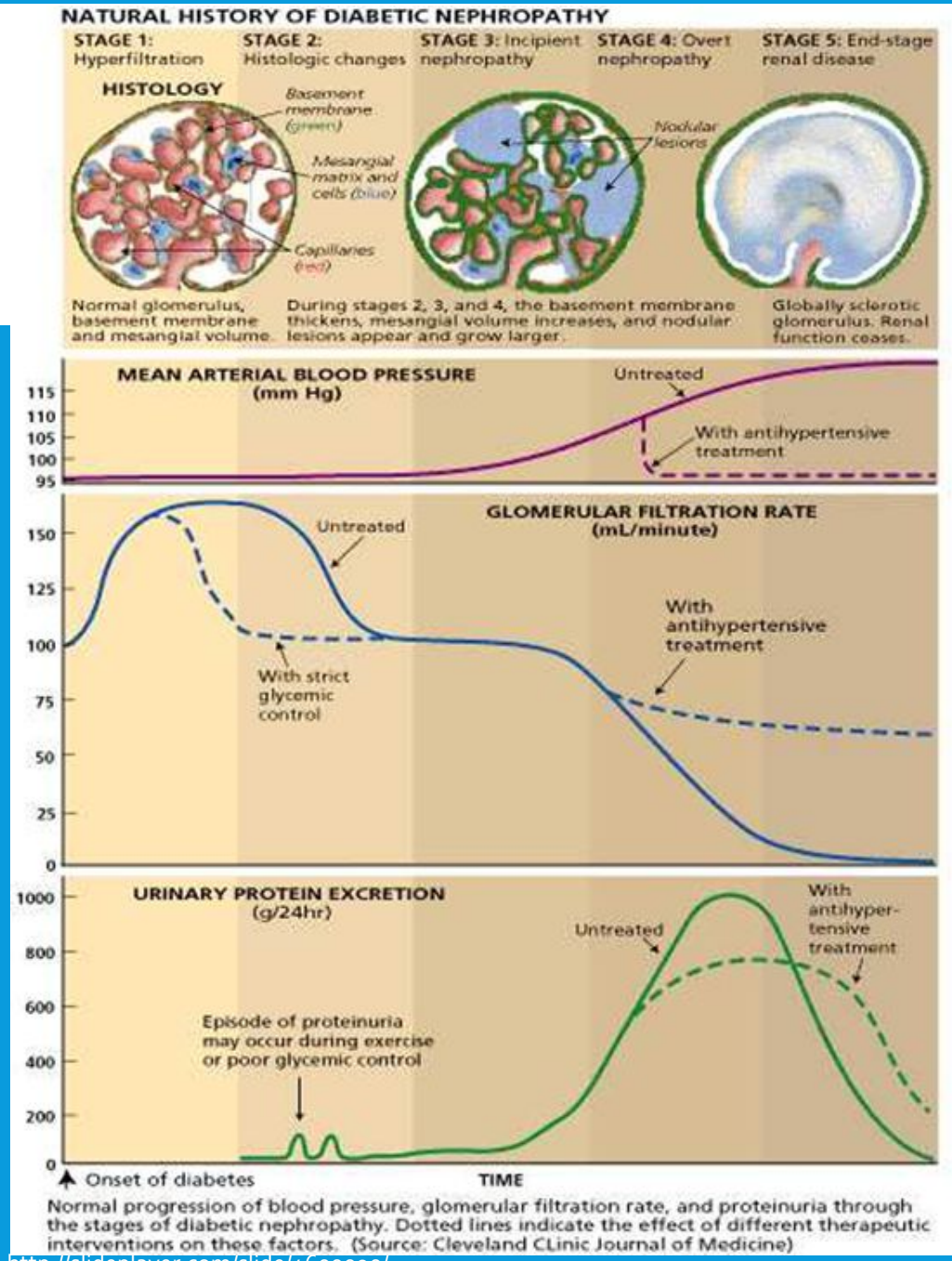






HOW LONG DOES THIS DISEASE TAKE TO PROGRESS?

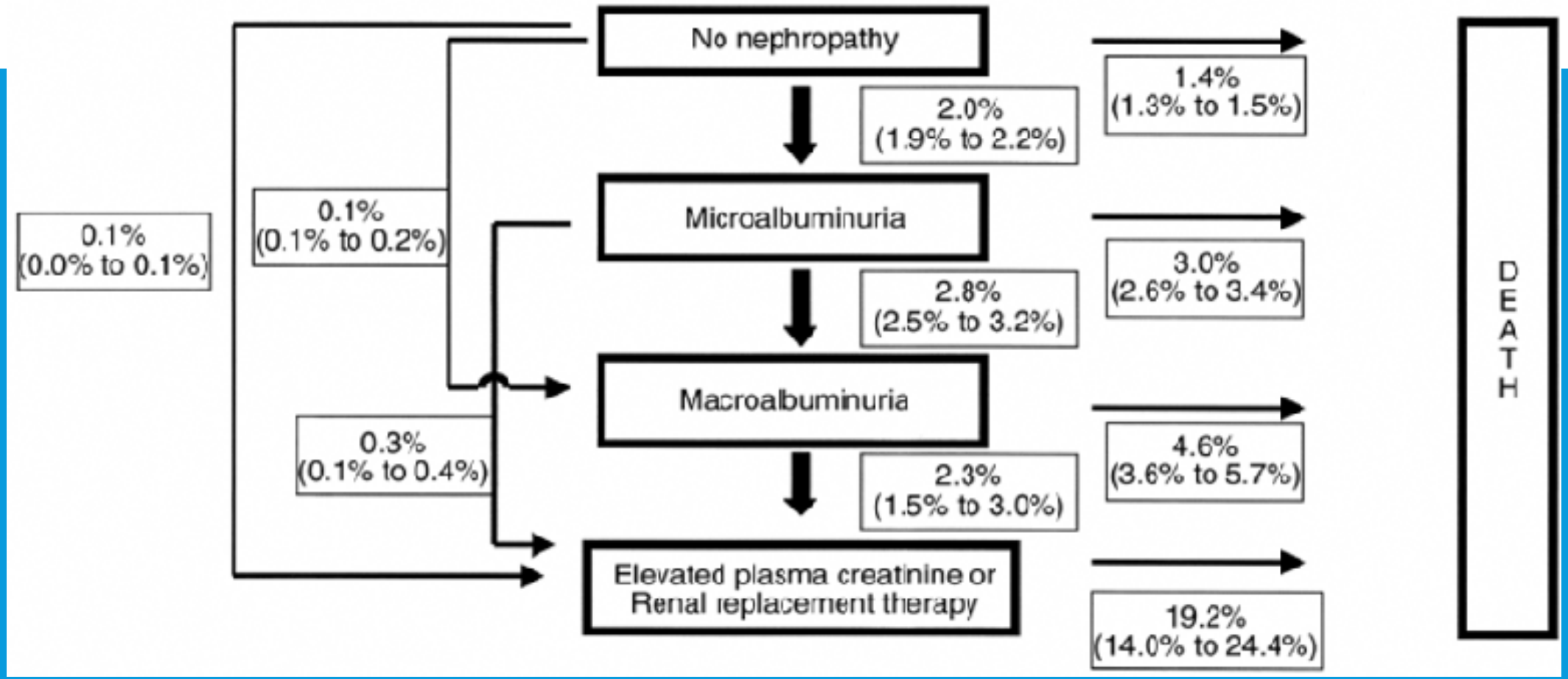




STAGES OF DM nephropahty

- STAGE-1 **HYPERFILTRATION**
- STAGE-2 **SILENT STAGE**
- STAGE-3 **INCIPIENT NEPHROPATHY**
- STAGE-4 **OVERT NEPHROPATHY**
- STAGE-5 **CHRONIC RENAL FAILURE → ESRD**

http://slideplayer.com/slide/4600090/

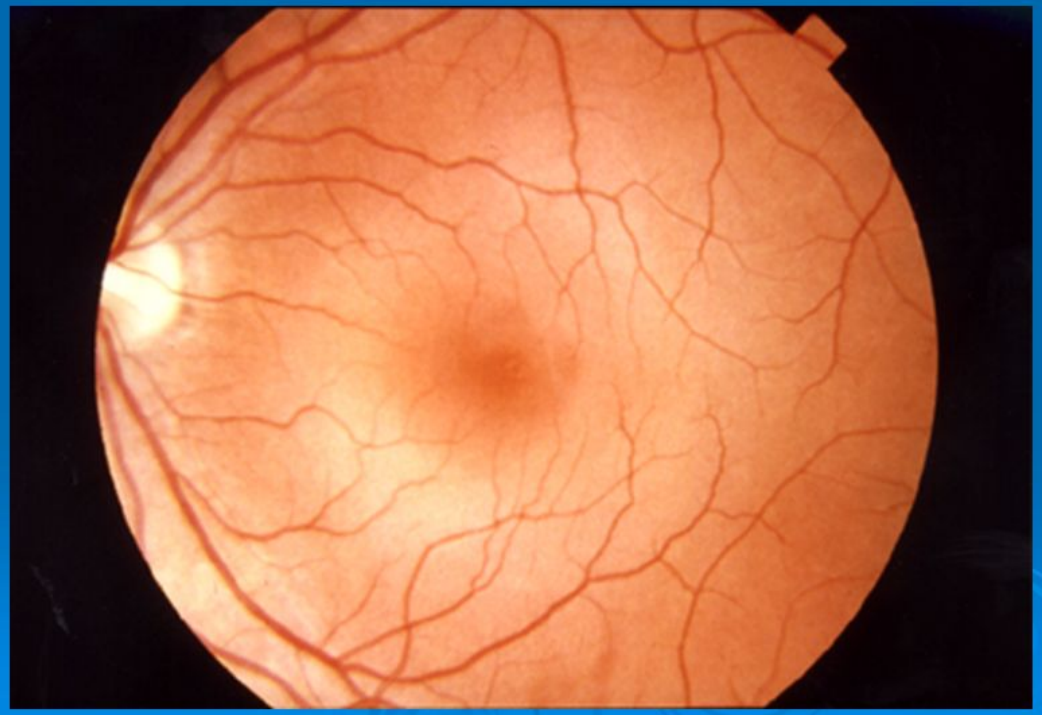

No nephropathy
Microalbuminuria
Macroalbuminuria
Elevated plasma creatinine or
Renal replacement therapy
0.1%
(0.0% to 0.1%)
0.1%
(0.1% to 0.2%)
0.3%
(0.1% to 0.4%)
2.0%
(1.9% to 2.2%)
2.8%
(2.5% to 3.2%)
2.3%
(1.5% to 3.0%)
1.4%
(1.3% to 1.5%)
3.0%
(2.6% to 3.4%)
4.6%
(3.6% to 5.7%)
19.2%
(14.0% to 24.4%)
DEATH

HOW CAN MY DOCTOR MEASURE IT'S IMPACT?

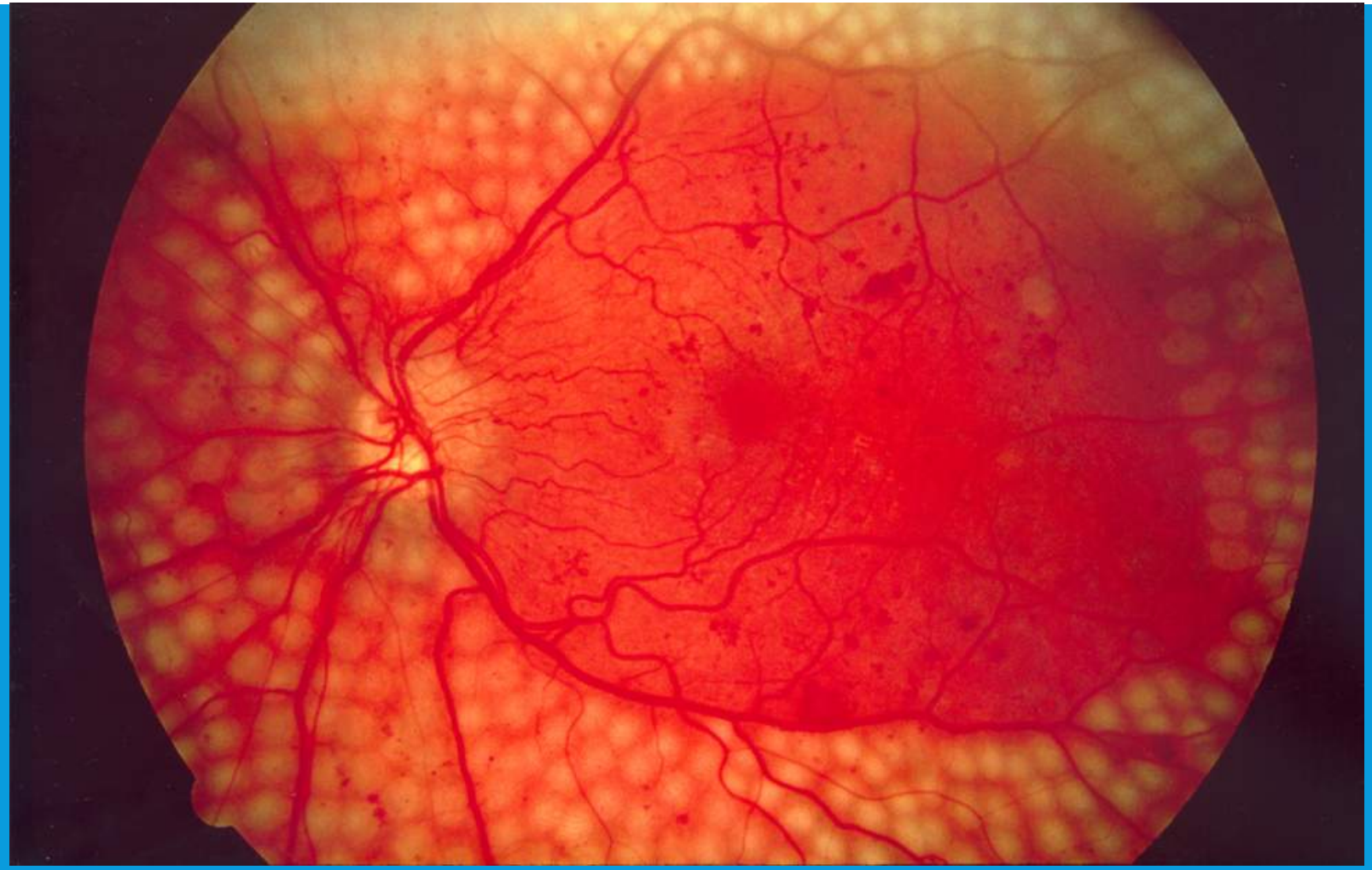
- **Measures to determine impact of diabetes on kidneys**
- Urinalysis
- Urine protein / creatinine ratio
- Urine albumin/ creatinine ratio
- 24 hour urine protein
- Blood tests for blood urea nitrogen
- Blood tests for creatinine
- Blood test for cystatin C

DIABETES AND THE EYE-KIDNEY CONNECTION

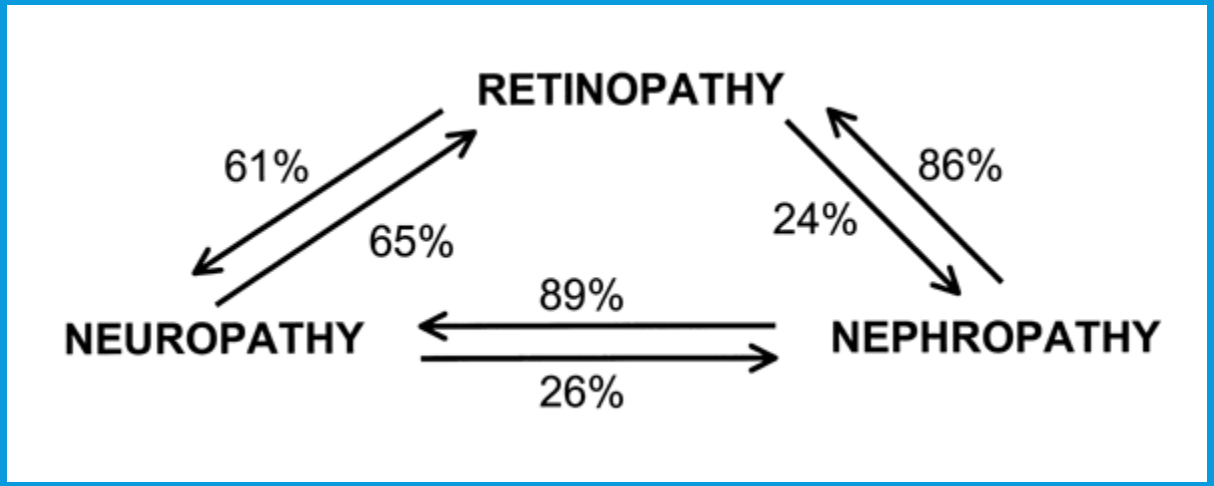
Normal Retina



ABNORMAL RETINA (DIABETIC RETINOPATHY)

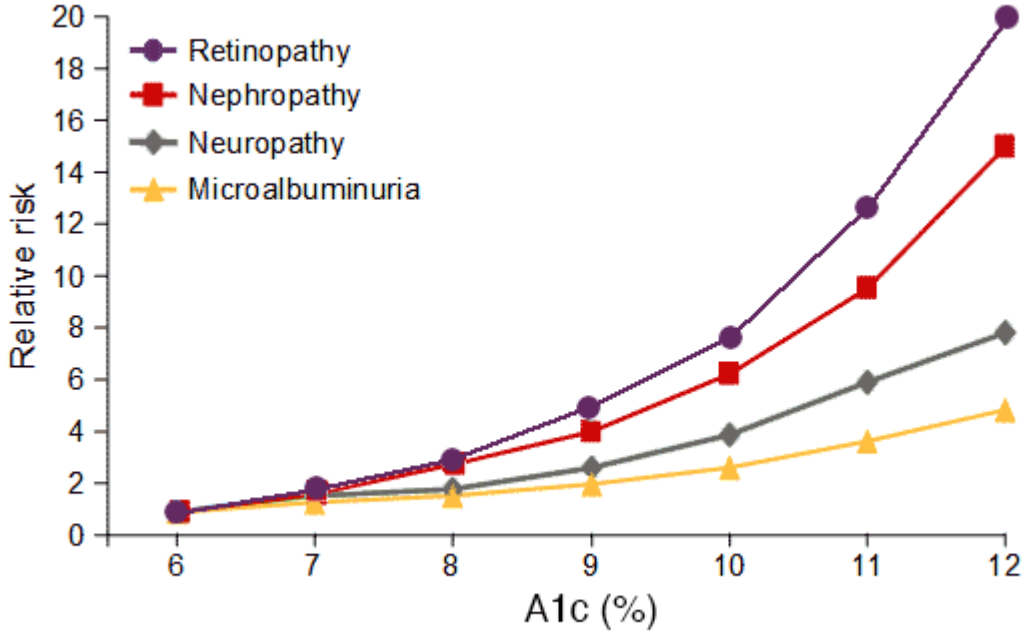


THE THREE HORSEMEN OF DIABETES



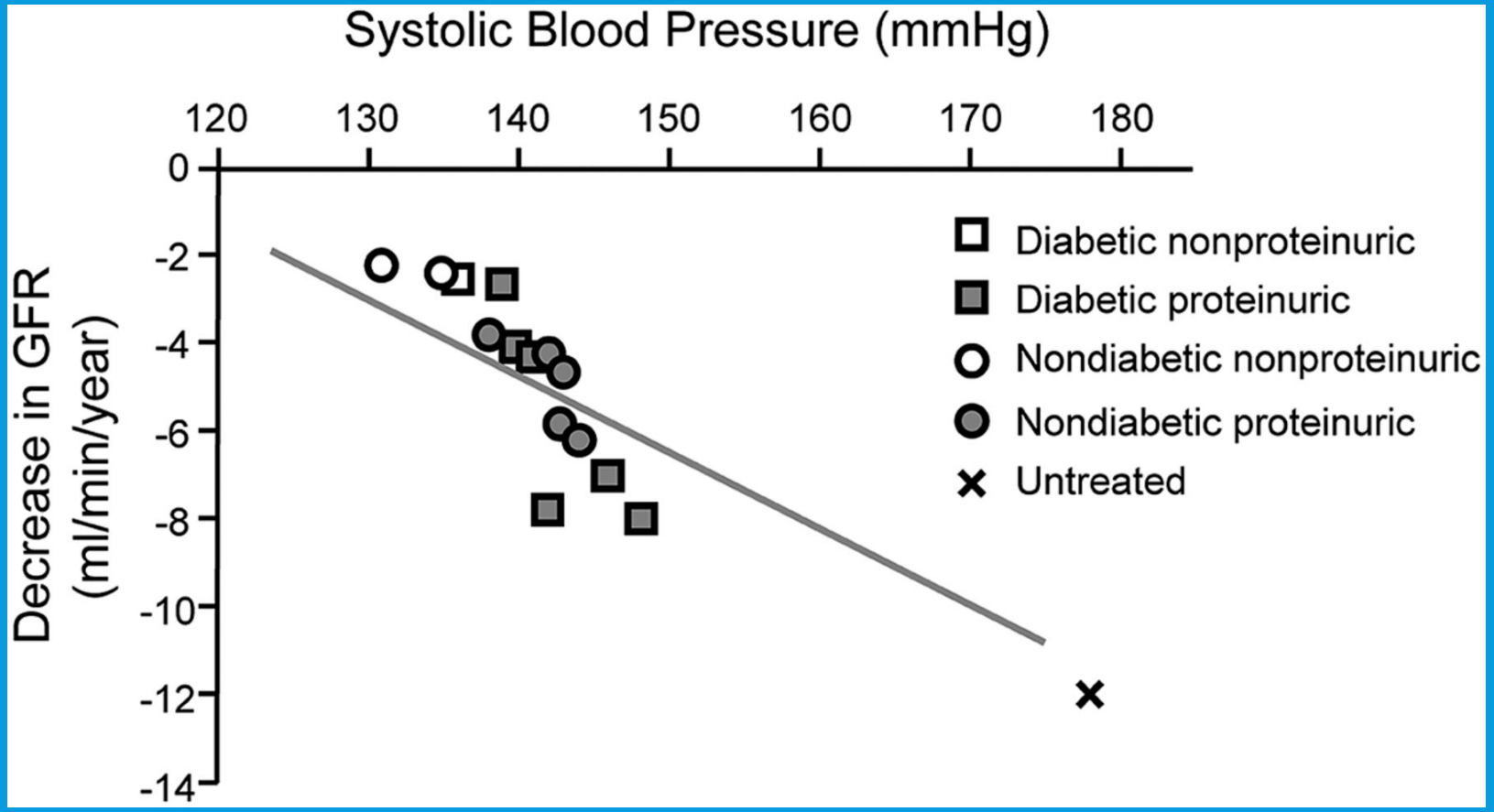
The presence of nephropathy and retinopathy is 86% meaning if a doctor sees protein leakage in a Diabetic 70-90% of patients will have eye damage. Conversely if someone has kidney disease and diabetic eye disease is Confirmed 70-90% chance that kidney disease is also due to diabetes this is called concurrence.

KEEP YOUR A1C AT GOAL



http://www.ptsdiagnostics.com/a1c-and-complications.html

KEEP YOUR BLOOD PRESSURE AT GOAL



NKF GUIDELINES ON OTHER FACTORS THAT CAN HELP PREVENT PROGRESSION OF DM/DN OR OTHER VASCULAR COMPLICATIONS.

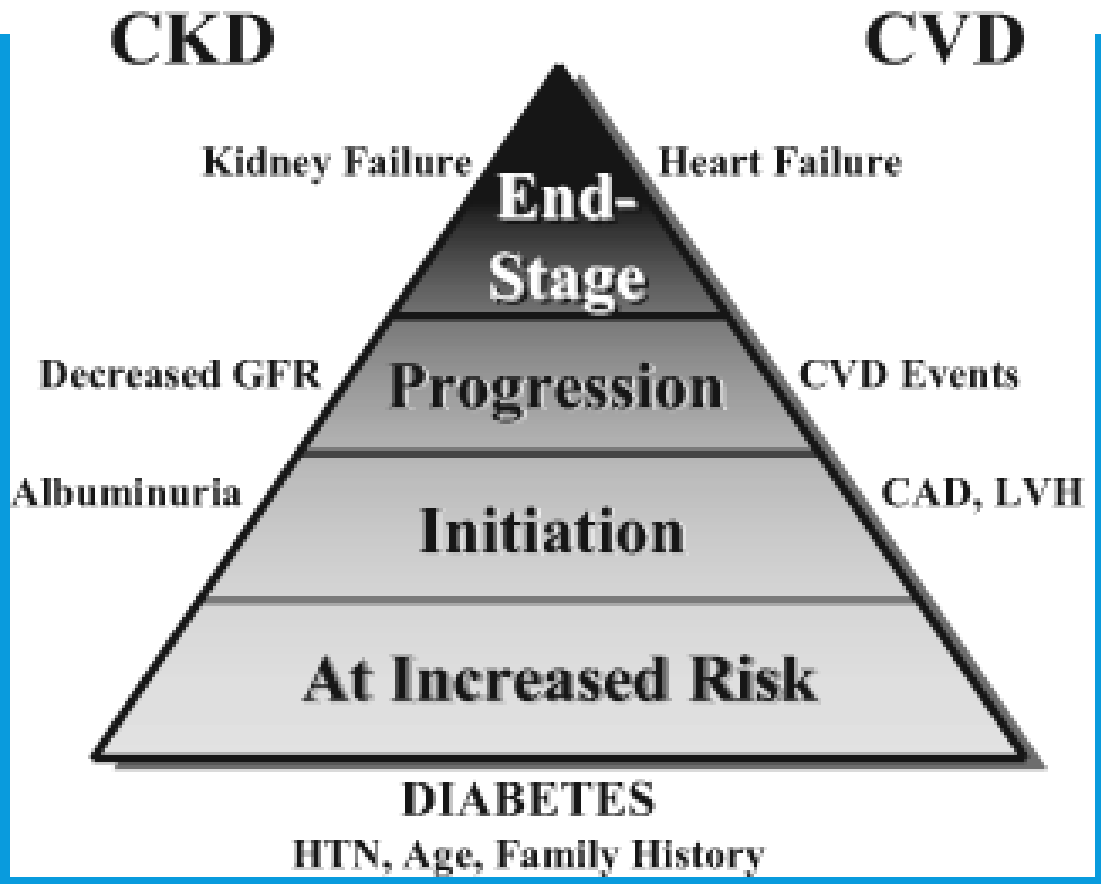
Risk Factor	Goal of Therapy	Recommending Body
Cigarette smoking	Complete cessation	ADA
Blood pressure	<130/80 mm Hg	JNC 7 (NHLBI), ADA
LDL-C	<100 mg/dL <70 mg/dL is a therapeutic option	ATP III (NHLBI), ADA
Triglycerides, 200-499 mg/dL; HDL-C < 40 mg/dL	Non–HDL-C <130 mg/dL Increase HDL-C (no set goal)	ATP III (NHLBI), ADA
Prothrombotic state	Aspirin (75-162 mg/d)	ADA
Glucose	HbA_{1c} < 7%	ADA
Overweight and obesity (BMI ≥ 25 kg/m^2)	Lose 10% of body weight in 1 year	OEI (NHLBI)
Physical inactivity	Exercise prescription	ADA
Adverse nutrition	Limit intake of saturated fat, cholesterol, sodium; control carbohydrate and caloric intake; protein, 0.8 g/kg/d if CKD present	ADA, AHA, and NHLBI ATP III, OEI, and JNC 7

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NHLBI, National Heart, Lung, and Blood Institute; ATP III, National Cholesterol Education Program Adult Treatment Panel III; OEI, Obesity Education Initiative Expert Panel on Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.

HEART DISEASE IS A MAJOR KILLER IN DIABETES AND IN PROTEIN LEAKING DN ESPECIALLY

Indication	Test	Comments	Professional Society Recommendation
Typical or atypical chest discomfort Other symptoms that may suggest ischemia • Unexplained dyspnea or fatigue • Jaw, neck, arm, or shoulder discomfort • Abnormal ECG result	Exercise ECG Consider imaging modality for nondiagnostic ECG test result or with pharmacological stress test • Nuclear perfusion scan • Echocardiography Consider pharmacological stress testing for those unable to exercise • Dobutamine • Persantine Coronary angiography • Clinically significant ischemia on noninvasive testing • Diagnostic uncertainty on noninvasive testing	Obtain cardiology consultation for pharmacological stress testing, imaging, or coronary angiography No guidelines have specifically addressed the subset of patients with diabetes and CKD	ADA yes[34] AHA yes[38]
Consider screening for silent ischemia • Patient > 35 years and sedentary with plans to begin a vigorous exercise program • Carotid or lower-extremity atherosclerotic disease	Same approach as above	*Controversial* *Data on improved clinical outcomes is lacking*	ADA yes[34] AHA nc[38]

Abbreviation: ECG, electrocardiogram.


CKD
CVD
Kidney Failure
Heart Failure
End-Stage
Decreased GFR
Progression
CVD Events
Albuminuria
Initiation
CAD, LVH
At Increased Risk
DIABETES
HTN, Age, Family History

WEIGHT AND DM/DN

Physical compression of the kidneys by visceral obesity
RAS activation
Hyperinsulinemia
Sympathetic activation
Overnutrition
Glomerular hyperfiltration
Proteinuria-associated kidney damage
Blood pressure elevation

WHAT TO ASK ABOUT IN DOCTOR'S OFFICE

- Blood pressure goals 130/80 in protein-uric disease
- 140/90 otherwise per JNC-8

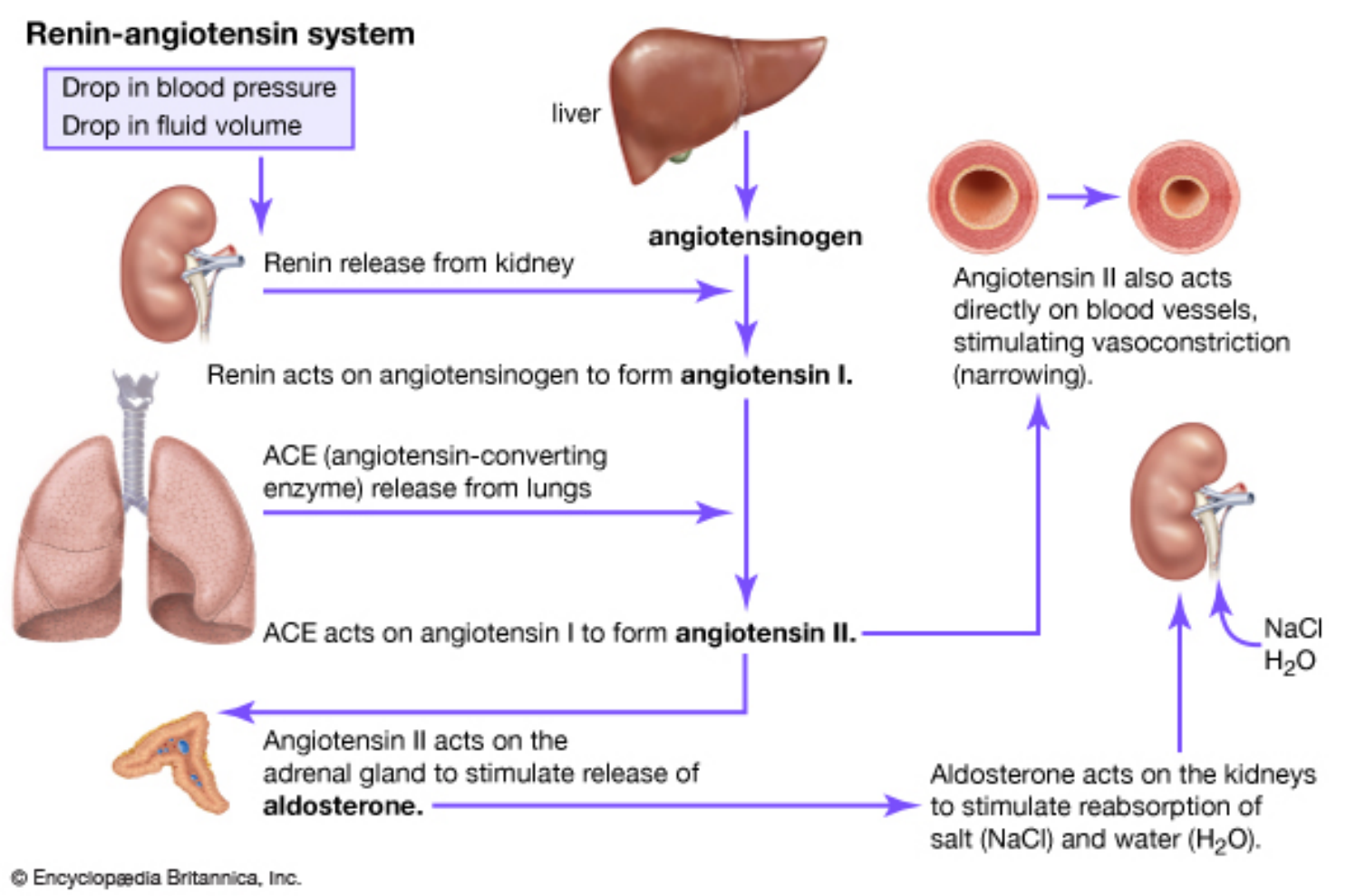
		KDIGO	JNC8
NON DIABETIC CKD	albuminuria <30 mg/d	>140/>90 (1B)	>140/>90 • E for SBP • A for DBP if over 30 • E for DBP if under 30 ACEi or ARB for all CKD regardless of diabetic or proteinuric status
NON DIABETIC CKD	albuminuria 30-300 mg/d	>130/>80 (2D) ACEi or ARB (2D)	
NON DIABETIC CKD	albuminuria >300 mg/d	>130/>80 (2C) ACEi or ARB (1B)	
DIABETIC CKD	albuminuria <30 mg/d	>140/>90 (1B)	
DIABETIC CKD	albuminuria >30-300 mg/d	>130/>80 (2D) ACEi or ARB (2D)	
DIABETIC CKD	albuminuria >300 mg/d	>130/>80 (2C) ACEi or ARB (1B)	

RENAL FUNCTION ASSESSMENT EVERY VISIT

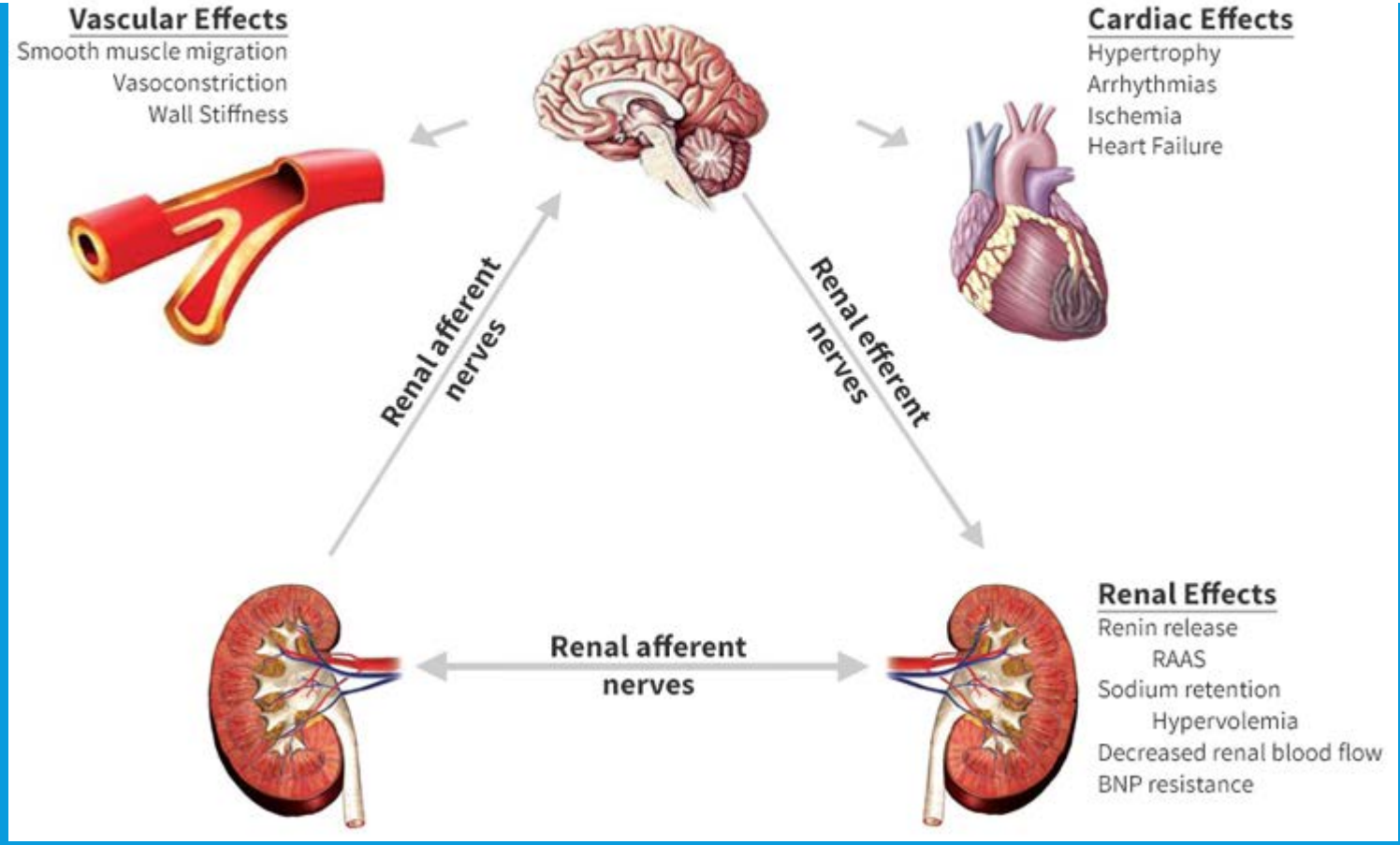
Urine protein assessments (Urine protein/creatinine ratio), (urine albumin/creatinine ratio, 24 hour protein collections).

- Less specific but easily available urinalysis
- BUN and Creatinine
- Cystatin C and other new kidney health markers

RENIN ANGIOTENSIN ALDOSTERONE (RAAS) BLOCKADE



Renal Sympathetic Activation in Hypertension



HOW TO CONTROL PROTEINURIA

- Control blood pressure at above goals (<130/80)
- Renin angiotensin aldosterone system
  - ACE: Lisinopril (end in pril)
  - ARB: Valsartan (end in sartan)
  - Direct angiotensin blockers (rarely used)
- Aldosterone blockers (mineralocorticoid antagonists)
- Calcium channel blockers (CCB non-dihydropyridine class)
  - They don't end in "ine": diltiazem and verapamil

OTHER ASPECTS OF KIDNEY DISEASE

- Lipid control (cholesterol – LDL, HDL, triglycerides)
- Increased risk as above
- Aspirin for prevention of heart attacks (MI)

Vitamin D metabolism

Vitamin D_3
Cholecalciferol
- made in the skin
- found in oily fish, egg yolks, and fortified food

Vitamin D_2
Ergocalciferol
- found in fortified foods, salmon, mushrooms, and egg yolks

Liver
Converts Vitamin D_3 and D_2 to 25-hydroxyvitamin D

25-hydroxyvitamin D
25(OH)D
Calcidiol

Kidney
Converts 25-hydroxyvitamin D to 1,25 dihydroxyvitamin D

Biologically active form

1,25 dihydroxyvitamin D
1,25 $(OH)_2D$
Calcitriol

VITAMIN D AXIS

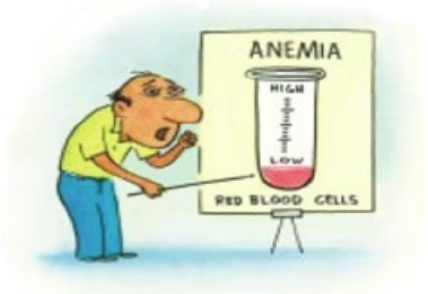
- Many patients with chronic kidney disease (CKD) are vitamin D deficient
- D_2 is sufficient in early disease
- D_3 (active vitamin D) or vitamin D analogues (VDRA) are needed in more severe disease
- Keeping D_2 replete may have beneficial effects on kidneys

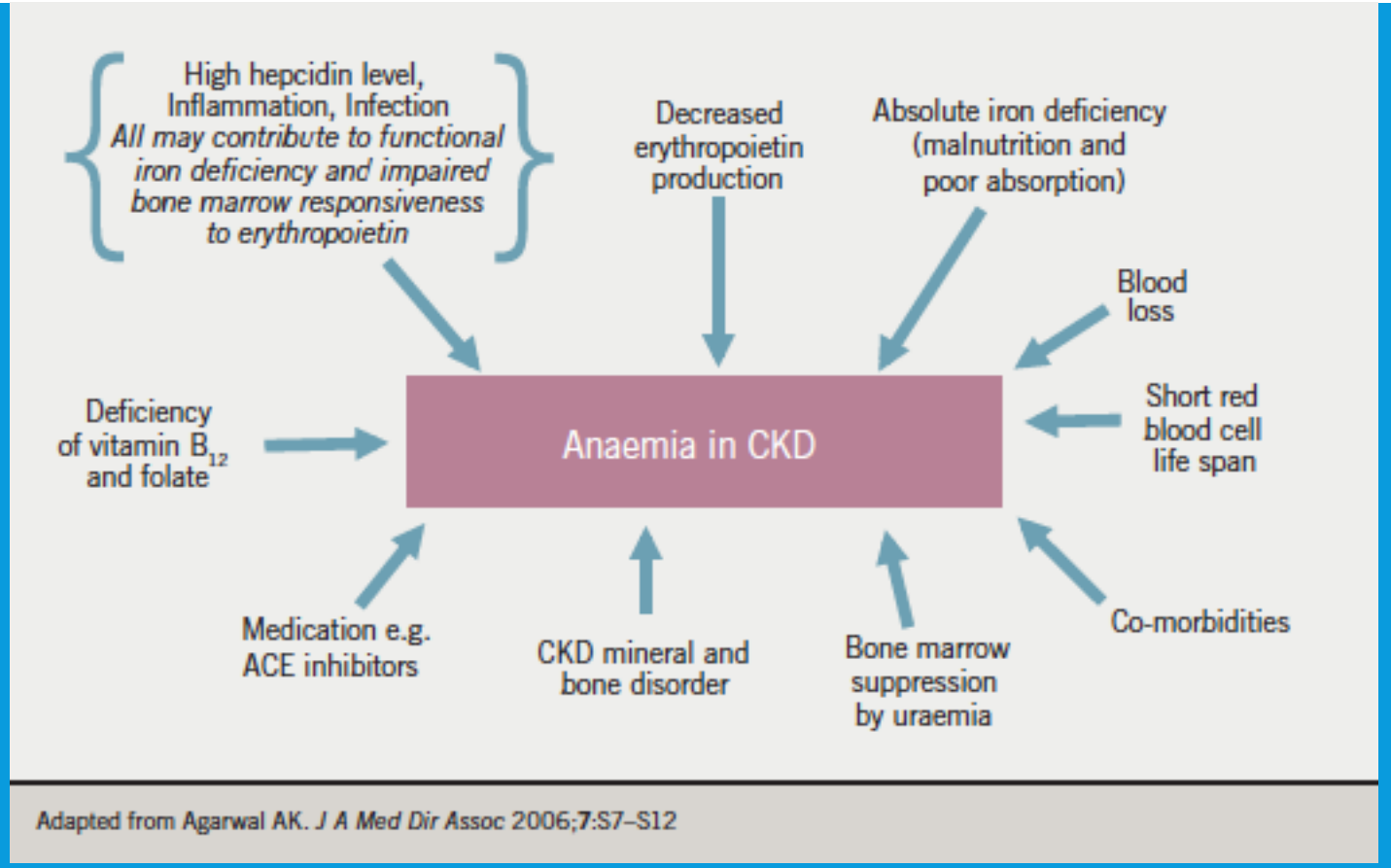
SECONDARY HYPERPARATHYROIDISM

- Vitamin D
- Calcium
- Phosphorous
- PTH (parathyroid hormone) maybe affected by this.
- Poor Phosphorous clearance can result in increased PTH levels in a futile attempt to get rid of excess phosphorous. This results in damage to blood vessels and possible calcification in body.
- This is opposed to primary and tertiary forms of hyperparathyroidism-which are beyond scope of our seminar.

URIC ACID

- Good chronic kidney disease care should also encompass measuring and controlling uric acid which is a risk factor for gout and accelerated kidney function decline.
- Allopurinol and febuxostat are agents that can control this within goal
- Not used in gout flares (other agents such as corticosteroids, colchicine, and if no kidney disease NSAIDS can be used)





Adapted from Agarwal AK. *J A Med Dir Assoc* 2006;**7**:S7–S12

CONTROLLING ANEMIA

- Poor control of anemia can result in worsening renal function due to higher likelihood of ischemia.
- Kidney disease results in anemia from erythropoietin deficiency and iron deficiency and/or iron unavailability due to inflammation (anemia of chronic disease)
- Erythropoeitin in its synthetic form(s) can be given to correct this problem

MAINTAINING A HEALTHY PROTEIN INTAKE

- Though protein can stress kidneys and force need to increase GFR
- A complex relationship exists between protein intake and progression in diabetics
- Low protein diets may be easier on kidney but protein calories are replaced by carbohydrates worsening diabetic and hypertensive control
- Moderate protein intake is acceptable in chronic kidney disease-though some people (Kalantarzadeh et.al.) advocate very low protein diets
- On dialysis this changes and a higher protein diet is advocated to avoid malnutrition
- In all cases low albumin or malnutrition increases risks for chronic kidney disease and dialysis patients tremendously

MAINTAINING ACID BASE BALANCE

- Serum bicarbonate is part of buffer system to keep body's pH balance
- Kidneys usually regulate
- As kidneys become less effective in kidney disease organic acids (phosphate sulfate build up)
- This makes blood acidic – called a metabolic acidosis (since its due to kidneys and not lungs)
- Fixing this usually involves citrate or sodium bicarbonate- baking soda
- It has been shown control of acid base level with target of bicarbonate of 20 meq/L or more has been show to have effect of slowing down decline of kidney function in chronic kidney disease

PHOSPHOROUS

- A very dangerous relationship exists between kidney disease, cardiovascular health and phosphorous
- High phosphorous drives up PTH, FGF-23 and other really dangerous markers
- Clinical calcification is rare but can be deadly.
- Even with high normal phosphorous and calcium increased risk of heart disease occurs
- Goal is to control phosphorous with binders on dialysis but increasingly also with chronic kidney disease

PHOSPHOROUS AND RISK OF DEATH

Table 2. Age- and Sex-Adjusted Cumulative Incidence Rates of CVD According to Quartiles of Serum Phosphorus and Serum Calcium Levels*

Quartile	Events, No.	Patients at Risk, No.	Age- and Sex-Adjusted 20-Year Incidence of CVD, % (95% CI)
Serum Phosphorus Level			
1	137	815	16.4 (13.2-19.6)
2	140	868	17.9 (14.6-21.2)
3	129	915	17.5 (14.2-20.8)
4	118	770	21.1 (17.1-25.0)
Serum Calcium Level			
1	132	816	19.4 (15.7-23.0)
2	142	1023	16.4 (13.4-19.4)
3	102	698	17.2 (13.7-20.7)
4	148	831	19.9 (16.4-23.5)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease.
SI conversion factor: To convert serum calcium to millimoles per liter, multiply by 0.25.
*Quartile cutoff points for serum phosphorus level are shown in Table 1. Serum calcium level quartiles (in milligrams per deciliter) were 1 (6.1-9.3), 2 (9.4-9.6), 3 (9.7-9.8), and 4 (9.9-11.2).

FGF 23 AND RISK OF DEATH

Table 3. Levels of cFGF-23 and Associated Risk of Death within Serum Phosphate Quartiles in the Case–Control Sample.

Phosphate Level	Median cFGF-23 Level (interquartile range)		P Value	Odds Ratio for Death (95% CI)*
	Patients Who Died (N = 200)	Patients Who Survived (N = 200)		
	reference units per milliliter			
All levels	2260 (1196–5296)	1406 (989–2741)	<0.001	1.5 (1.2–1.8)
<3.5 mg/dl	1790 (1175–3941)	1148 (927–2169)	0.008	1.8 (1.2–2.8)
3.5–4.4 mg/dl	2049 (1109–4865)	1131 (893–1629)	0.003	1.8 (1.2–2.7)
4.5–5.5 mg/dl	2207 (1186–5238)	1499 (1044–2262)	0.02	1.8 (1.1–3.0)
>5.5 mg/dl	3541 (1871–10,491)	2686 (1527–6210)	0.29	1.1 (0.7–1.6)

* The odds ratios are for a one-unit increase in the natural log-transformed cFGF-23 level in all 400 patients and in each quartile of 100 patients.

http://www.nejm.org/doi/full/10.1056/NEJMoa0706130?viewType=Print&viewClass=Print

AVOIDING DRUGS TOXIC TO THE KIDNEYS

- NSAIDs
- Toxic medications to kidneys (antibiotics, certain blood pressure medications and diuretics ***if*** used inappropriately)
- Certain herbal medications
- Heavy metal exposure
- ?certain eye injections? (stay tuned)
- Any drug in wrong dose can be dangerous if dosing is not correct for level of kidney function

KLOTHO

- FGF 23 and klotho are new markers that we have found correlate with kidney disease
- This is very new but suffice it to say that premature kidney damage is associated with premature aging
- Klotho is known to play a role in aging in mice
- Klotho for the classically inclined is known to be one of the three fates from greek mythology who weaves the thread of life
- This link between the kidney health and aging is not lost on anyone I am sure

LIFE AND DEATH ARE IN THE KIDNEYS?

THANK YOU!

- Questions
- For more information please visit UCLA CORE KIDNEY WEBSITE
- https://www.uclahealth.org/core-kidney/
- These slides will be on there too under patient education… thanks!