Diabetes on Renal Biopsy - Current Appraisal

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Renal biopsy in patients with diabetes

- On renal biopsy a review of 48 studies revealed high % (up to >80%) of dual disease superimposed on DM or non-diabetic (ND) entities
- ~30–40% of patients with diabetes with at least 10 years of history of disease usually present with a frank DN
- ~3% of newly diagnosed DM have renal involvement
- 20-30% of Type I diabetes will develop DN over a lifetime
- 2012 about 347 million people had DM
- Most common cause of ESRD requiring dialysis

DM on renal biopsy

- 23.5% (620 biopsies) had DN among 2,642 renal biopsies
- ~50% of these patients had stage 4-5 CKD
- 37% had DN alone
- 36% had NDRD alone and 27% had DN + NDRD
- ATN (43%), IgA (7%), FSGS (13%) and hypertensive nephrosclerosis (17%)
- >12 year diabetes duration was the best predictor for DN alone (sensitivity 58%, specificity 73%)

Columbia University, NY: Sharma S etal CJASN, 2013
Arkana Laboratories: Jan 2014-Apr-2015
~15,000 renal biopsies

- 2,739 renal biopsies from diabetic patients (~18%)
- 144 biopsies performed for significant proteinuria (~6%)
- The majority of biopsies showed diabetes only.
- ~10% had other superimposed glomerular disease
- Disease breakdown is currently pending
When is renal biopsy performed in diabetic patients?

- If presentation is atypical
- Hematuria
- Hematuria and proteinuria (active urine)
- Diabetes of less than 5 years duration
- Positive serological tests (ANA, ANCA) or abnormal urine tests (UPEP)
- Rapid fall in GFR
- No retinopathy
- AKI
Diabetic (Kimmelsteil-Wilson) Nodules are characteristic but not always present

K-Ws stain positive (black) with silver stain. Silver negative nodules are not diabetic. DD includes: LCDD, Fibrillary glomerulopathy, immunotactoid GP, amyloidosis, smoking, gout and late stage MPGN, idiopathic nodular glomerulosclerosis (ING)
K-Ws represent mesangial remodeling and failed resolution of ↑ matrix deposition caused by sustained hyperglycosuria
Classification of Diabetic Nephropathy (DN)

Class I Mild or nonspecific LM changes and EM-proven GBM thickening (≥395-430 nm)

IIa Mild mesangial expansion ≥ 25% of the observed mesangium

IIb Severe mesangial expansion

III Nodular sclerosis (Kimmelstiel–Wilson) at least 1 lesion

IV Advanced diabetic glomerulosclerosis

Global glomerular sclerosis in 50% of glomeruli

Lesions from classes I through III

Pathologic classification of diabetic nephropathy.

Marked GBM thickening and linear IgG and Albumin staining are unique features of diabetes (normal GBM~350nm)

Diffuse podocyte injury in diabetes
Early Type 2 diabetes in children and young adults with metabolic syndrome
Renal biopsy from an 18 year-old female with proteinuria with history of diabetes mellitus

Albumin
IgG
Armanni-Ebstein tubulopathy
Incidence of a 2\textsuperscript{nd} disease on diabetes is difficult to access accurately. A short list in our material:

- IgA nephropathy
- IgA dominant infection related GN
- C3 glomerulopathy and post-streptococcal
- Membranous Glomerulopathy
- FSGS
- MPGN secondary to HEPC
- Light chain deposition disease (LCDD)
- Fibrillary glomerulopathy
- ANCA vasculitis and anti-GBM
- Minimal change disease
- Thin Basement Membrane Disease
- Collapsing glomerulopathy
- Acute interstitial nephritis
- Calcium Oxalate nephropathy
- Cholesterol emboli
- Smoking related nodular glomerulosclerosis
- TMA
- Cryoglobulinemia
- Dense deposit disease
69 year-old white man with acute RF on CKD stage III h/o diabetes type 2, HTN, gout and recent right great toe infection treated with antibiotics. His sCR is 6.7mg/dl; on admission sCR was 13.7mg/dl. His baseline sCR: 1.4-1.6mg/dl

Acute proliferative GN with IgA dominant immune complex deposits
Thick GBM and subepithelial immune type deposits
IgA Spectrum in Diabetes

- A total of 132 patients-55 with outcome data
- Seventy-three (55.3%) patients had no proliferative glomerular changes and no clinical history of infection and were most consistent with IgA nephropathy on DN
- 19 (14.4%) showed proliferative glomerular changes, had a history of infection, and were most consistent with IgA-dominant infection-associated glomerulonephritis.
- Forty (30.3%) patients showed a mixture of these findings and did not fit into either category
- Overall poor prognosis, with 59% of all respondents proceeding to renal replacement therapy or death over an average of 23 (range, 4-54) months


Defining the spectrum of immunoglobulin A-dominant/codominant glomerular deposition in diabetic nephropathy. Cossey LN, Messias N, Messias E, Walker PD, Silva FG.
Fibrillary Glomerulopathy

- It is defined by EM finding of haphazardly arranged, fibrils measuring 10 to 30 nm in thickness
- Congo red negative amyloidosis
- Some have crescents mimicking vasculitis
- Mean age at diagnosis is 53 years
- 25% have an underlying malignancy
- 15% have autoimmune disease
- Prognosis is poor
- >400 cases in our lab, several cases were superimposed on diabetes. A good number in our series have underlying diabetes

_Fibrillary glomerulonephritis: a report of 66 cases from a single institution._
54 year-old African American man with DM, HTN HEPC, renal dysfunction sCR 2.9mg/dl and proteinuria 6 gm/24hours. Serologies are positive for ANA and hepatitis C. Complement levels are normal.
Fibrillar intramembranous and mesangial deposits
Diabetes and Collapsing Glomerulopathy, likely ischemic change, not a 2\textsuperscript{nd} disease

Salvatore SP. Nephrol Dial Transplant. 2014
Clinical diabetes without diabetic nephropathy
Diabetic nephropathy without clinical diabetes

- 65 year old woman with h/o diabetes type 2, HTN, and acute renal failure
- 85 year-old African American female with CKD, HC and nephrotic proteinuria with creatinine 2.1 mg/dL. Glucose at 104 mg/dl. No clinical diabetes

No diabetes, but severe arterionephrosclerosis
prediabetic state, gout, hyperuricemia, smoking can cause nodular glomerulosclerosis
Strong linear IGG staining in nodular glomerulosclerosis with weak Albumin staining: Anti-GBM-like GN mimics Diabetes

The patient is a 37 year-old woman with history of CKD stage IV, CR 2.3 mg/dl. She has history of hypertension, diabetes and obesity, retinopathy, neuropathy and nephropathy

Batal et al CKJ 2014
Diabetes presenting with nephrotic syndrome

- A subset of patients with diabetic nephropathy develop proteinuria >3.5 g/day, hypoalbuminemia, hypercholesterolemia, and peripheral edema usually after a long period of subnephrotic proteinuria.
- Podocyte injury is very frequent on renal biopsy and may relate to acute onset of proteinuria and accelerated progression of DN.
- The question on renal biopsy: is this a podocytopathy, e.g., MCD superimposed on diabetes or the diabetic injury itself?
74 year old man with diabetes, HTN and recent onset proteinuria 12 grams/24hrs

Diffuse foot process effacement c/w minimal change on diabetes
The podocyte in diabetes: Hypertrophy, Binucleation, detachment in Bowman’s space
Binucleated podocytes
Trinucleated podocyte in diabetes
Tetranucleated podocyte
Detached podocytes
Multinucleated podocytes: a form of podocyte loss - Mitotic Catastrophe (MC)

- Thought to be a failed attempt of podocyte regeneration
- May occur abruptly and manifest with acute onset nephrotic syndrome in diabetes
- May be the turning point leading to progressive disease in diabetes
- Pharmacologic manipulation to deter MC may be possible


Diabetic glomerular microaneurysms result from focal mesangiolysis and bleeding representing failed mesangial repair needed to stabilize the glomerulus

Suárez-Álvarez B, Liapis H, Anders HJ. [Links between coagulation, inflammation, regeneration, and fibrosis in kidney pathology](Lab Invest. 2016)
33 year old man with AKI, h/o DM

Early diabetes and microangiopathic injury

Fibrin thrombi
Endothelial injury in diabetes

Summary

• The pathologic spectrum in diabetes is increasing
• Early diabetes type 2 in the young, pre-diabetics, metabolic syndrome not seen before, is on the rise
• IgA dominant infection related GN, Fibrillary glomerulopathy and diabetic podocyte injury are increasingly recognized as 2nd diseases on diabetes
• New investigations into the pathogenesis of diabetic glomerular injury reveal novel targets for halting disease progression including: podocyte hypertrophy and podocyte loss, glomerular endothelial injury and aggressive mesangial remodeling