Diabetic Nephropathy

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Introduction

- Diabetes Mellitus is one of the most common diseases in the primary care office.
- There are approximately 1 million Type 1 diabetics in the US, with about a 50% risk of developing renal disease.
- There are approximately 8 million Type 2 diabetics with about a 20% risk of developing renal disease, which works out to about 2,000,000 people in the US with renal failure due to diabetes.

Progression to Dialysis

- About 700,000 Americans annually are diagnosed with diabetes, which eventually translates into about 25,000 people annually who start dialysis due to diabetes. (USRDS 2014).

Progression of Diabetic renal disease

- Stage I Hyperfiltration (at initial diagnosis)
- Polyuria, glycosuria, Microalbuminuria 20-200 mg/day.
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- Stage II Silent stage
- Microalbumin normalizes, normalized GFR
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- Stage III Incipient Nephropathy (REVERSIBLE)
- Structural changes are occurring
- Hypertension
- Microalbuminuria recurs
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- Stage IV Overt Nephropathy
- Starts around 15-17 years
- Clock starts ticking to end stage in 5 years
- Proteinuria is fixed and not reversible
- Hypertension, Type IV RTA with hyperkalemia
- Declining GFR

Other causes of Renal Dysfunction in Diabetes

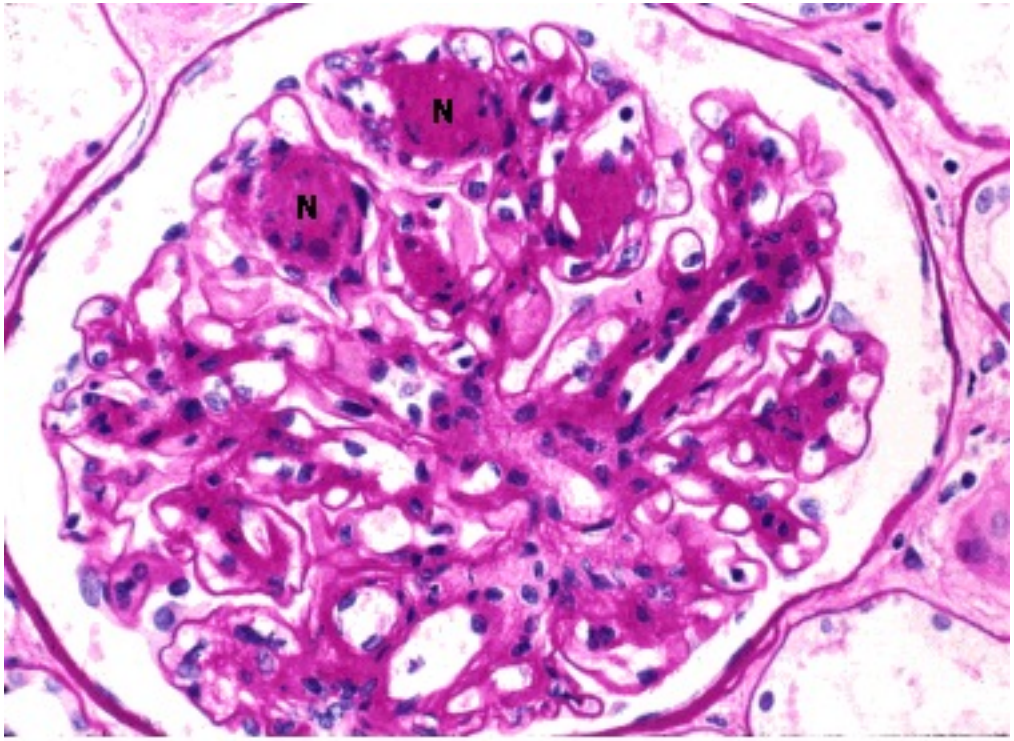
- Not all Diabetic Nephropathy is Diabetic Nephropathy! Consider other possibilities:
- Neurogenic bladder
- Pyelonephritis
- Papillary Necrosis
- ACE inhibitors/other drugs
- Other Glomerular diseases
- Other Proteins - especially myeloma.

Pathogenesis

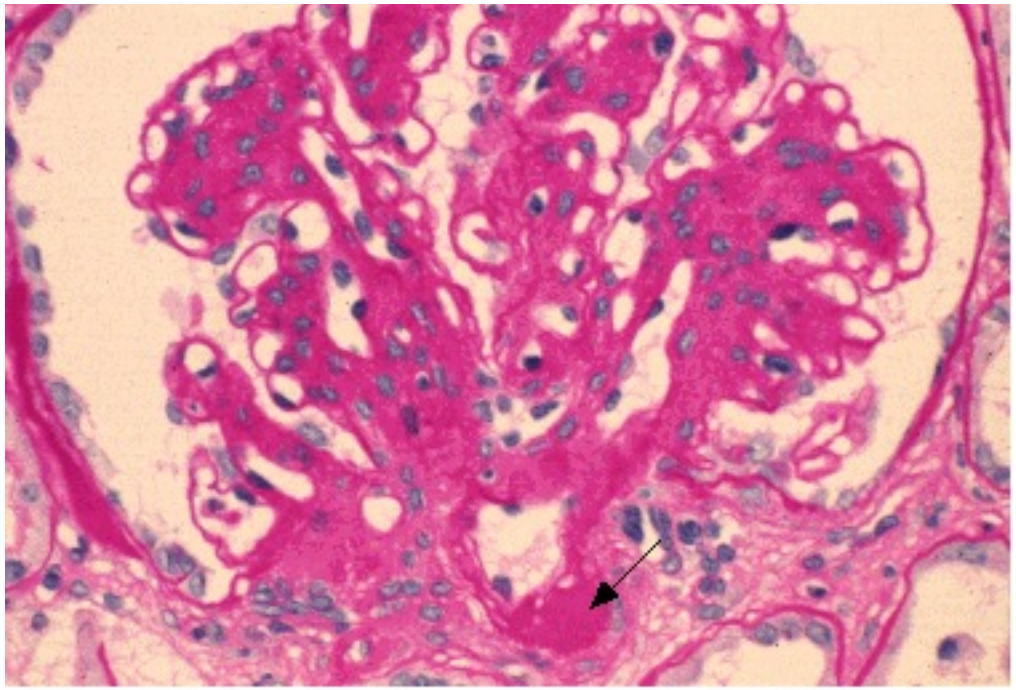
- Multifactorial but increasingly well worked out:
- - Genetic predisposition - Metabolic syndrome includes the following features: families with a diabetic have a higher risk of high blood pressure, Gout, and high cholesterol. Once one of these problems crops up, the others are more likely to show up down the road.
- - Intraglomerular Hypertension[7]
- - Hyperglycemia
- = Glycosolated End Products (GEP's or AGE's)[1]

Pathogenesis

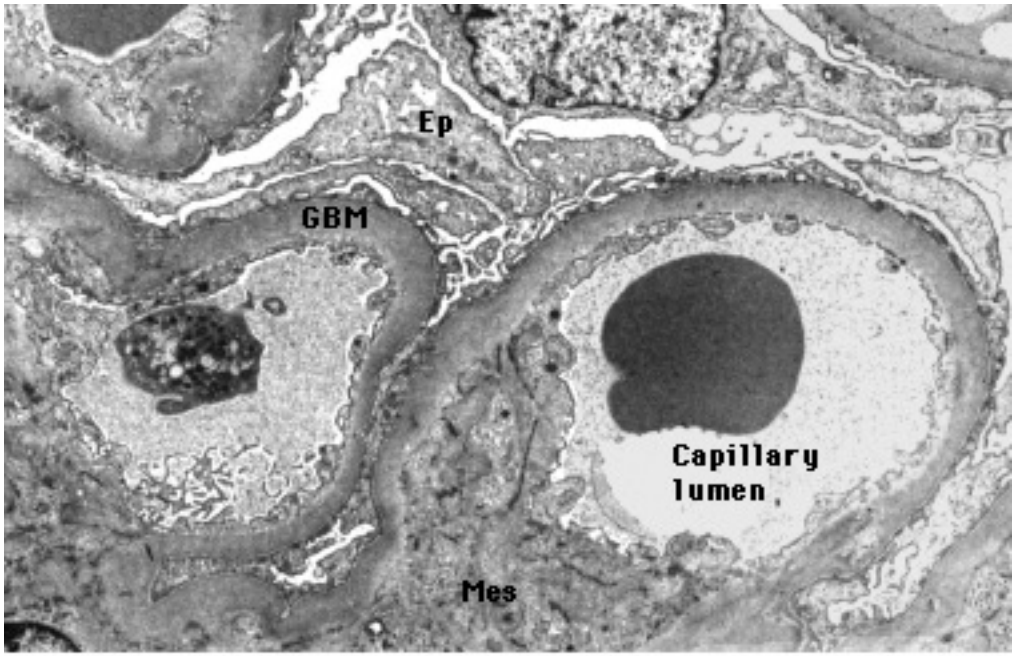
- GEP's result in :
- Kimmelstiel Wilson Nodules and sclerotic kidney with normal size
- Nerve damage
- Heart wall thickening and stiffening, which leads to swelling
- Dermopathy - the thickened smooth skin that heals poorly
- Vascular Thickening and weakness - leads to retinal vessel hemorrhage, strokes and heart attacks.
- Microalbuminuria correlates with mesangial expansion and GBM thickening.



Diabetic nephropathy Light micrograph showing diffuse and nodular (N) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis. Courtesy of Helmut Rennke, MD.

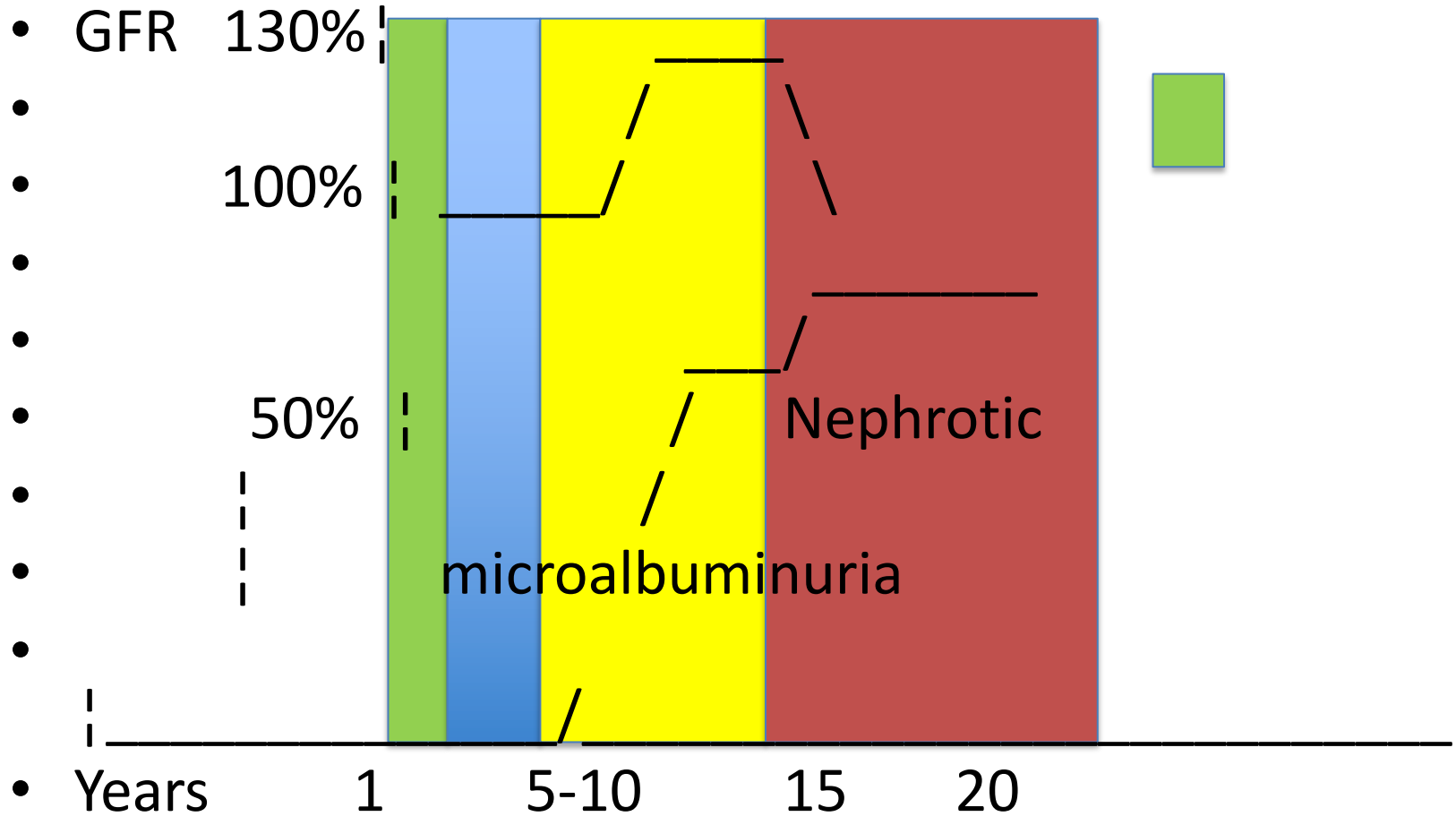


Advanced diabetic glomerulosclerosis Light micrograph in advanced diabetic nephropathy shows diffuse and nodular mesangial expansion and characteristic hyaline thickening of the arteriole at the glomerular hilum (arrow). Although not shown, diabetes typically affects both afferent and efferent arterioles; in comparison, only the afferent arteriole is usually involved with hypertensive injury. Courtesy of Helmut Rennke, MD.



Basement membrane thickening in diabetic nephropathy Electron micrograph in diabetic nephropathy shows a 2 to 3 fold increase in the thickness of the glomerular basement membrane (GBM). Mes = mesangium; Ep = epithelial cell. Although not seen, the mesangium is also expanded by basement membrane-like material, a process that contributes to nodule formation and glomerulosclerosis. Courtesy of Helmut Rennke, MD.

Clinical stages



Treatment

- Prevent GEP formation in the early stages! Time is kidney!
- Attack High blood pressure
- Keep blood sugar normal as possible.
- Stage III with microalbuminuria is still reversible - Stage IV too late.
- Can reduce rate of decline by 5-6 ml/min/year[2]

Proof that Diabetic Nephropathy is reversible.

- 1. Correction of microalbuminuria with treatment using ACEi / ARBs
- 2. Renal Transplant case - 37 y.o. diabetic donor kidney with proteinuria and normal renal function. biopsy of the allograft kidney showing extensive sclerosis which resolved within 6 months in normal recipient.
  - (Abouna et al. Lancet 1983; 2: 1274-6.)

Treatment Guidelines

- **Primary Prevention:**
- Control BP aggressively - Target 140/80 or LESS
- Control Blood Sugars - DCCT[3]
- Target HgA1c <8.0 Correlates with accuchecks 80-150
- Used insulin pump
- Hypoglycemia 2/week accepted as the price of doing business
- Achieved 50% reduction in retinopathy and microalbuminuria.

Treatment Guidelines

- **Secondary Prevention**: After Microalbuminuria detected
- Protein restricted diet
- 0.8 gm/kg/day
  - (easiest way is to minimize red meat in diet)
- Add or switch to ACE inhibitors[4],
- or Cardizem or Coreg if hyperkalemic
- or possibly Amlodipine
- not short acting nifedipine.
- Add Angiotensin Receptor Blocker too! [7]

Treatment Guidelines

- Overt Nephropathy not reversible, but progression can be slowed by BP control and glycemic control.
- Refer to nephrologist as early as possible to allow for dialysis education and preparation[5].
- Try to Avoid oral hypoglycemic agents once the creatinine is over 3.0
- Glimipizide, Januvia may be used safely with close monitoring
- Glipizide, Actos, Avandia, and others also have been used and can be done safely if careful
- Anticipate reduced requirement for insulin
  - (average 10-20 units/day once pt on dialysis)
- Avoid Metformin in creatinine over 2.0, or GFR less than 30 ml/min

SGLT-2 Inhibitors

- sodium-glucose cotransporter 2 (SGLT2) inhibition leads to elimination of glucose—about 80 g/day—from the body by the kidney. Removal of glucose, salt, and water results in positive effects on the heart and the circulatory system, and prominent reductions in cardiovascular and all-cause mortality.

SGLT-2 Inhibitors

- EMPA-REG OUTCOME study 2015
- Improved risk for development or reduction in macroalbuminuria,
- Reduced rate of doubling of serum creatinine,
- Reduced need for renal replacement therapy, or dialysis.
- The relative risk for this composite was reduced by 39% in patients receiving empagliflozin

SGLT-2 i reduce CV risk

Table. Summary of cardiovascular and kidney outcomes in randomized clinical trials of SGLT-2 inhibitors

Study	N	Inclusion criteria	Intervention	Follow-up	Main outcomes
EMPA-REG OUTCOME[6]	7,020	Patients with T2DM and established CV disease	Empagliflozin (10 mg/dL or 25 mg/dL) vs. placebo	3.1 years	• CV death, non-fatal MI or stroke • Hospitalization for HF • Doubling of SCr, dialysis or kidney death
CANVAS[7]	10,142	Patients with T2DM, age at least 30 years with established CV disease or age at least 50 years with at least two additional CV risk factors	Canagliflozin (100 mg/dL or 300 mg/dL) vs. placebo	2.4 years	• CV death, non-fatal MI or stroke • Hospitalization for HF • At least 40% eGFR decline, dialysis or kidney death
DECLARE-TIMI-58[9]	17,160	Patients with T2DM, age at least 40 years with established CV disease or age at least 55 years (men) or at least 60 years (women) with at least one additional CV risk factor	Dapagliflozin (10 mg/dL) vs. placebo	4.2 years	• CV death, non-fatal MI or stroke • Hospitalization for HF • At least 40% eGFR decline, dialysis or kidney death
CREDENCE[10]	4,401	Patients with T2DM, age at least 30 years and overt nephropathy defined as eGFR of 30 ml/min/1.73m^2 to 90 ml/min/1.73m^2 and UACR at least 300 mg/g	Canagliflozin (100 mg/dL) vs. placebo	2.6 years	• Doubling of SCr, dialysis or death from CV or kidney causes • CV death, non-fatal MI or stroke • Hospitalization for HF

Abbreviations: CI=confidence interval; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; MI=myocardial infarction; SCr=serum creatinine; T2DM=type 2 diabetes mellitus; UACR=urinary albumin-to-creatinine-ratio

Source: Panagiotis I. Georgianos, MD, PhD; Rajiv Agarwal, MD, MS

SGLT2 inhibitors may reduce risk for AKI

- Meta-analysis of 18 studies
- SGLT2i had lower risk for AKI than placebo
  - OR 0.76
- SGLT2i had lower risk for AKI than
  - GLP-IRAs (OR 0.79)
  - DPP-4inhibitors. (OR 0.68)
    - Zhao M et al. Clin J Am Soc Nephro 2020 10.2215

Gliflozin info

- Dapagliflozin may decrease risk for progression of FSGS, and also reduced risk for cardiovascular events and mortality in FSGS patients.
    - ERA-EDTA 58th congress, data from the DAPA-CKD trial
- Renoprotective effect of the Gliflozins due to reduced volume, and can be measured by increases in hematocrit.
    - Data from EMPA-REG outcome study.

Semaglutide for Diabetic Kidney disease

- Study presented at the ERA-EDTA 58th congress in 2021.
- Monitored 122 patients with GFR 15-60, or proteinuria.
- Over 12 months, semaglutide reduced albuminuria by 50% and renal function remained stable.
- Drug discontinued in 5% of patients mainly due to GI side effects.

Treat Hypertension

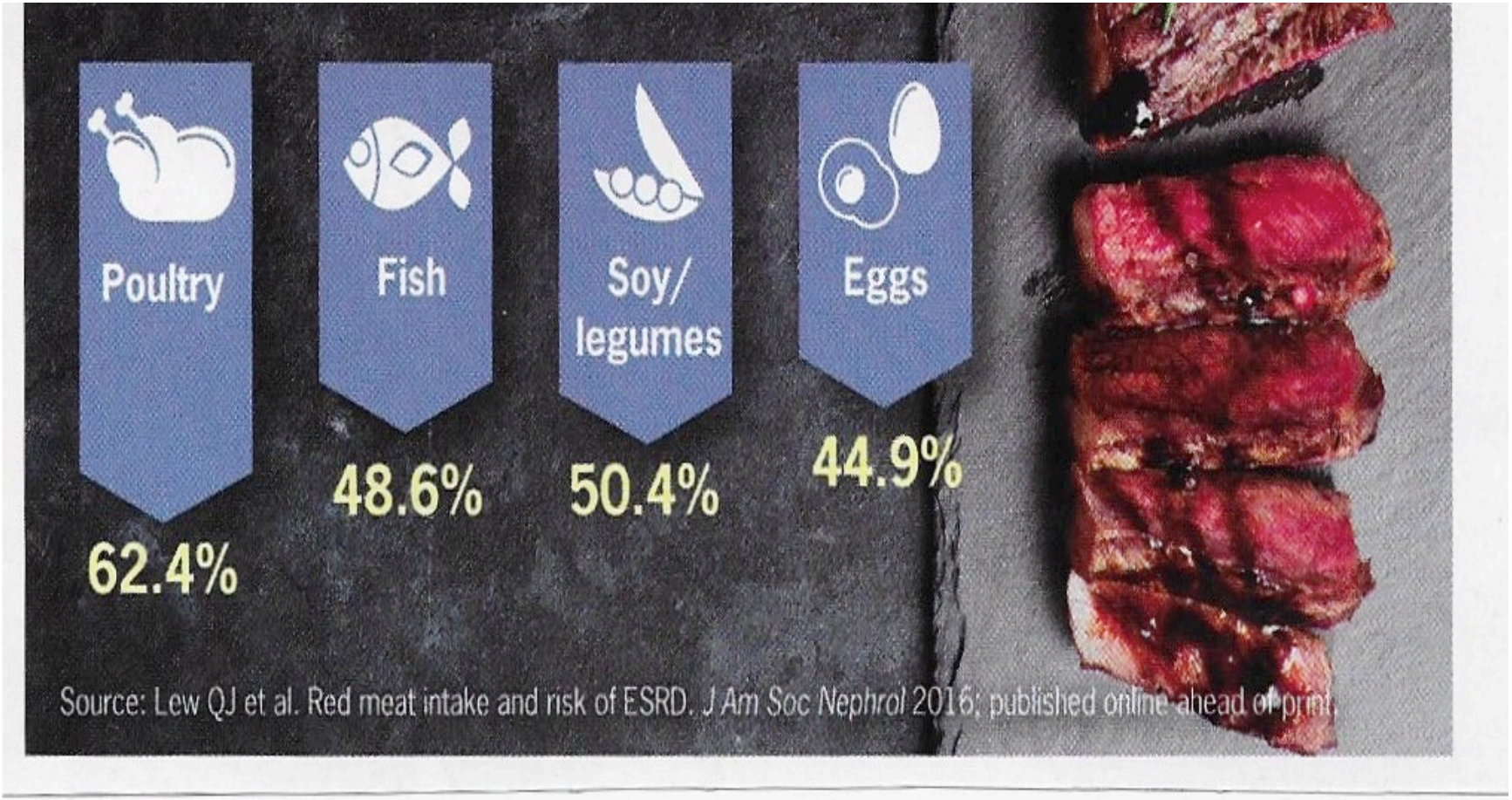
- Preferential use of ACE inhibitors and/or Angiotensin Receptor blockers (ARB)
- These drugs can lead to hyperkalemia, which can be treated with agents to lower potassium and allow more time on the ACE/ ARB
  - Kayexalate, Lokelma, Veltassa are potassium exchange agents

Treat Hypertension

- Resistant Hypertension becomes more common as the nephropathy progresses:
  - No albuminuria: 1.2%
  - Microalbuminuria 4.7%
  - Macroalbuminuria 28.1%
  - Dialysis patient 36.6%
  - After transplant 26.3%

  - RENAAL, study, IDNT study

Dietary Changes May Lower Risk



ESRD Risk Reductions by replacing 1 Serving of red meat per day

I hate Microsoft

- Previous slide:
  - Lew QJ et al. Red Meat intake and risk of ESRD. J Am Soc Nephrol (JASN) 2016.
  - Published online ahead of print.
  - As seen in Renal and Urology News December 6 2016
  - www.renalandurologynews.com

New markers that impact renal disease progression

- Diabetes Care May 2019
  - Pyruvate Kinase M2 (PKM2) is much more prevalent in glomeruli and plasma of patients who do not develop diabetic kidney disease.
  - Amyloid Precurser Protein (APP) also much more prevalent, but this is also assoc with higher risk for Alzheimer's.
    - From medscape May 30 2019.

Update on the Diabetes Epidemic

- Published May 28 2019 in *BMJ Open Diabetes Research and Care* by Stephen R. Benoit, MD, and colleagues from the Division of Diabetes Translation, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia.
- After nearly a two-decade increase in both prevalence and incidence of diagnosed diabetes in the United States, the prevalence — the number of people living with diagnosed diabetes — has stabilized for the past 8 years and there has been a decrease in incidence, driven mostly by that seen among non-Hispanic whites.
- This reduction means new cases declined by 35% from 2008 to 2017, a sign, perhaps, that efforts to stop the nation's diabetes epidemic are working, say the researchers.
    - From Medscape May 30 2019

References

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- 4. Lewis et al, for the Collaborative Study Group. The Effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. NEJM 1993;329:1460-8.
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- 7. Price, Porter et al. The Paradox of the Low-Renin State in Diabetic Nephropathy.
- JASN 10: 1999, 2382-2391.