Diabetic nephropathy

Budapest Nephrology School
August 28th, 2018
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Disclosures

- None

Learning Objectives

- Learn about the causes and consequences of the staggering rise of diabetes and diabetic nephropathy (DNP).
- Familiarize with the pathologic manifestations and classification of DNP.
- Explore the clinico-pathologic aspects of kidney biopsies in diabetic patients.
- Not everything that shines is gold. Mimickers and copy-cats.

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Learning Objective 1

Learn about the causes and consequences of the staggering rise of diabetes and diabetic nephropathy (DNP).

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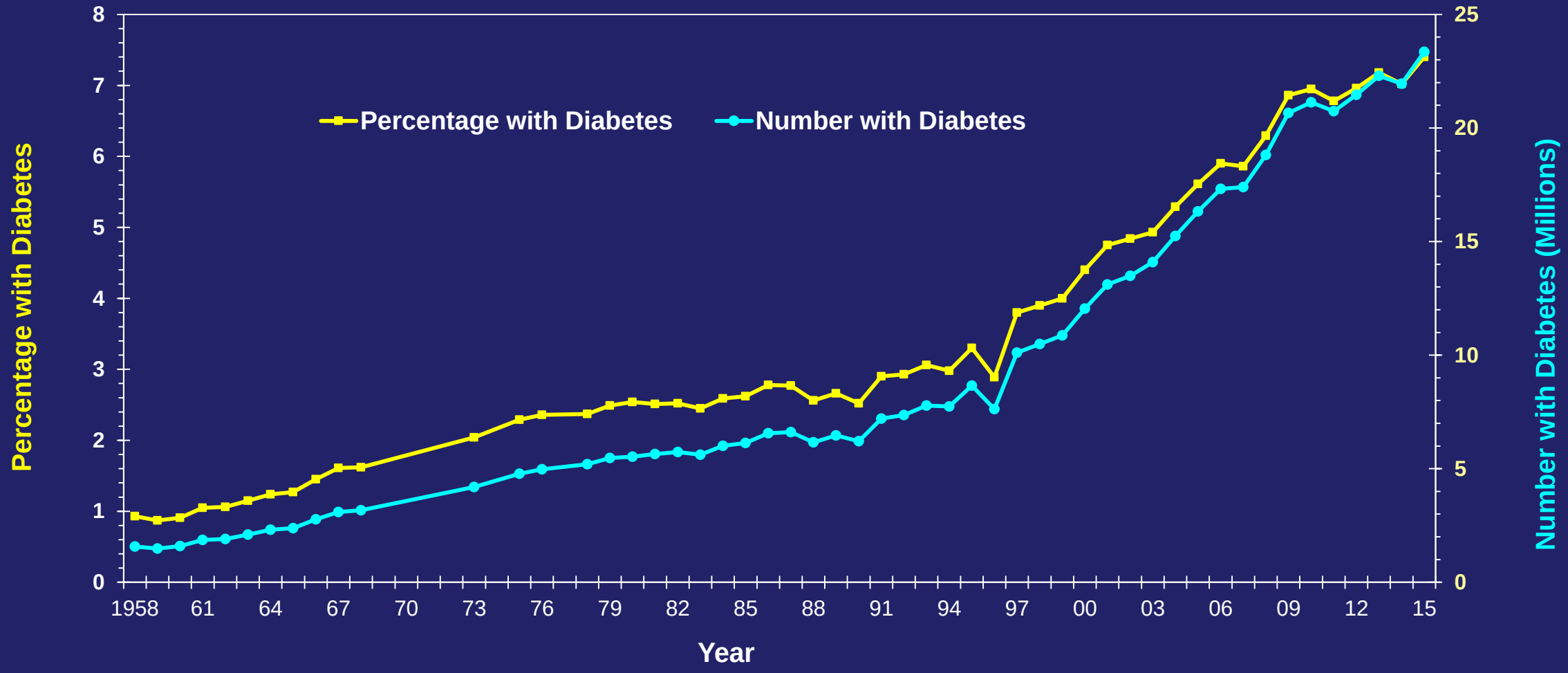
Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2015



CDC's Division of Diabetes Translation. United States Diabetes Surveillance System available at http://www.cdc.gov/diabetes/data

Diabetes prevalence in the US

- 29.1 million people have diabetes, but 8.1 million may be undiagnosed and unaware of their condition
- 1.4 million new cases of diabetes are diagnosed every year
- Type 2 diabetes accounts for about 90 to 95 percent of all diagnosed cases of diabetes in adults
- Cases of diagnosed diabetes cost an estimated $245 billion in 2012

NIDDK/CDC Data

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Risk factors to develop diabetes

- older age
- *excess weight, particularly around the waist*
- family history
- certain ethnicities
- *physical inactivity*
- *poor diet*

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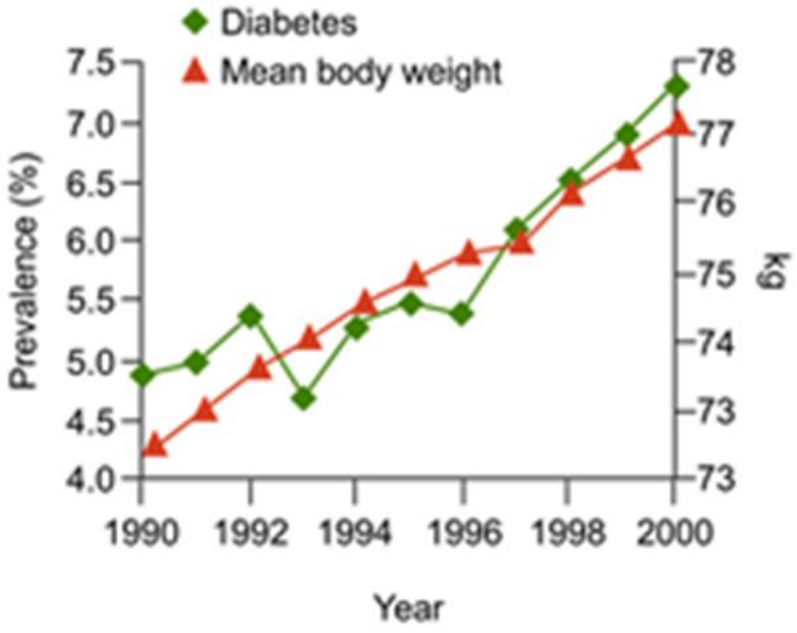
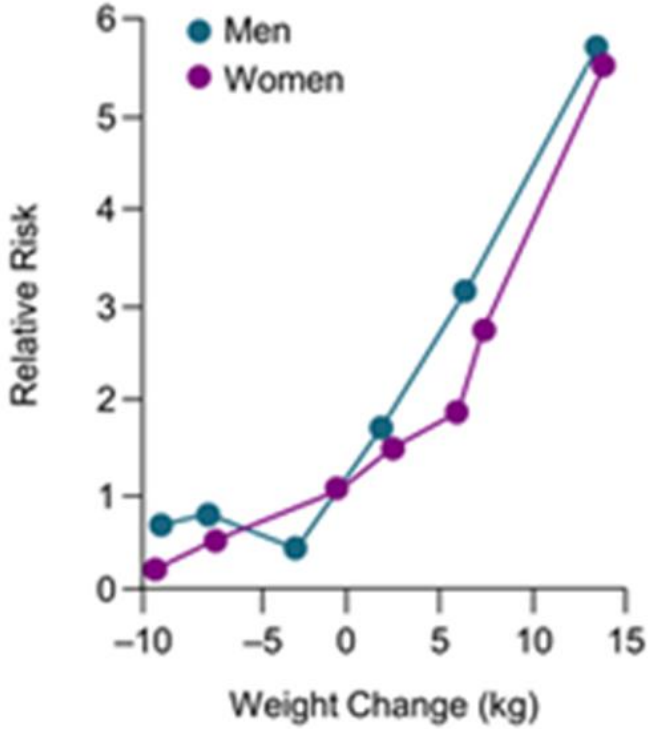
Relationship between body weight and diabetes

Relationship Between Increasing Body Weight and Diabetes Prevalence: 1990–2000



Relationship Between Weight Gain in Adulthood and the Risk of Type 2 Diabetes in Men and Women



Haffner SM. *Obesity (Silver Spring)*. 2006;14(suppl 3):121S–127S.

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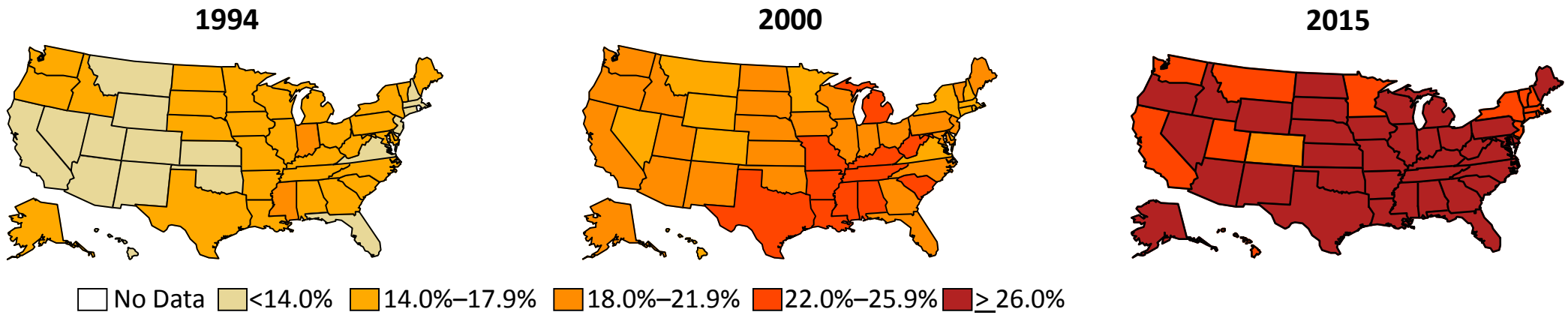
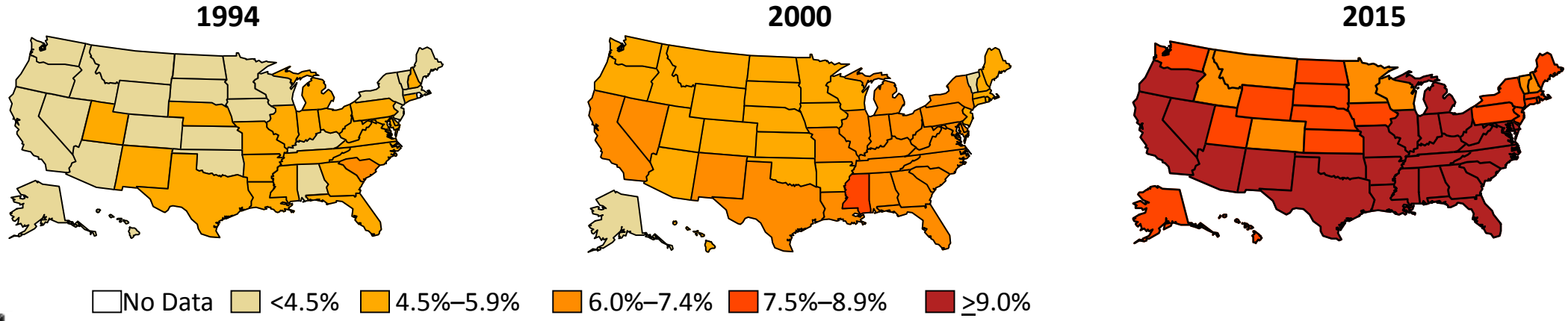
Age-adjusted prevalence of obesity and diagnosed diabetes among US adults

Obesity (BMI ≥30 kg/m^2

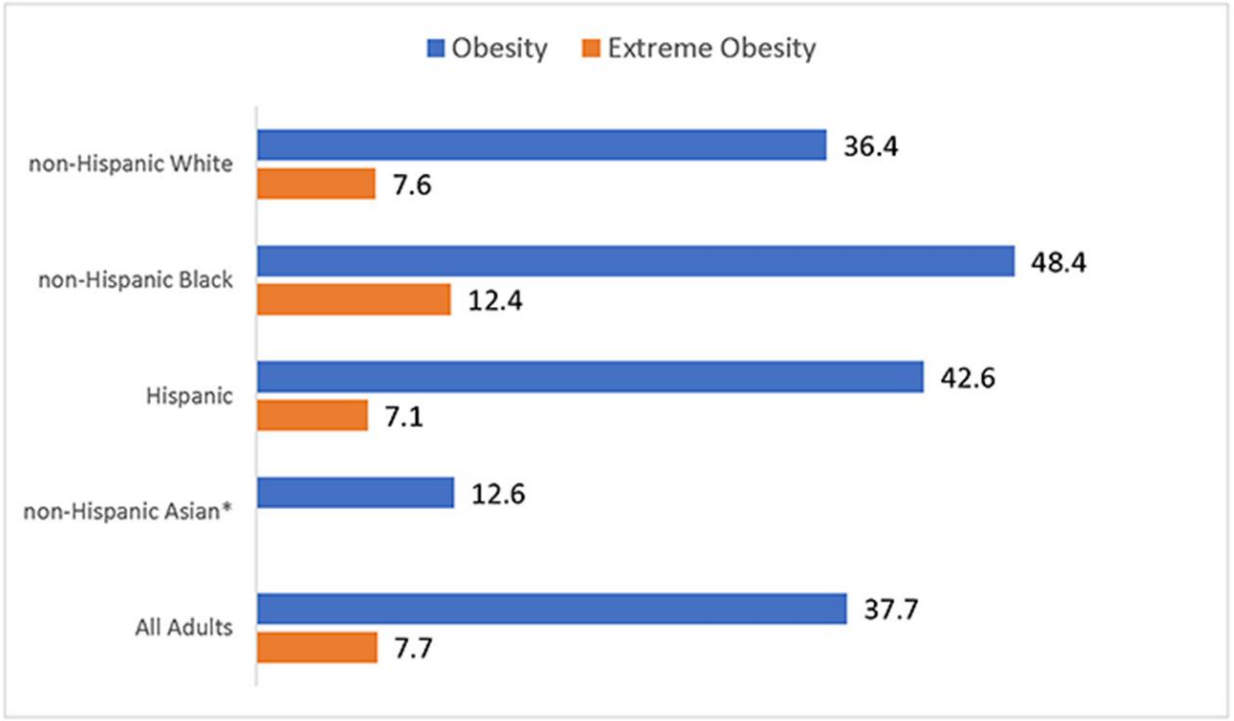


Diabetes



Estimated age adjusted percentage of US adults with obesity by race and ethnicity

Obesity



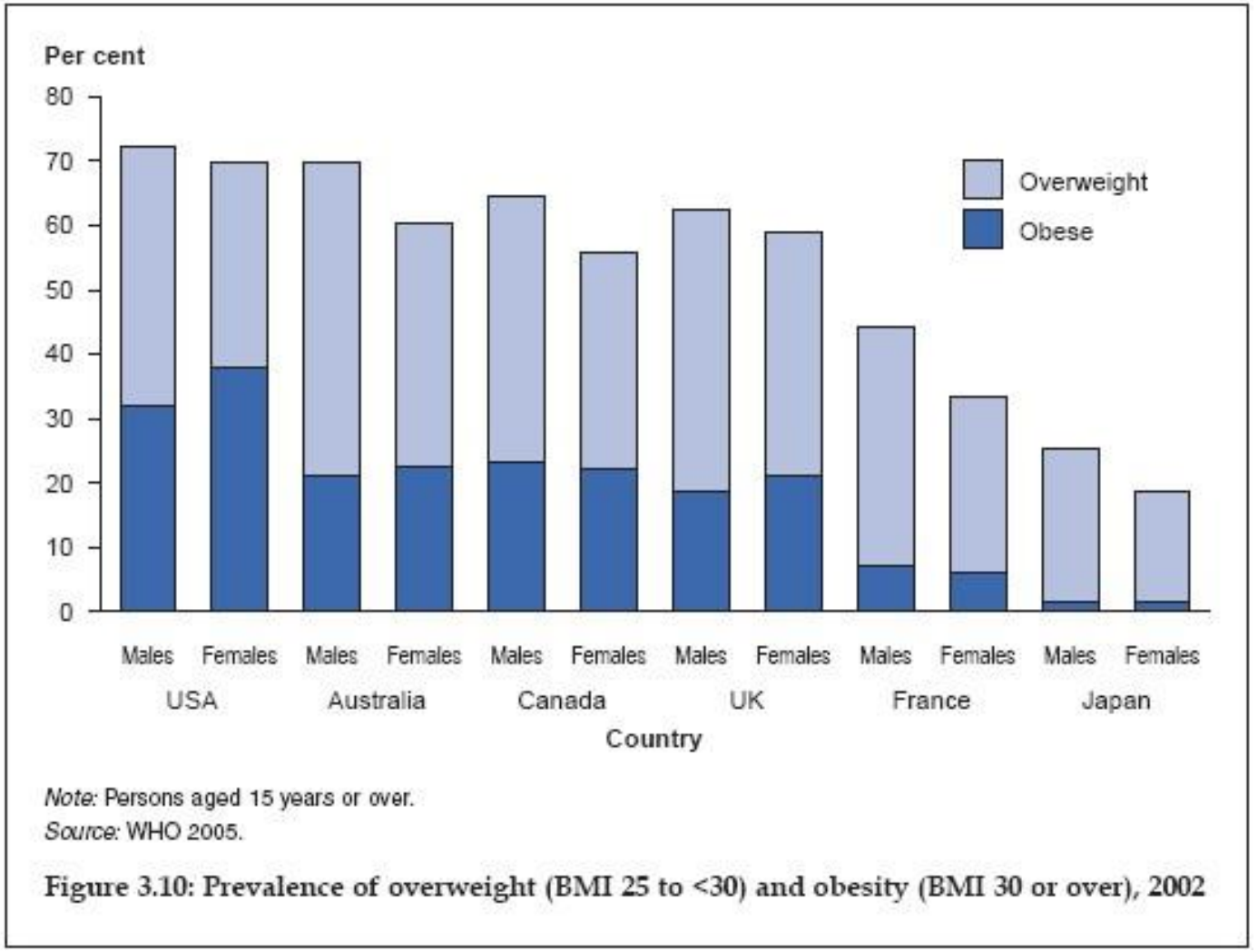
*data for extreme obesity in Asians were not reported since the numbers are close to zero.

Diabetes

- Native Americans
- African Americans
- Hispanics

NHANES Data

Obesity rates in various countries



Note: Persons aged 15 years or over.
Source: WHO 2005.

Figure 3.10: Prevalence of overweight (BMI 25 to <30) and obesity (BMI 30 or over), 2002

The discovery of insulin

The University of Toronto, 1921-22

"With the advent of insulin, we moved from the era of diabetic coma to the era of diabetic complications."

Dr. Elliot P. Joslin (1931)

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Chronic (late) diabetic complications

- Retinopathy
  - blindness: 25% of all newly reported cases
- Cardiovascular disease
  - coronary artery disease
  - peripheral vascular disease
- Nephropathy
- Neuropathy
- Dermatologic lesions

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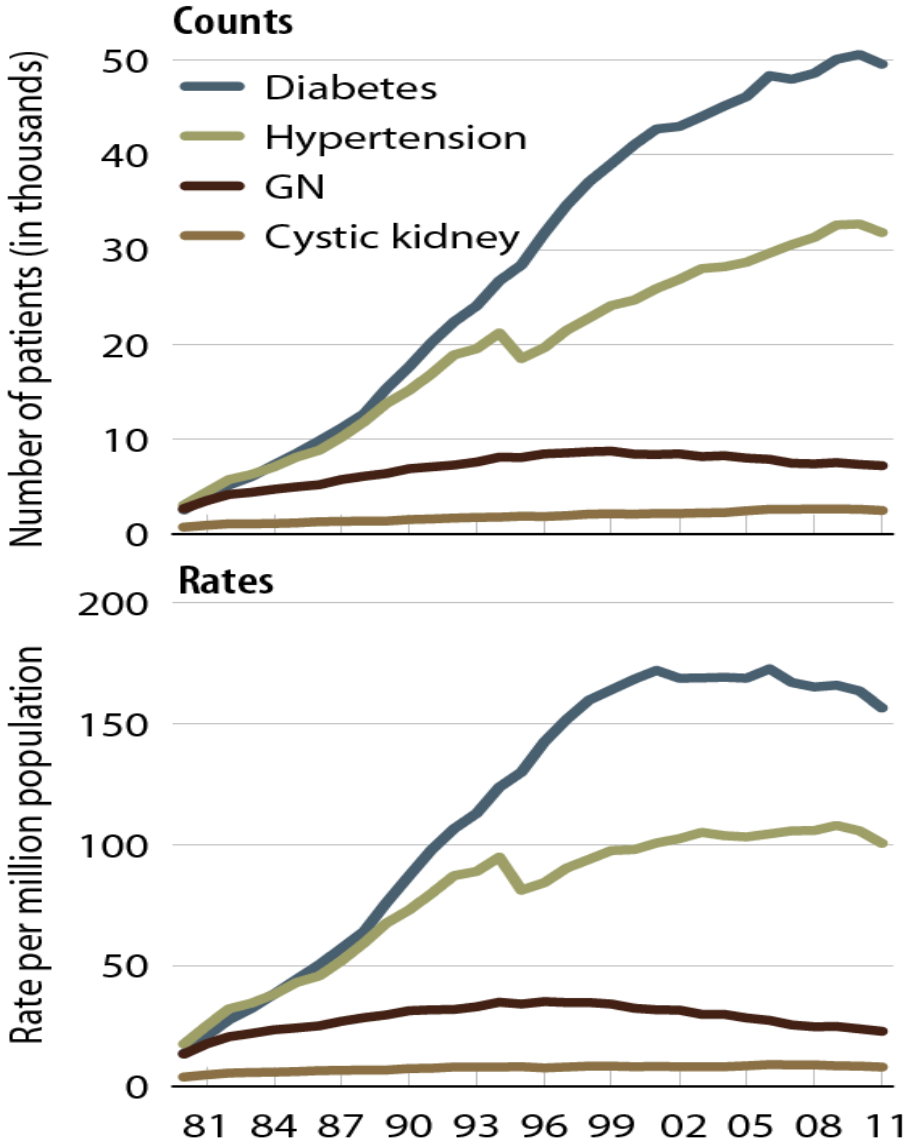
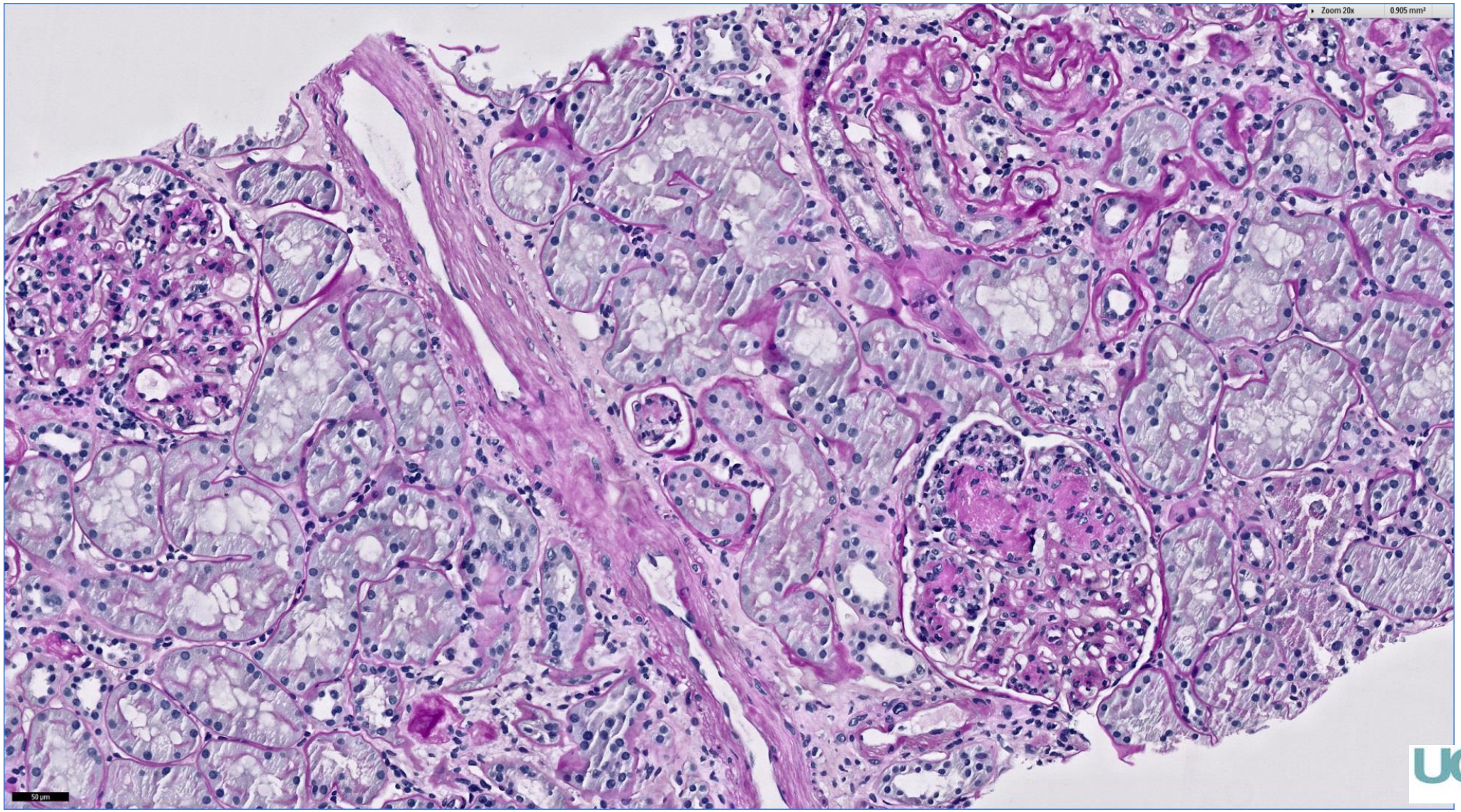
Incident counts & adjusted rates of ESRD, by primary diagnosis

Figure 1.7 (Volume 2)

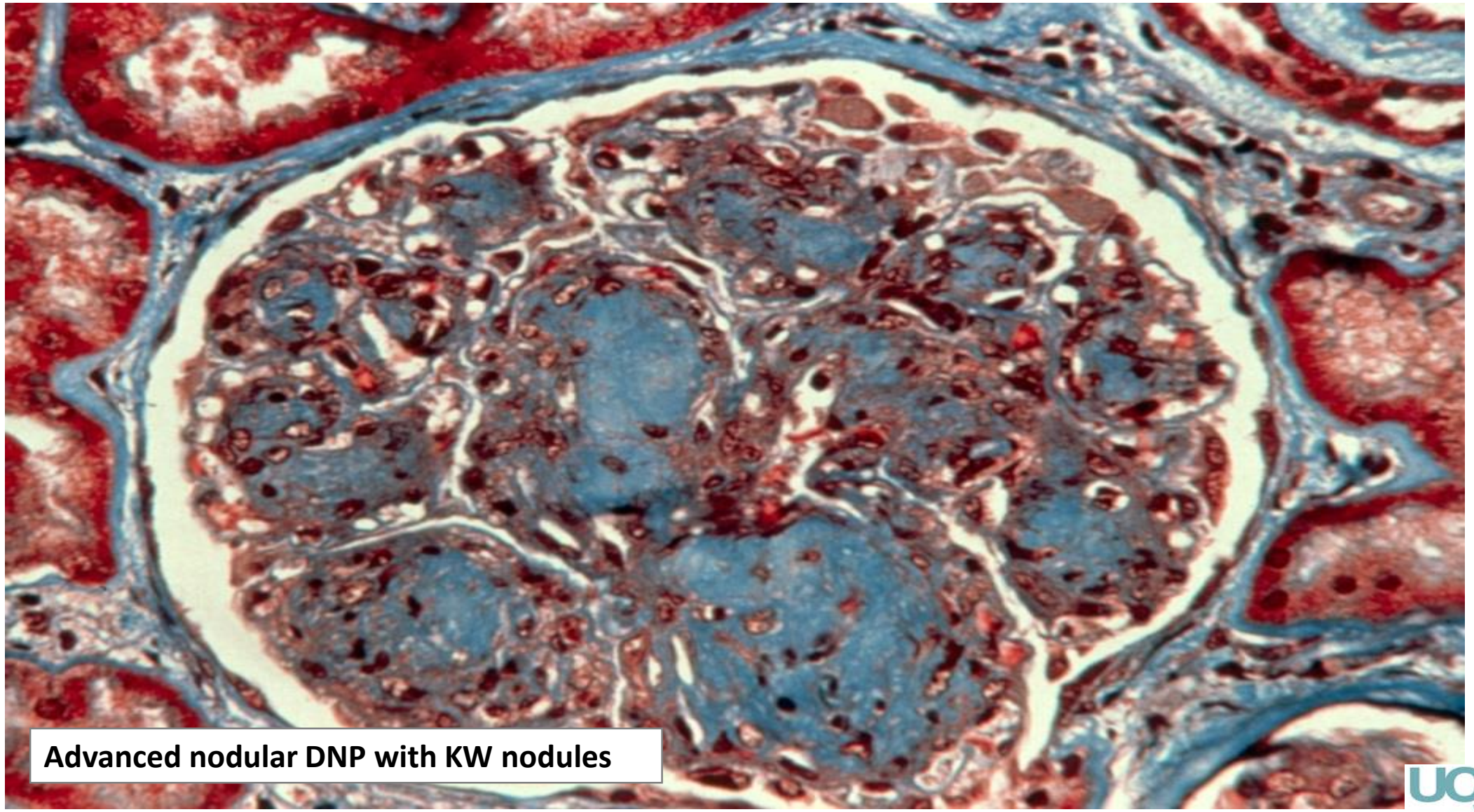


Incident ESRD patients.
Adj: age/gender/race; ref: 2010 ESRD patients.

Diabetic nephropathy

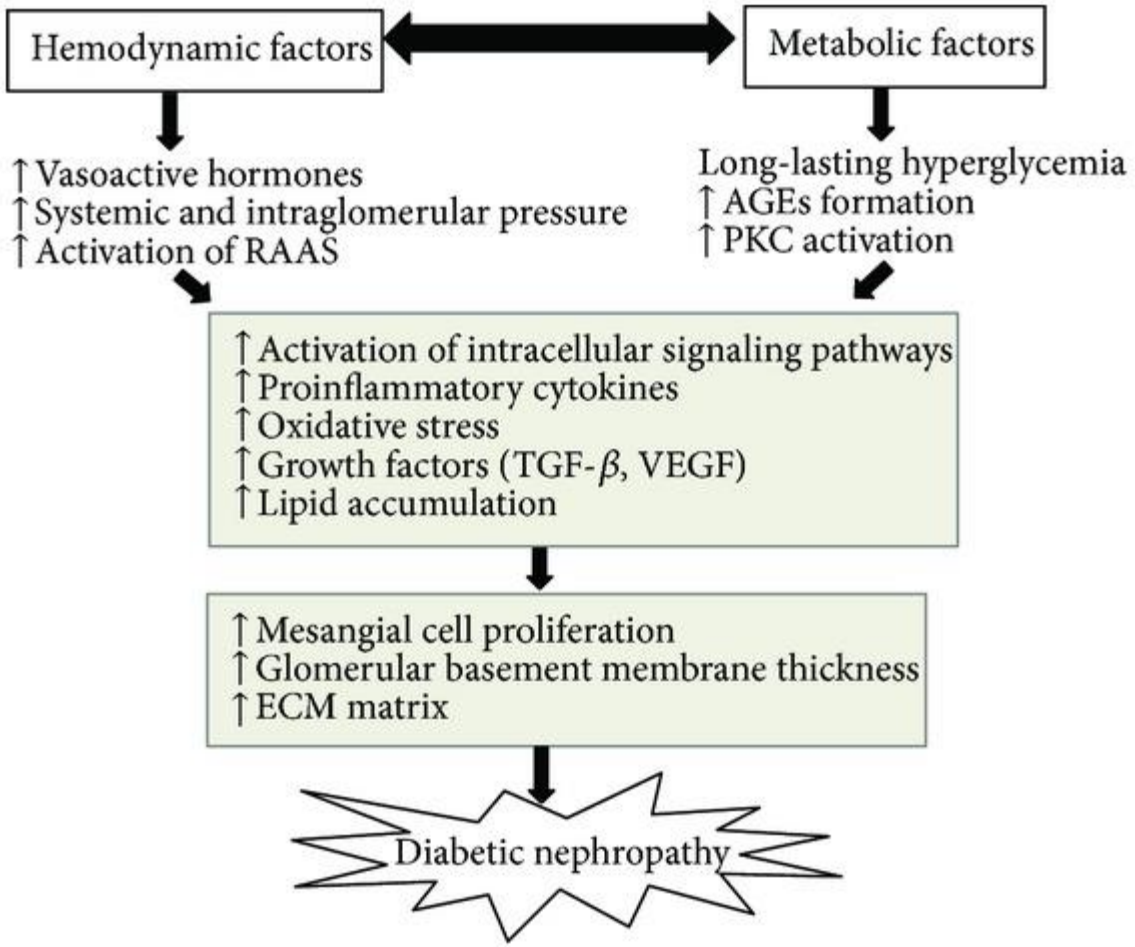


Diabetic nephropathy



Advanced nodular DNP with KW nodules

Pathogenesis of DNP



Clinical manifestations of diabetic nephropathy

- Persistent albuminuria (>300 mg/d or >200 µg/min) that is confirmed on at least 2 occasions 3-6 months apart
- Progressive decline in the glomerular filtration rate (GFR)
- Elevated arterial blood pressure

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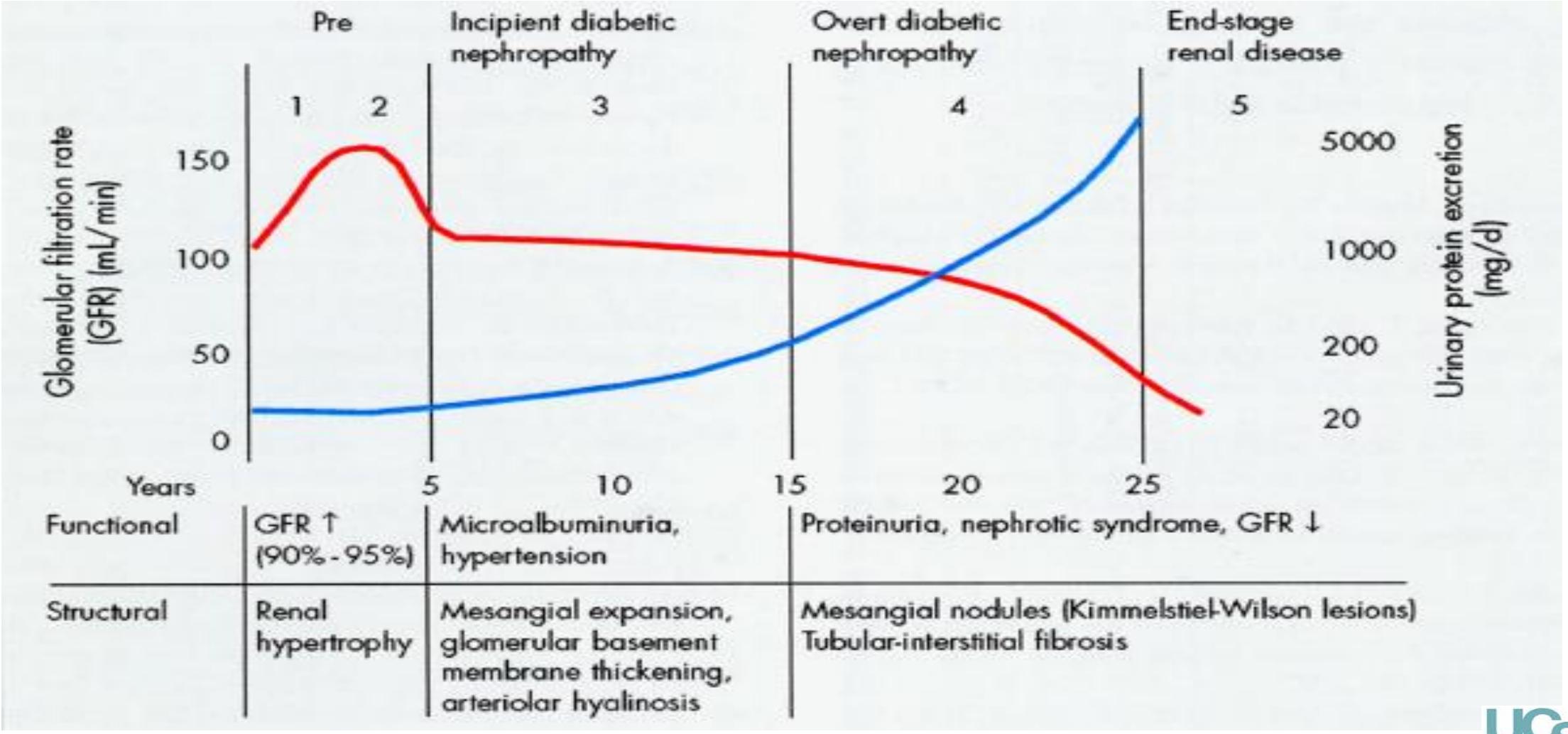
Functional-structural manifestations of DNP



Vora et al. Comprehensive Clinical Nephrology, 2000

Diabetic nephropathy

- Approximately 30% of patients with diabetes will develop DNP
- 30%/30 years = 1% of patients with diabetes develop ESRD per year
- Over 50% of patients will die within two years developing ESRD

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Risk factors of diabetic kidney disease

Modifiable	Non-modifiable
Hyperglycemia	Age
Hypertension	Sex
Albuminuria	Ethnicity
Dyslipidemia	Family history
Smoking	Duration of diabetes

Source: Macisaac RJ, Ekinci EI, Jerums G. Markers of and risk factors for the development and progression of diabetic kidney disease. Am J Kidney Dis. 2014 Feb; 63 (2 Suppl 2):S39-62

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Learning Objective 2

Familiarize with the pathologic manifestations and classification of DNP.

SPECIAL ARTICLE www.jasn.org

Pathologic Classification of Diabetic Nephropathy

Thijs W. Cohen Tervaert,* Antien L. Mooyaart,* Kerstin Amann,† Arthur H. Cohen,‡ H. Terence Cook,§ Cinthia B. Drachenberg,‖ Franco Ferrario,¶ Agnes B. Fogo,** Mark Haas,‡ Emile de Heer,* Kensuke Joh,†† Laure H. Noël,‡‡ Jai Radhakrishnan,§§ Surya V. Seshan,‖‖ Ingeborg M. Bajema,* and Jan A. Bruijn,* on behalf of the Renal Pathology Society

J Am Soc Nephrol 21: 556–563, 2010.

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Consensus classification of diabetic nephropathy

- Class I: glomerular GBM thickening
  - GBM thickening and only mild, nonspecific changes by LM
- Class II: mesangial expansion (in >50% of glomeruli)
  - mild (IIa)
  - severe (IIb)
- Class III: nodular sclerosis (at least one glomerulus)
- Class IV: advanced diabetic glomerulosclerosis
  - >50% global glomerulosclerosis with other clinical or pathologic evidence that sclerosis is attributable to DNP

JASN 21: 556–563, 2010.

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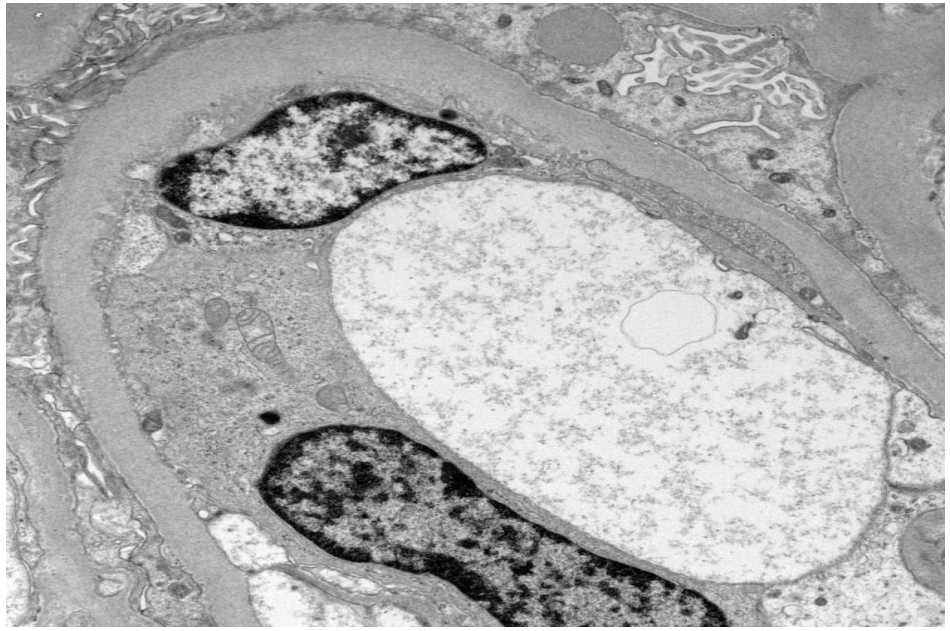

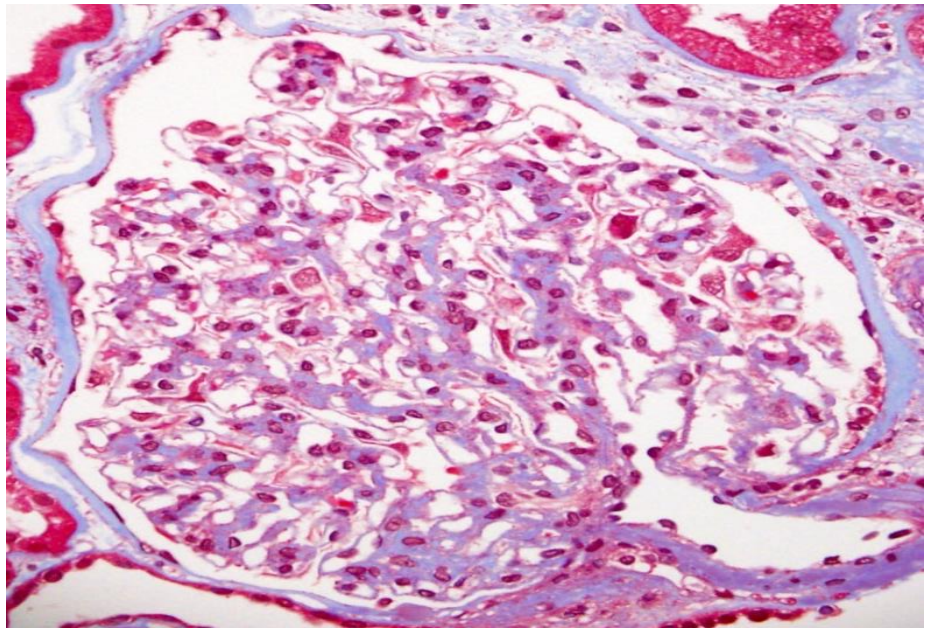

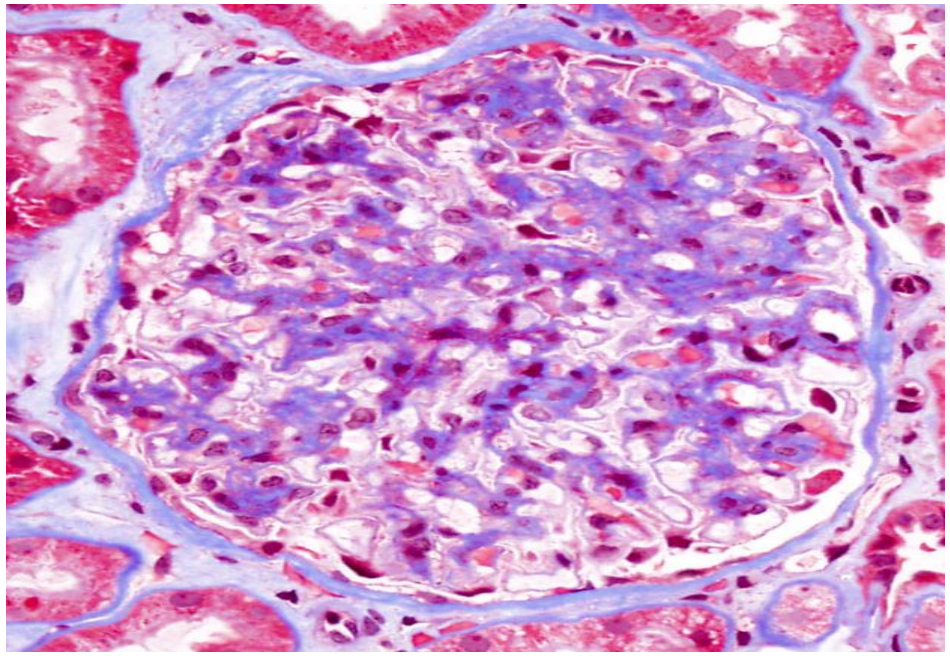

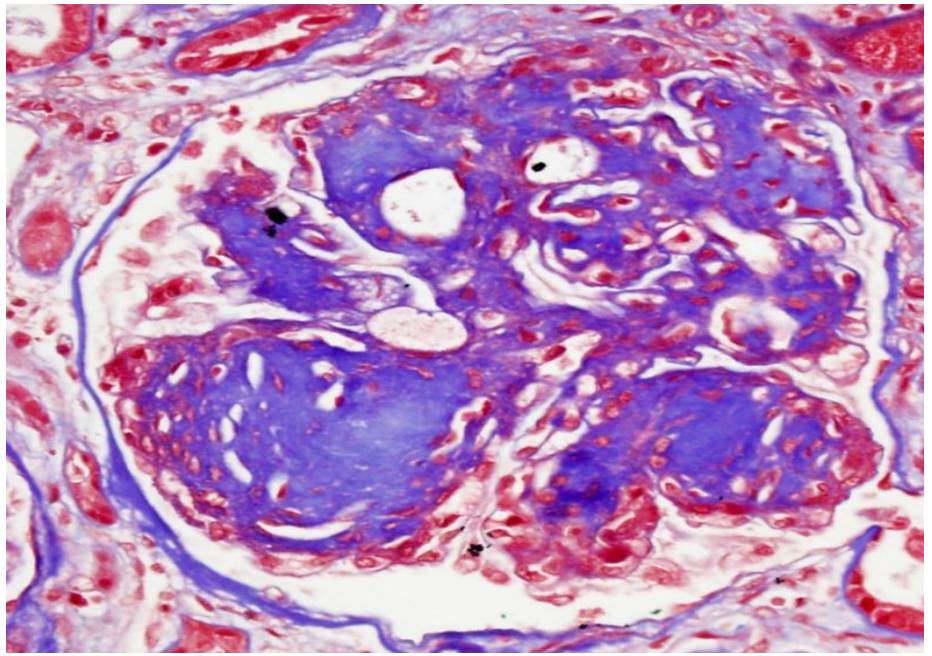

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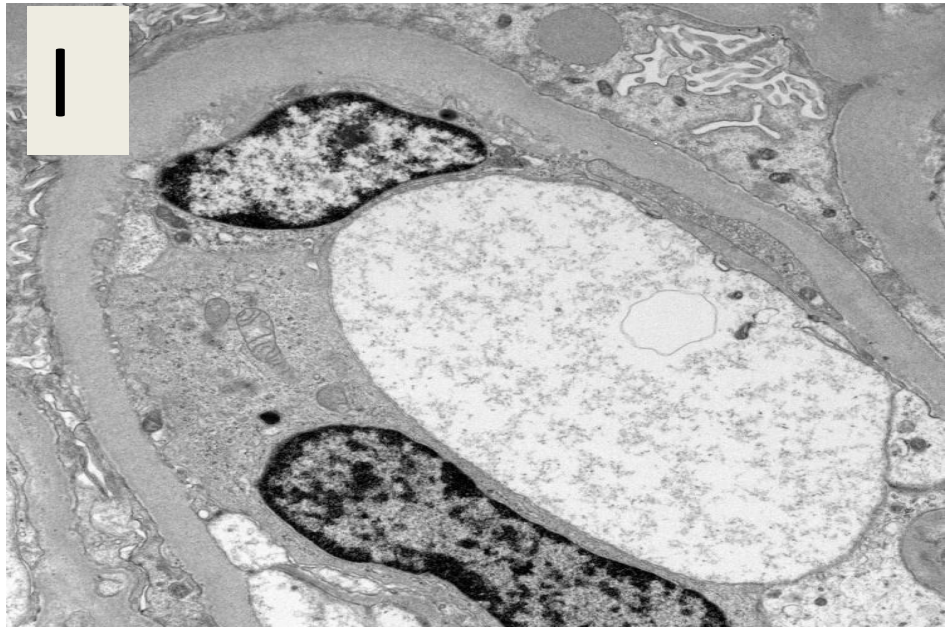
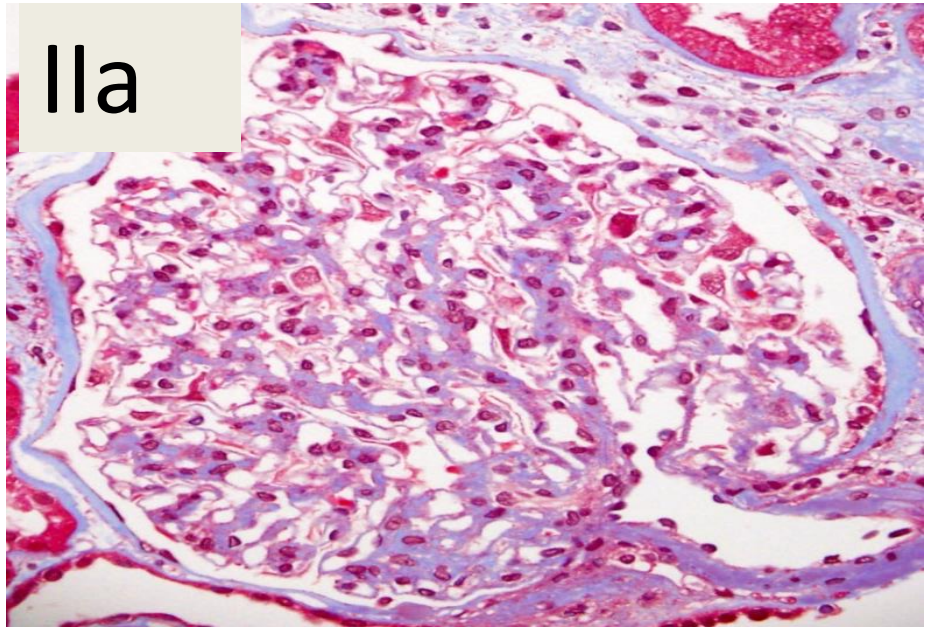
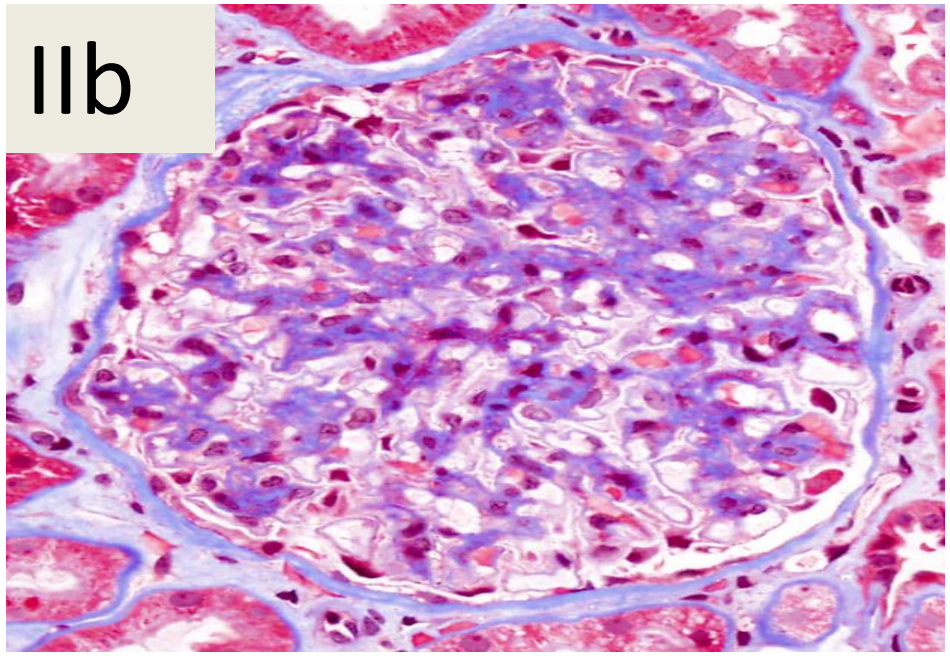
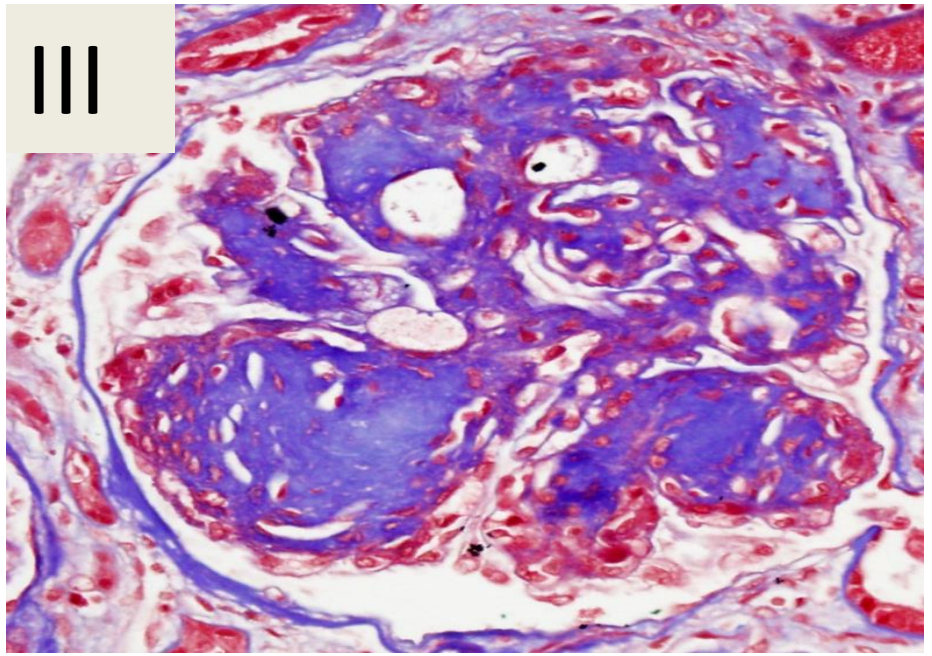
>395 nm (females) and >430 nm (males)









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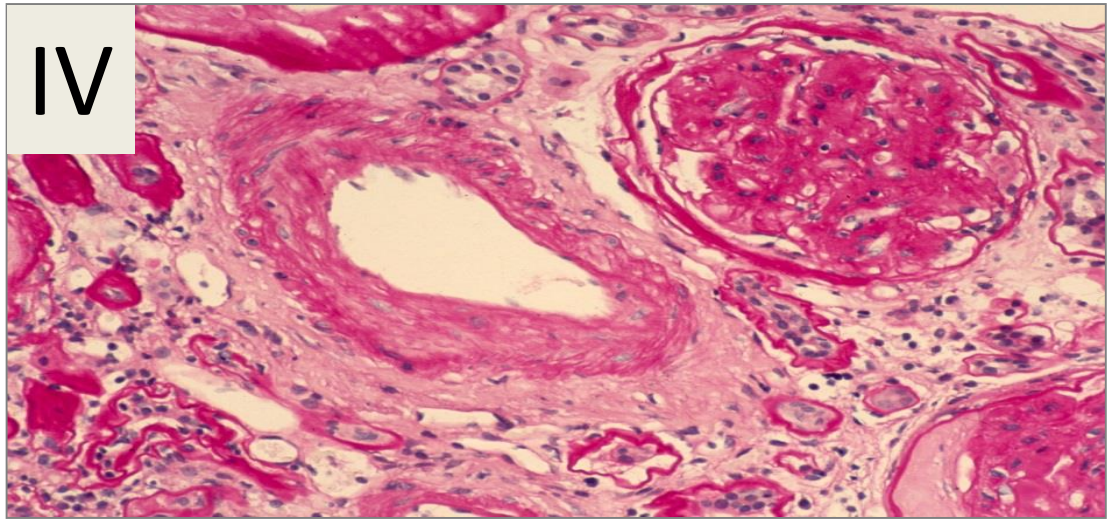
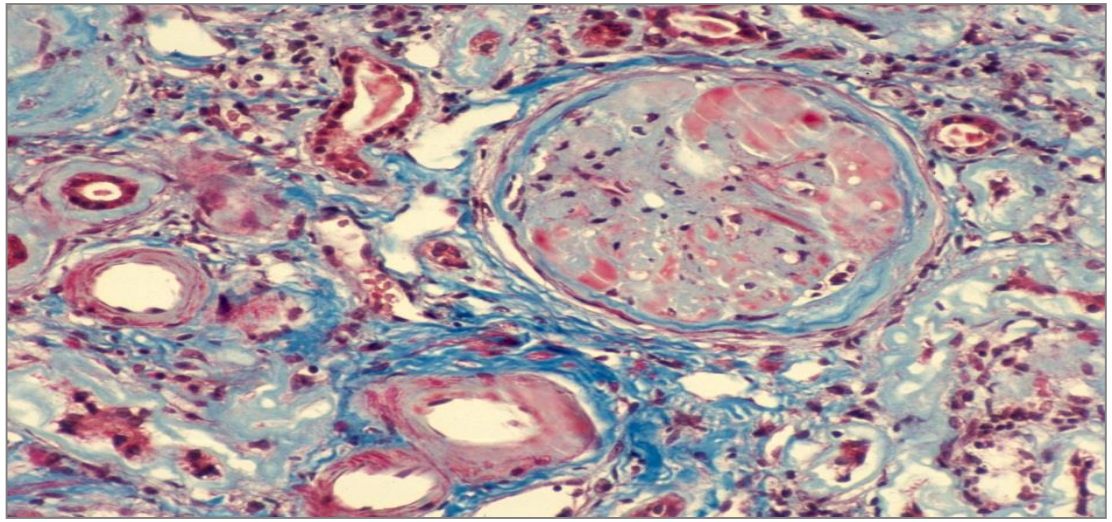
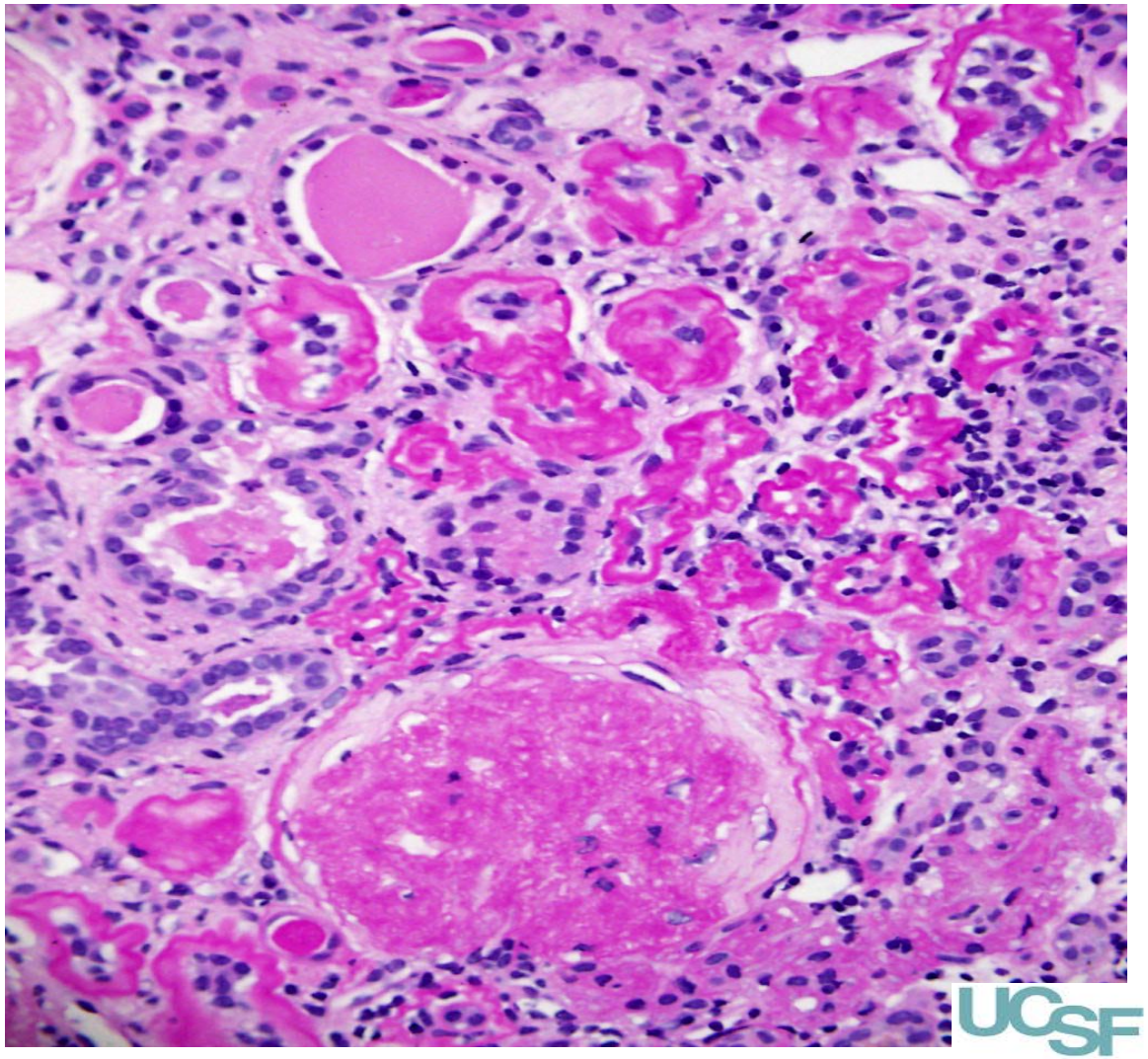
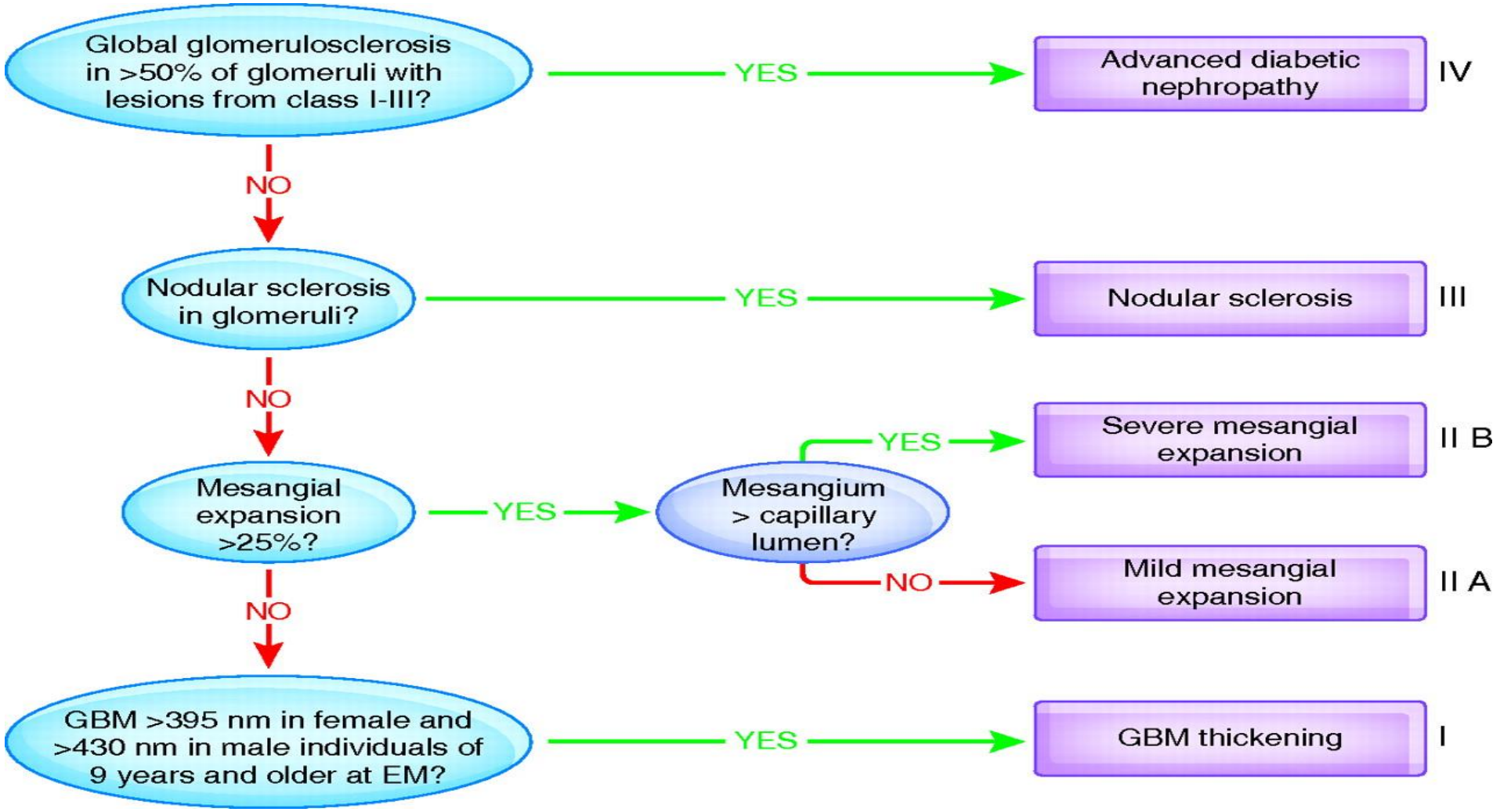
Advanced (stage IV) diabetic nephropathy







Flow chart for classifying DNP

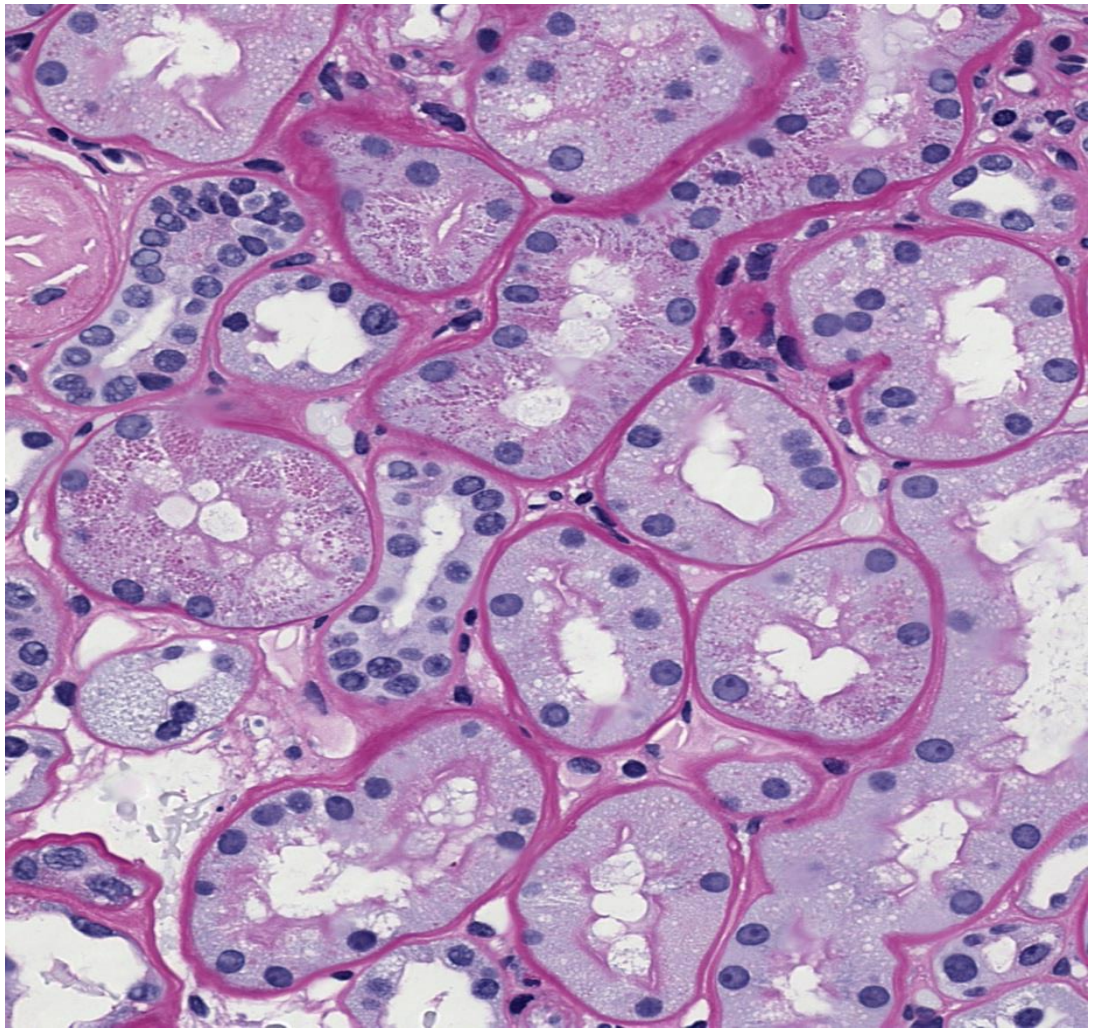


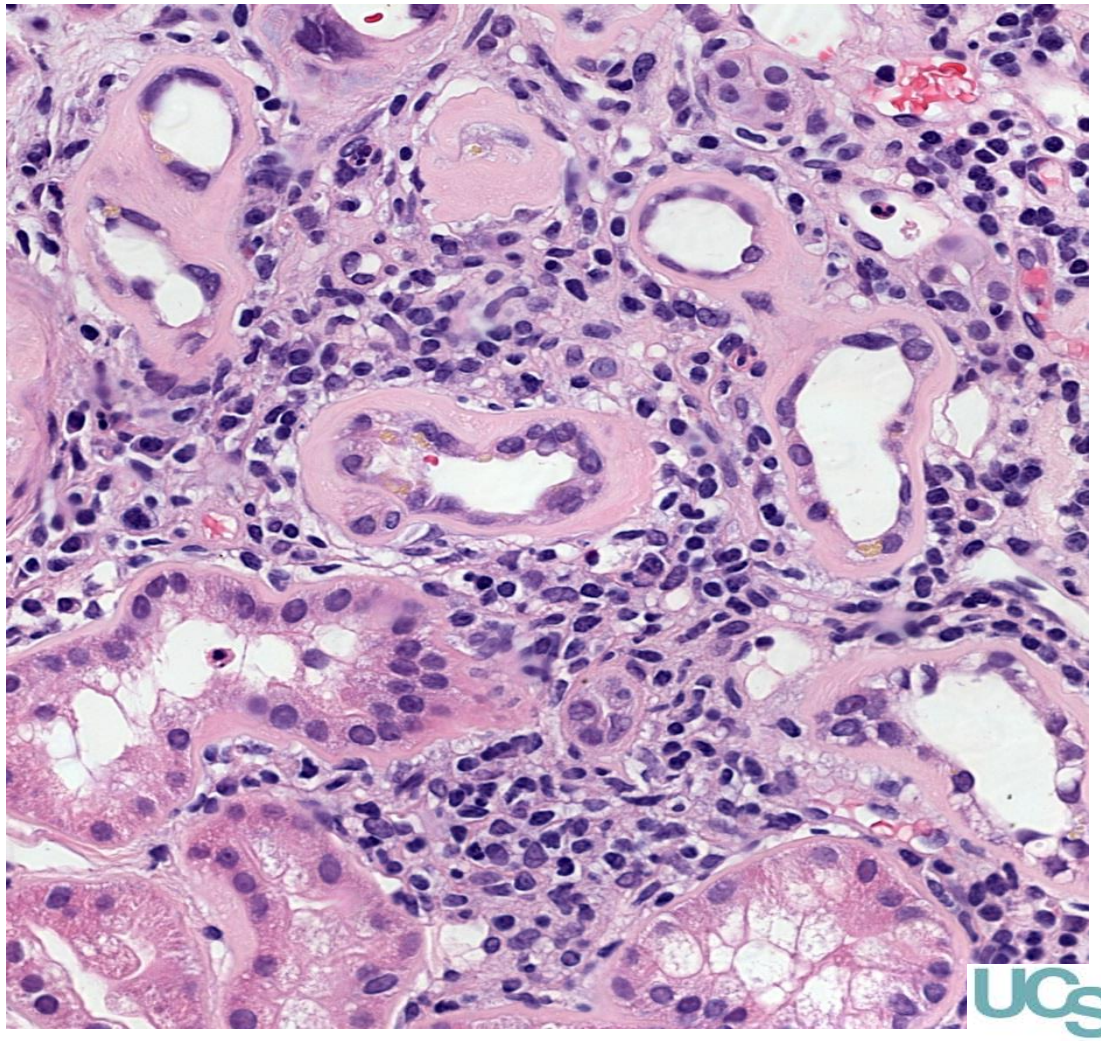
JASN 2010;21:556-563

Key characteristics of consensus classification of DNP

- Classification based on glomerular lesions
- Separate evaluation for interstitial and vascular lesions

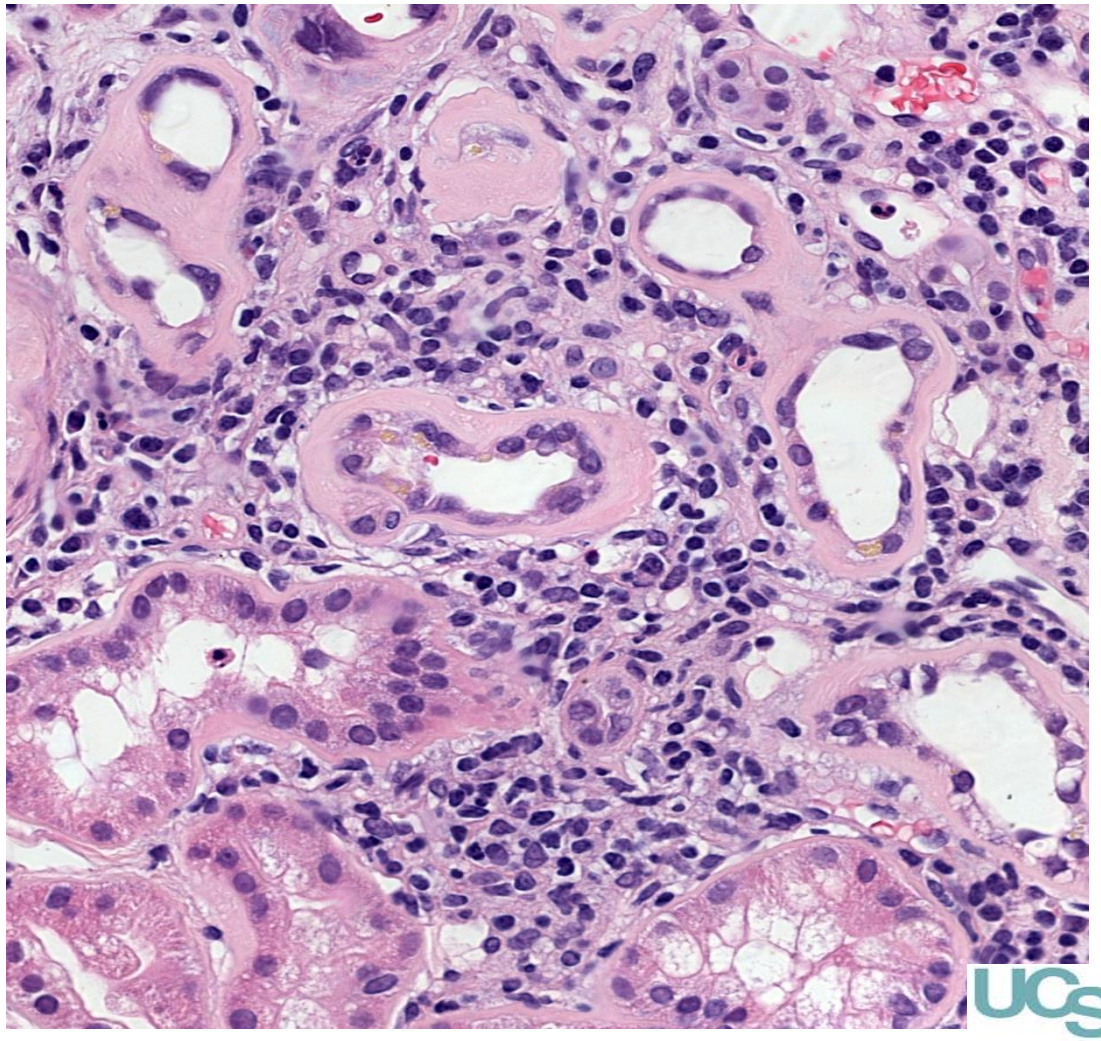
Tubulointerstitial changes of DNP





Tubulointerstitial changes of DNP

Lesion	Criteria	Score
IFTA	No IFTA	0
	<25%	1
	25% to 50%	2
	>50%	3
Interstitial inflammation	Absent	0
	Infiltration only in relation to IFTA	1
	Infiltration in areas without IFTA	2



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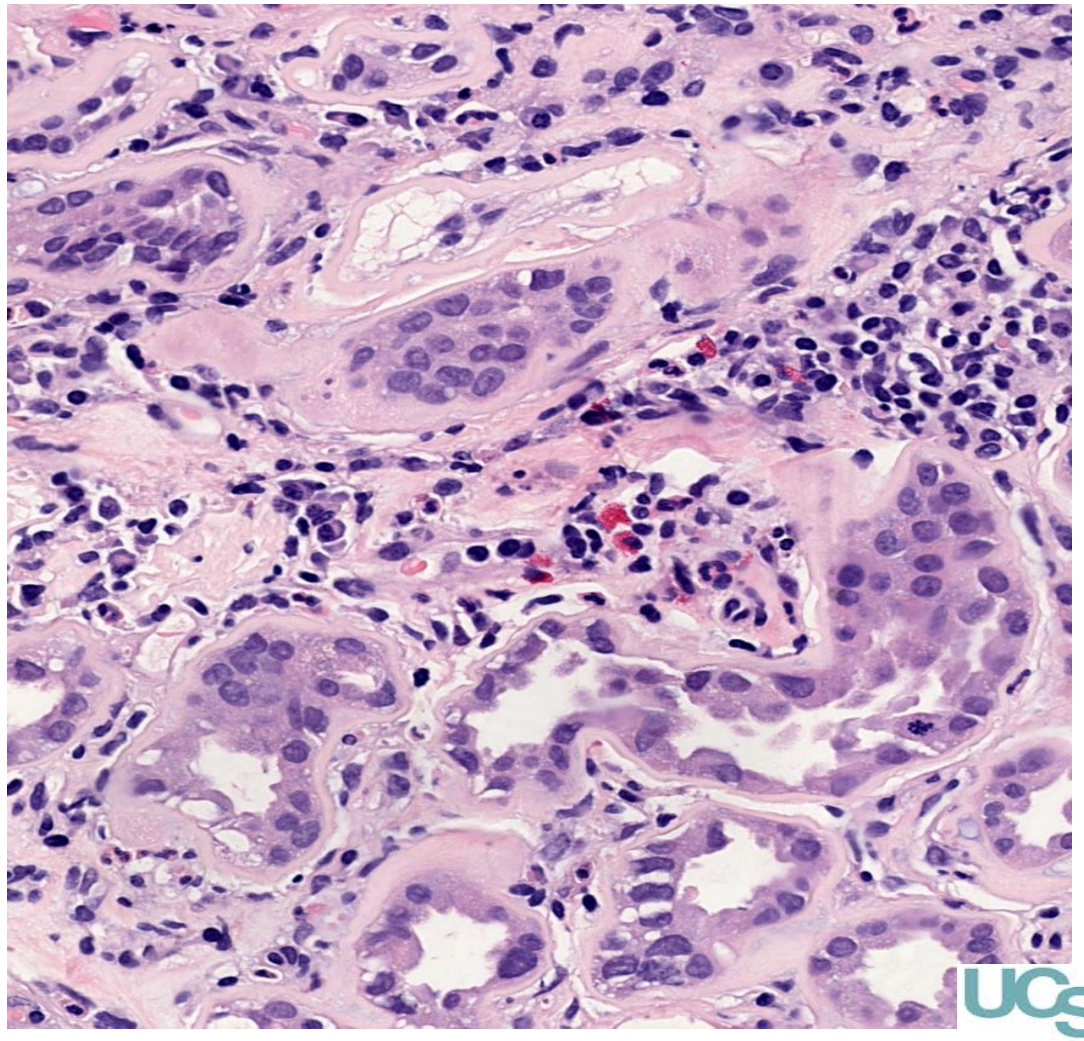
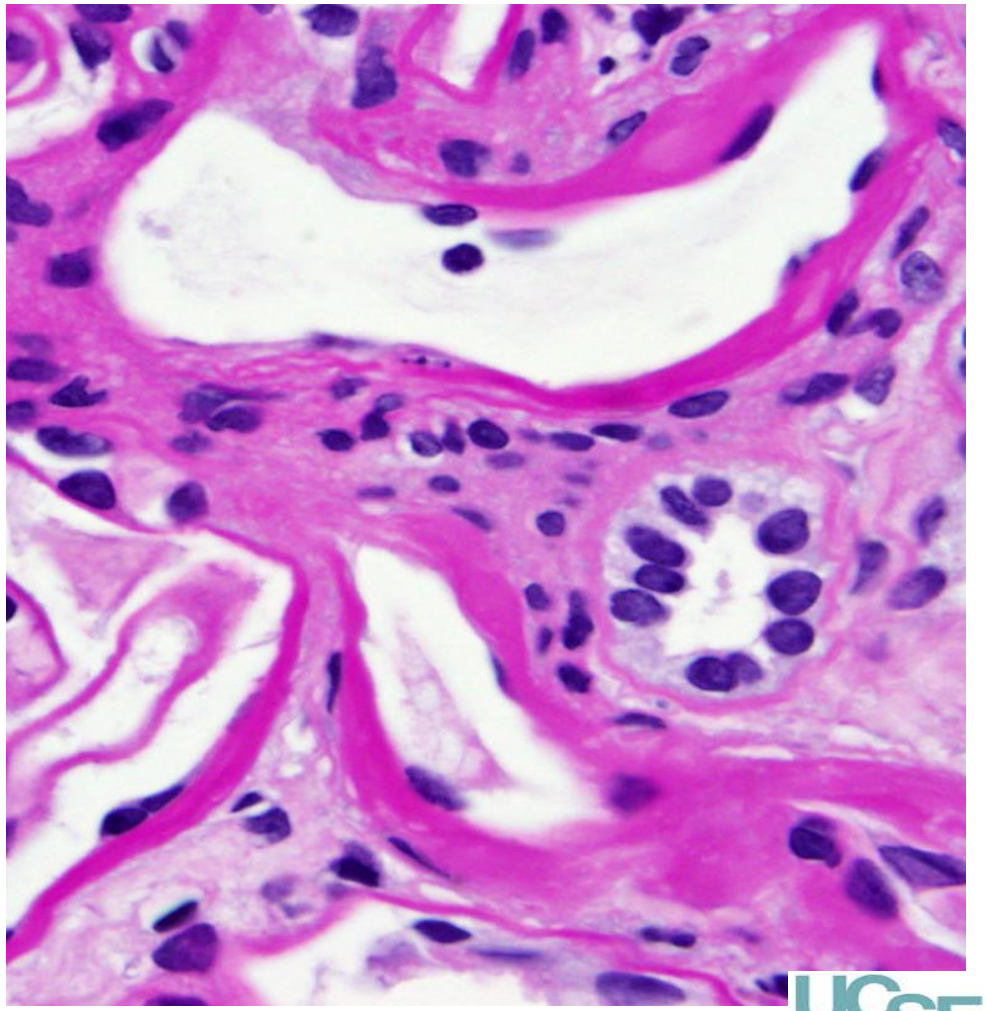


Vascular lesions of DNP

Lesion	Criteria	Score
arteriolar hyalinosis	Absent	0
	arteriolar hyalinosis (x1)	1
	arteriolar hyalinosis (>x1)	2
presence of large vessels	–	Yes/no
arteriosclerosis	No intimal thickening	0
	Intimal thickening less than thickness of media	1
	Intimal thickening greater than thickness of media	2



Rationale of glomerular lesion-based classification for DNP

- Good inter-observer reproducibility
- Glomerular lesions best reflect the natural course of progressive DNP
- Severity of chronic interstitial and glomerular lesions closely correlate
- Applicable to both type 1 and type 2 diabetes

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Critical appraisal of the consensus classification

- Diagnosis of class I based on GBM thickness
- Distinguishing class IIb from III
- Class III diagnosis based on a single Kimmelstiel-Wilson nodule
- Distinguishing global glomerulosclerosis due to vascular lesions from advanced diabetic global glomerulosclerosis

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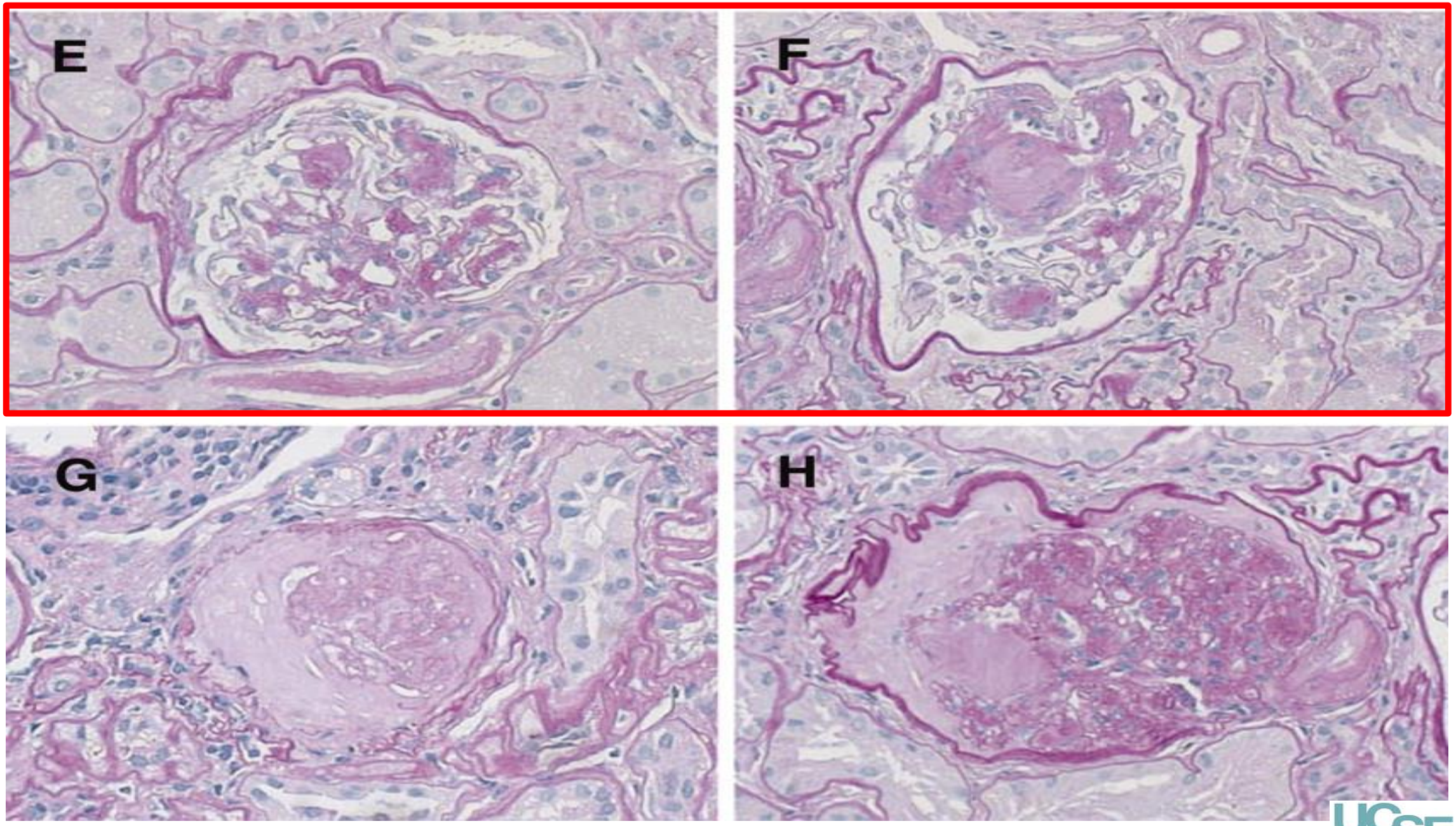

JASN 2010;21:556-563

Differences between the renal lesions of type 1 vs. type 2 DM

- Type 1
  - Glomerular, TIS and vascular changes are typically proportional
- Type 2
  - Glomerular and TIS changes often dysproportional
    - TIS changes usually “ahead” of glomerular disease
  - Spectrum of glomerular changes/diseases broader

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Histological predictors for renal prognosis in diabetic nephropathy in diabetes mellitus type 2 patients with overt proteinuria

1.TOMONARI OKADA[1,*],
2.TOSHITAKA NAGAO[2],
3.HIROSHI MATSUMOTO[1],
4.YUME NAGAOKA[1],
5.TOSHIKAZU WADA[1],
6.TOSHIYUKI NAKAO[1]

Article first published online: 28 DEC 2011
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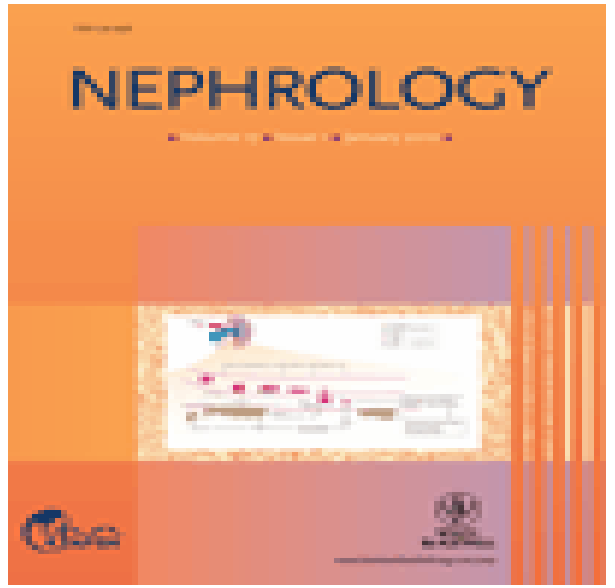


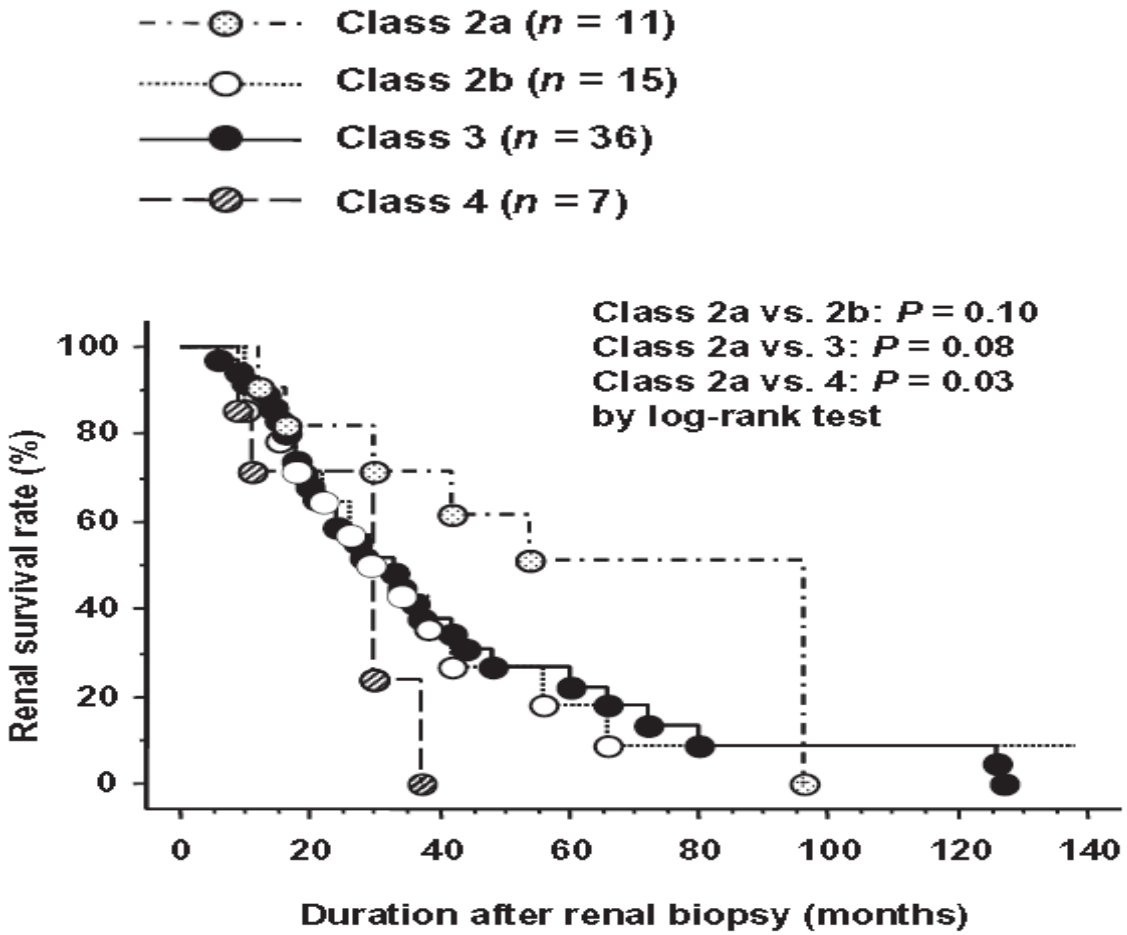
Nephrology Volume 17, Issue 1, pages 68–75, January 2012

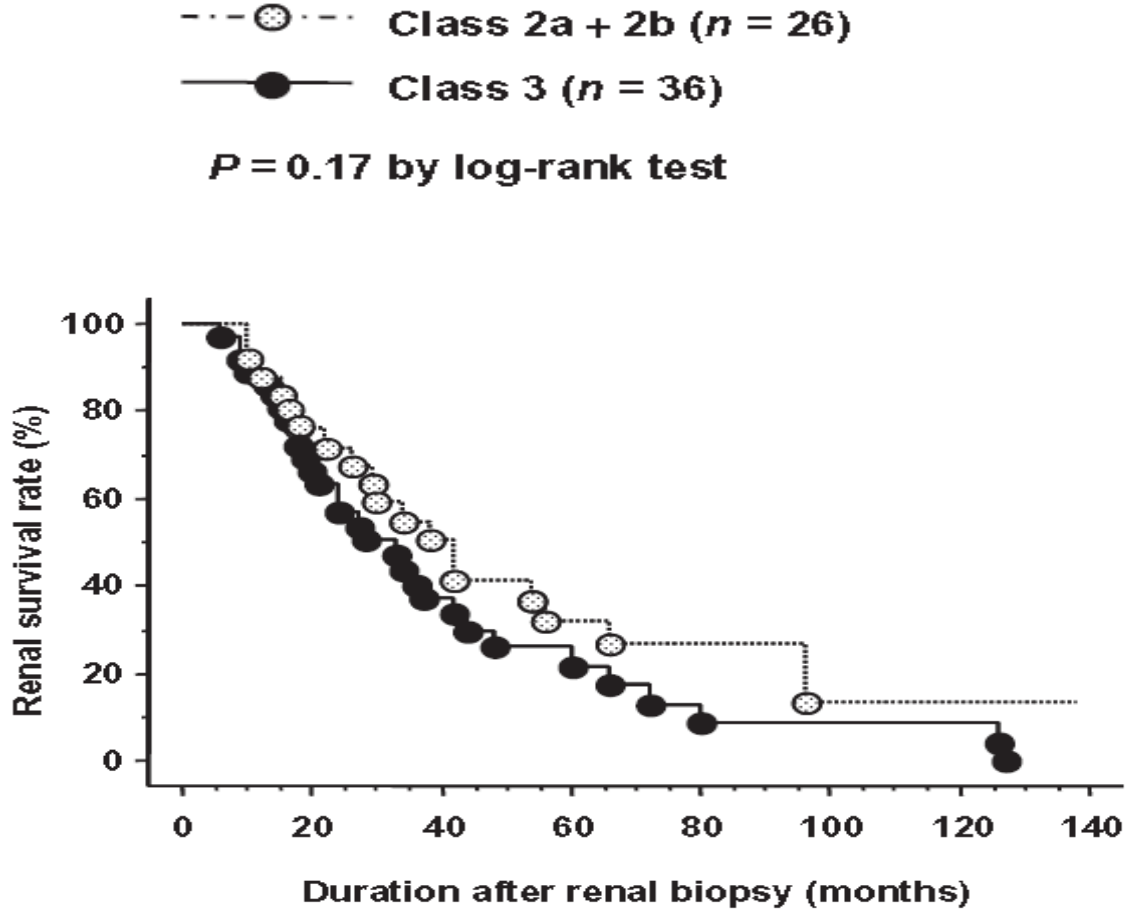
Study population and outline

- Patients with type 2 diabetes mellitus (n=69) with
  - overt proteinuria
  - biopsy-confirmed DNP with mesangial expansion
- Histology
  - class 2a (n = 11)
  - class 2b (n = 15)
  - class 3 (n = 36)
  - class 4 (n = 7)
- Retrospective analysis of histological and clinical findings with renal outcome
- Median follow-up: 52 months

Nephrology 17, 68–75, 2012

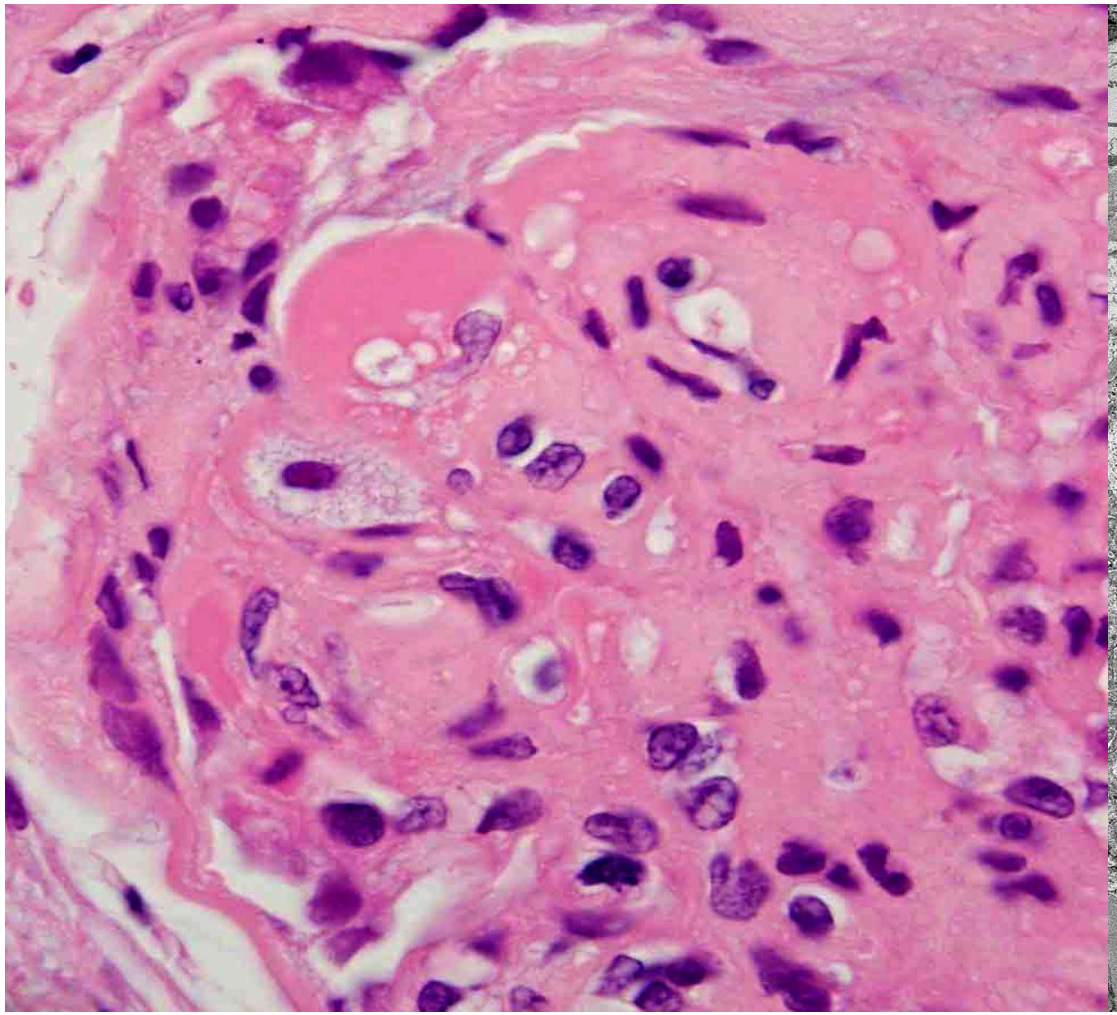
Survival rates based on pathology classes of DNP



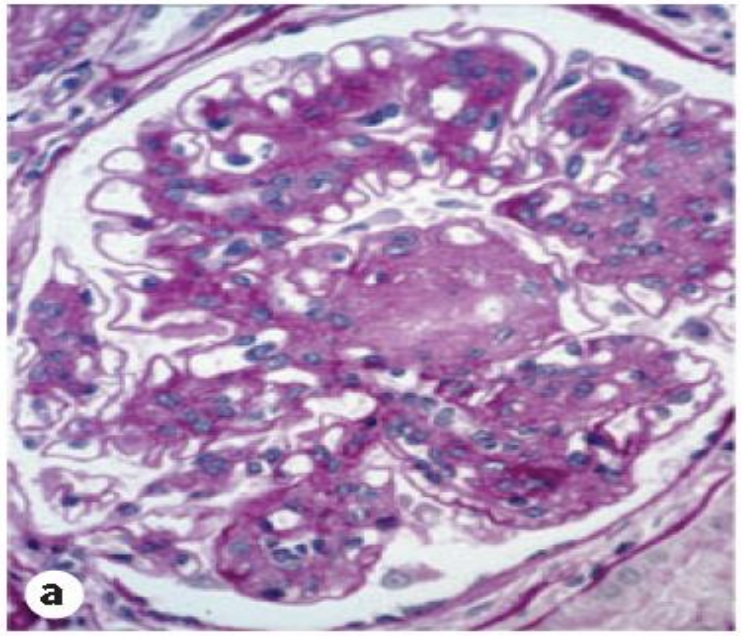


Nephrology 17, 68–75, 2012

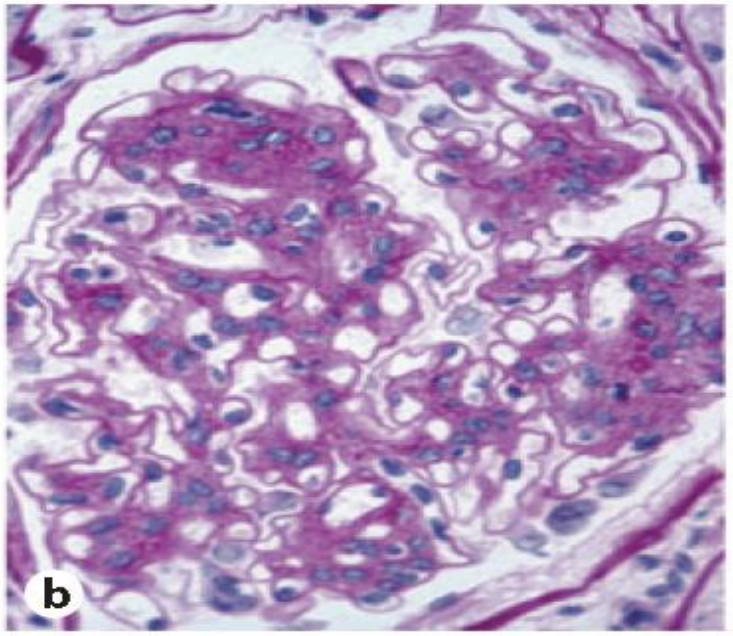
“Other” Glomerular Lesions of DNP
Hyalinosis



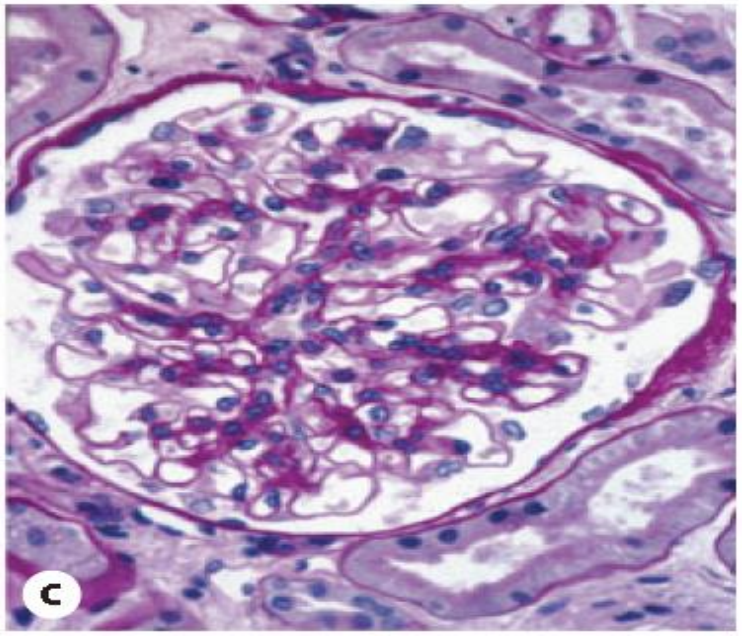
Reversibility of DNP after pancreas transplantation



baseline



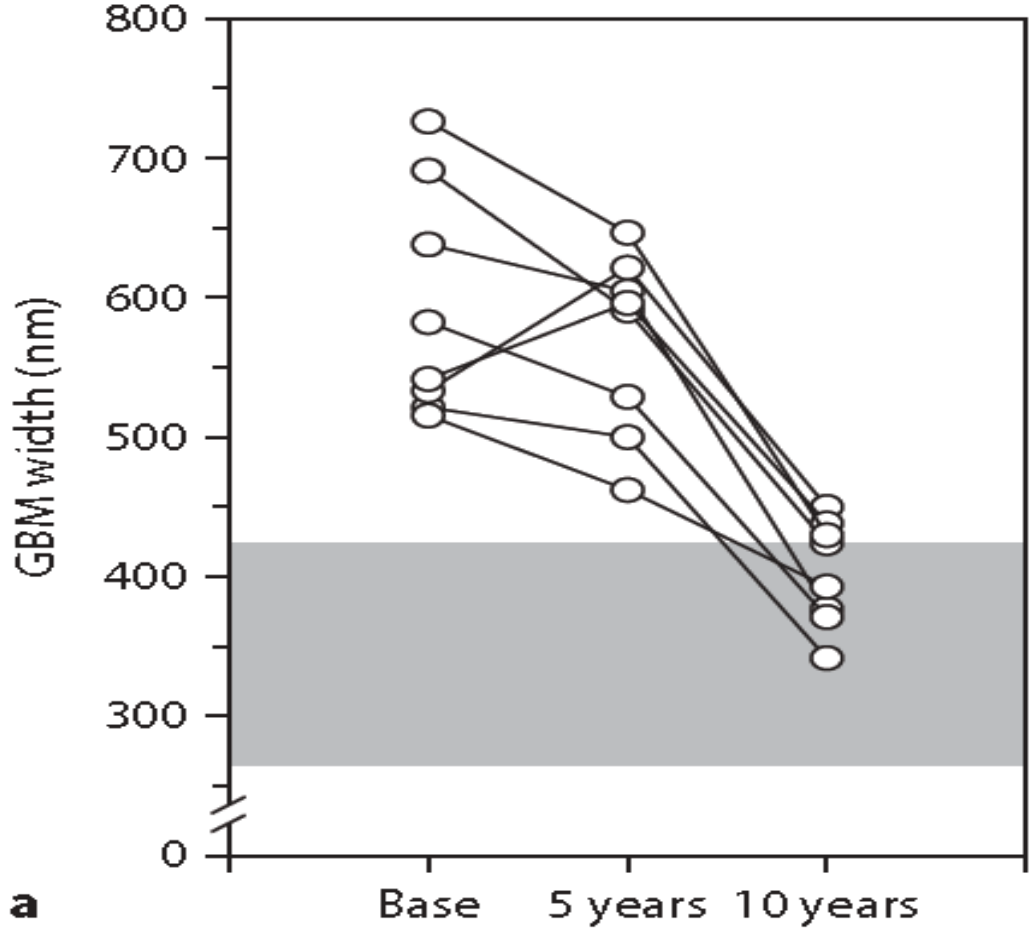
5 years after pancreas transplantation

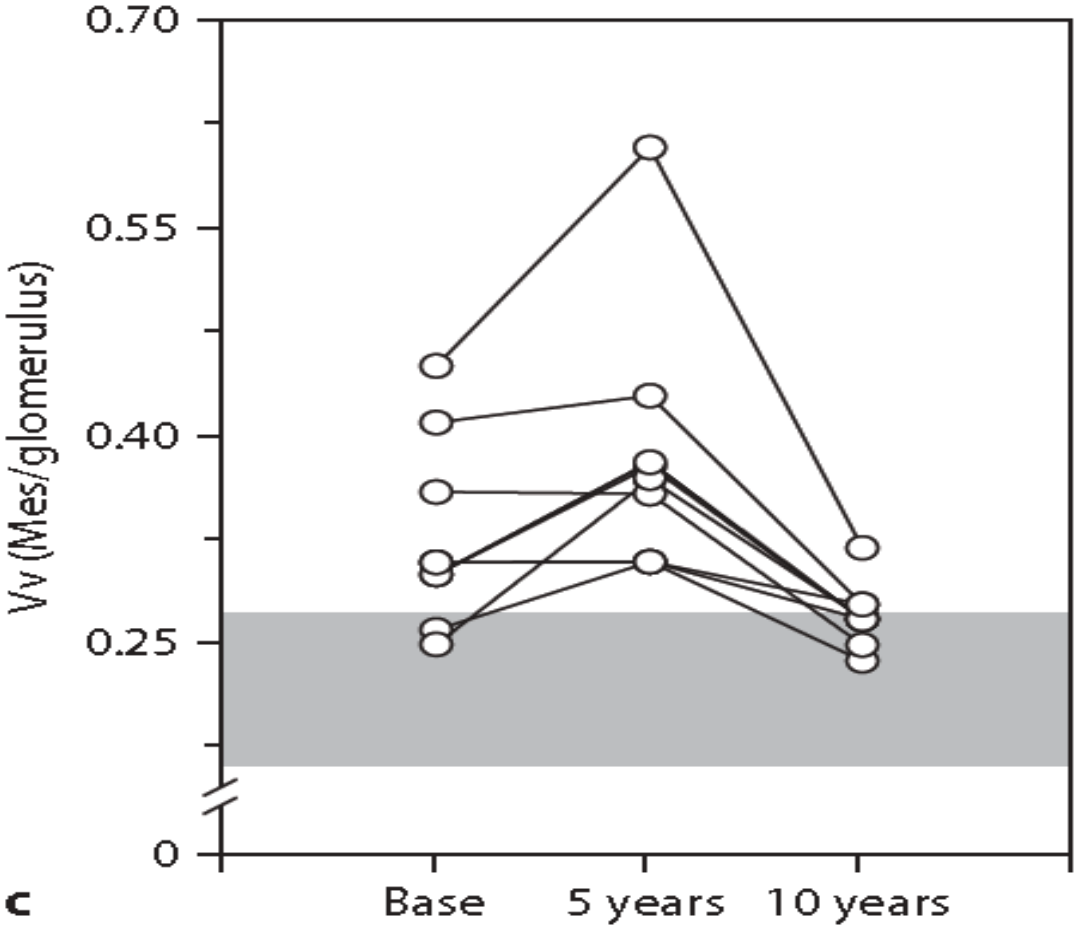


10 years after pancreas transplantation

N Engl J Med. 1998;339(2):69-75.

GBM thickness and fractional mesangial volume after pancreas Tx

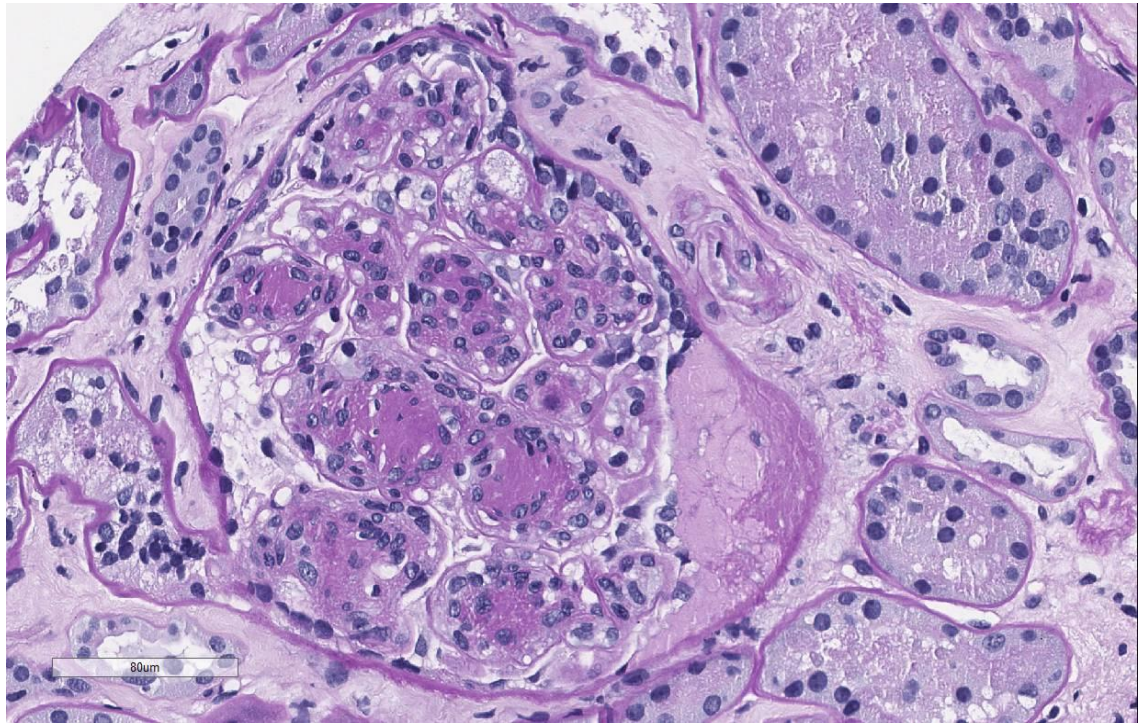




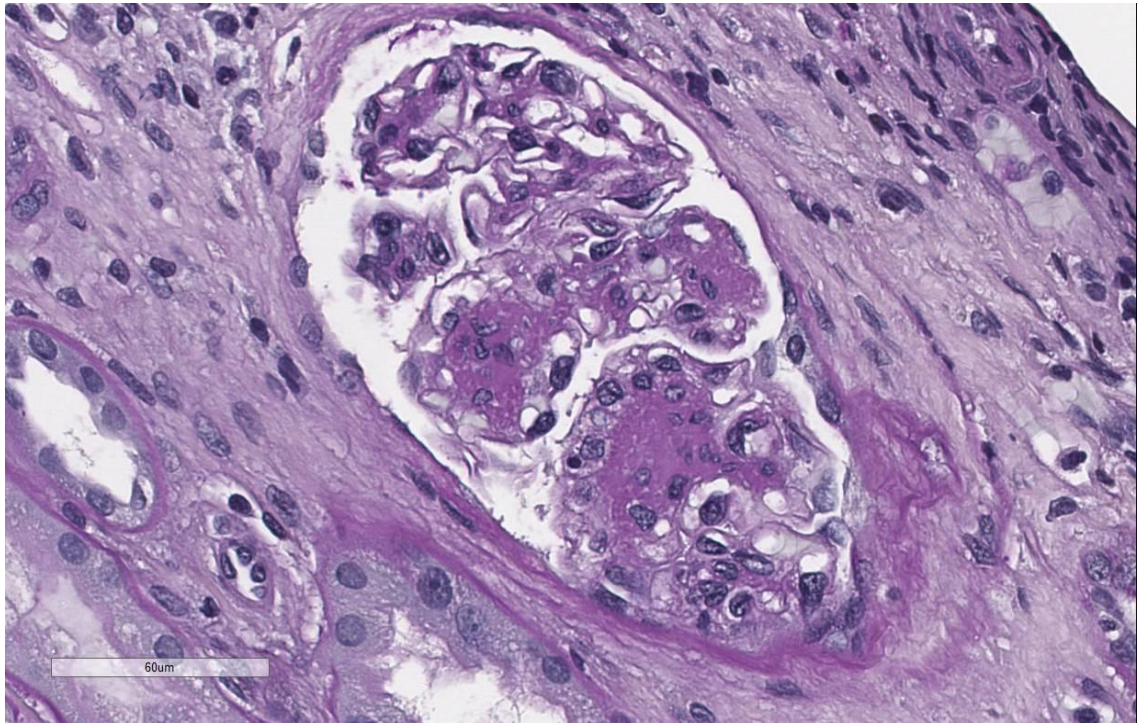
N Engl J Med. 1998;339(2):69-75.

Lack of reversal of DNP after Tx in a non-diabetic patient

3 years post-Tx



7 years post-Tx



Learning Objective 3

Explore the clinico-pathologic aspects of kidney biopsies in diabetic patients.

Renal biopsy practice in type 2 diabetes

- Acute presentations (acute kidney injury [AKI])
- Non-acute presentations in which there are atypical clinical features

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Is there a difference in outcome in diabetic patients with diabetic vs non-diabetic renal disease?

- The studies distinguishing between the types of presentation and pathologies that are associated with a better prognosis are sparse and inconclusive

UCSF

Open Access Original research

BMJ Open Diabetes Research & Care

Presentation, pathology and prognosis of renal disease in type 2 diabetes

Jasmine Tan,[1,2] L Jonathan Zwi,[3] John F Collins,[4] Mark R Marshall,[5] Tim Cundy[1,6]

- Renal biopsy findings in a large group of patients with type 2 diabetes, the pathologies associated with particular renal presentations were reviewed and correlated their relationship to renal and survival outcomes.

Jasmine Tan et al. BMJ Open Diab Res Care 2017;5:e000412

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Open Access Original research

BMJ Open Diabetes Research & Care

Presentation, pathology and prognosis of renal disease in type 2 diabetes

Jasmine Tan,[1,2] L Jonathan Zwi,[3] John F Collins,[4] Mark R Marshall,[5] Tim Cundy[1,6]

Table 1 Baseline characteristics at the time of biopsy

	Data (%)	Diabetic nephropathy only (n=94)	Mixed pathologies (n=97)	Non-diabetic renal disease only (n=72)	p Value
Age	100	58±10	55±11	59±11	0.12
Male (n (%))	100	62 (66)	64 (66)	39 (54)	0.18
Ethnicity (n (%))	100				
Māori/Pāsifika		65 (69)	70 (72)	39 (55)	
European		14 (15)	13 (13)	21 (29)	0.31
East or South Asian		14 (15)	13 (14)	11 (15)	
Others		1 (1)	1 (1)	1 (1)	

Jasmine Tan et al. BMJ Open Diab Res Care 2017;5:e000412

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BMJ Open Diabetes Research & Care

Presentation, pathology and prognosis of renal disease in type 2 diabetes

Jasmine Tan,[1,2] L Jonathan Zwi,[3] John F Collins,[4] Mark R Marshall,[5] Tim Cundy[1,6]

Table 2 Characteristics of patients with acute and non-acute presentations

	Acute	Non-acute	p Value
Number (%)	146 (56)	116 (44)	-
Histological diabetic nephropathy (n (%))			
Absent	25 (17)	47 (41)	
Grades 1 and 2	15 (10)	19 (16)	<0.001
Grades 3 and 4	106 (73)	50 (43)	
Non-diabetic renal diseases (n (%))			
Focal segmental glomerulosclerosis	18 (12.5)	38 (33)	<0.001
Membranous nephropathy	2 (1.5)	6 (5)	0.08
Minimal change disease	0 (0)	6 (5)	0.005
IgA nephropathy	0 (0)	3 (2.5)	0.05
Interstitial nephritis	32 (22)	8 (7)	0.001
Immune complex glomerulonephritides	21 (14.5)	4 (3.5)	0.003
Acute tubular necrosis	9 (6)	0 (0)	0.007
Acute pyelonephritis	3 (2)	1 (1)	0.43
Others	2 (1.5)	7 (6)	0.04

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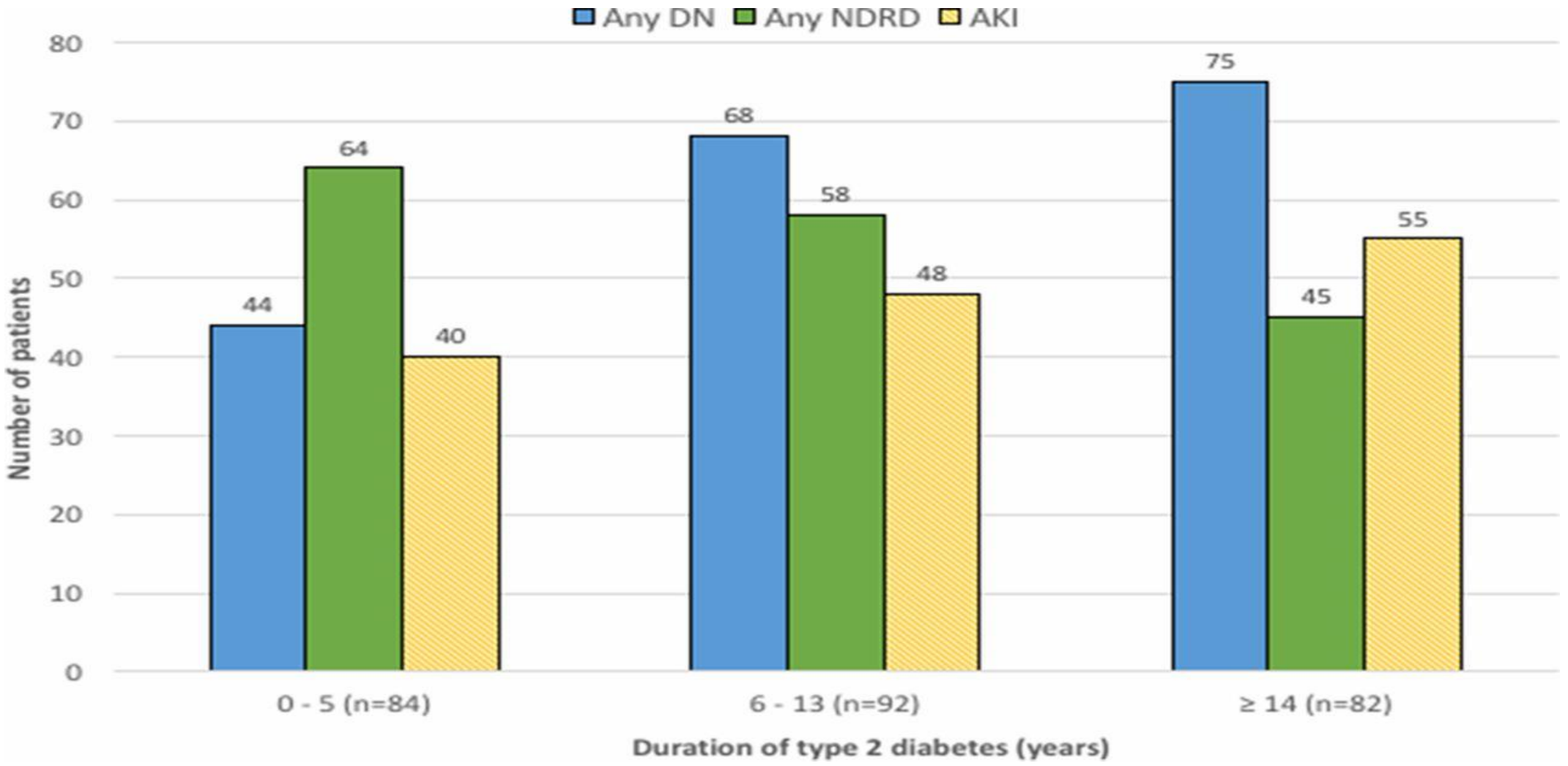
Relationship between time from diagnosis of type 2 diabetes to renal biopsy and the proportion of biopsies with any diabetic nephropathy (DN) and any non-diabetic renal disease (NDRD) (n=258). The proportion of any DN increased with duration of type 2 diabetes



Jasmine Tan et al. BMJ Open Diab Res Care 2017;5:e000412

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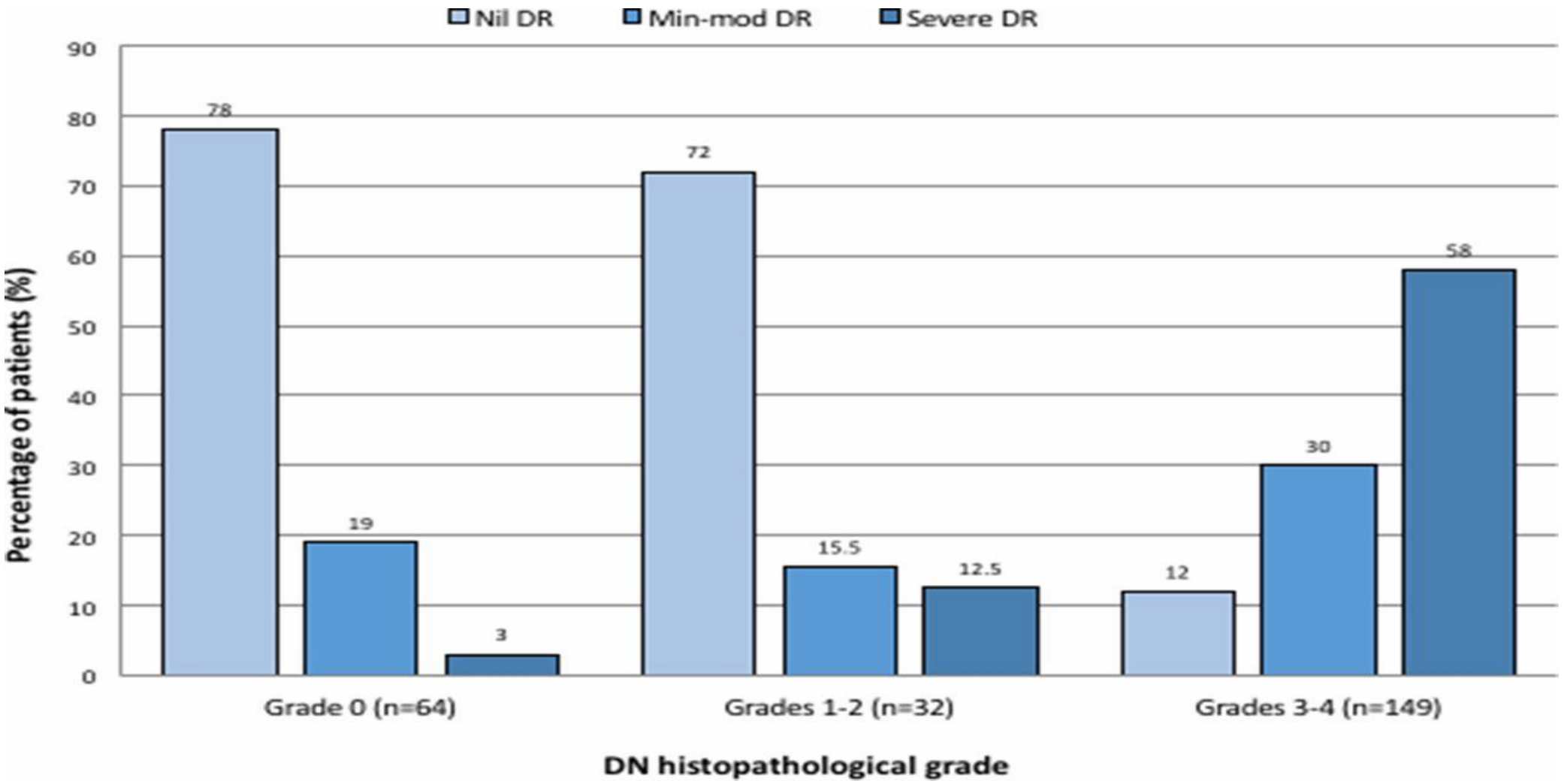
Relationship between grades of diabetic retinopathy and severity of diabetic renal lesions (n=245).



Jasmine Tan et al. BMJ Open Diab Res Care 2017;5:e000412

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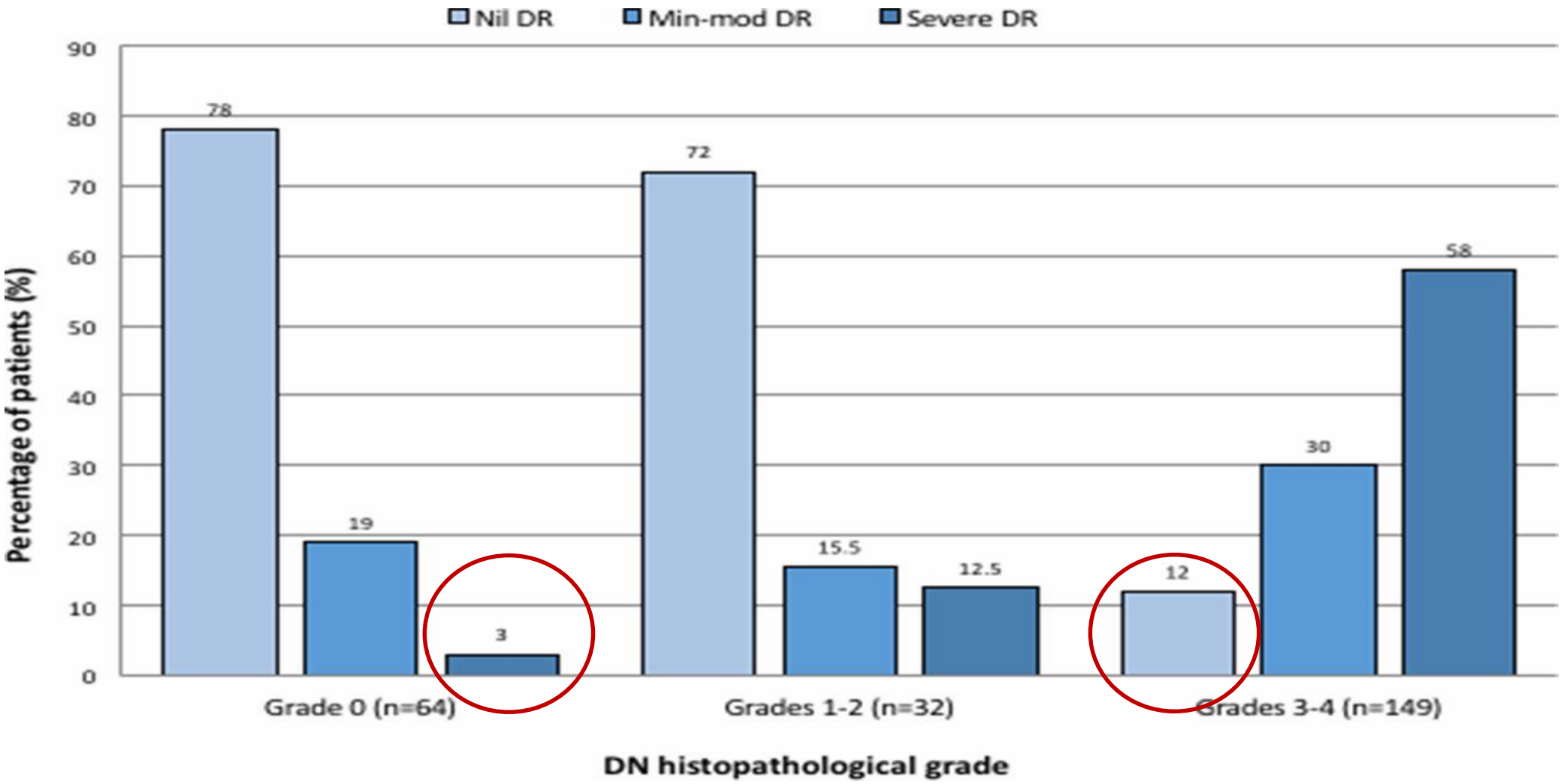
Relationship between grades of diabetic retinopathy and severity of diabetic renal lesions (n=245).



Jasmine Tan et al. BMJ Open Diab Res Care 2017;5:e000412

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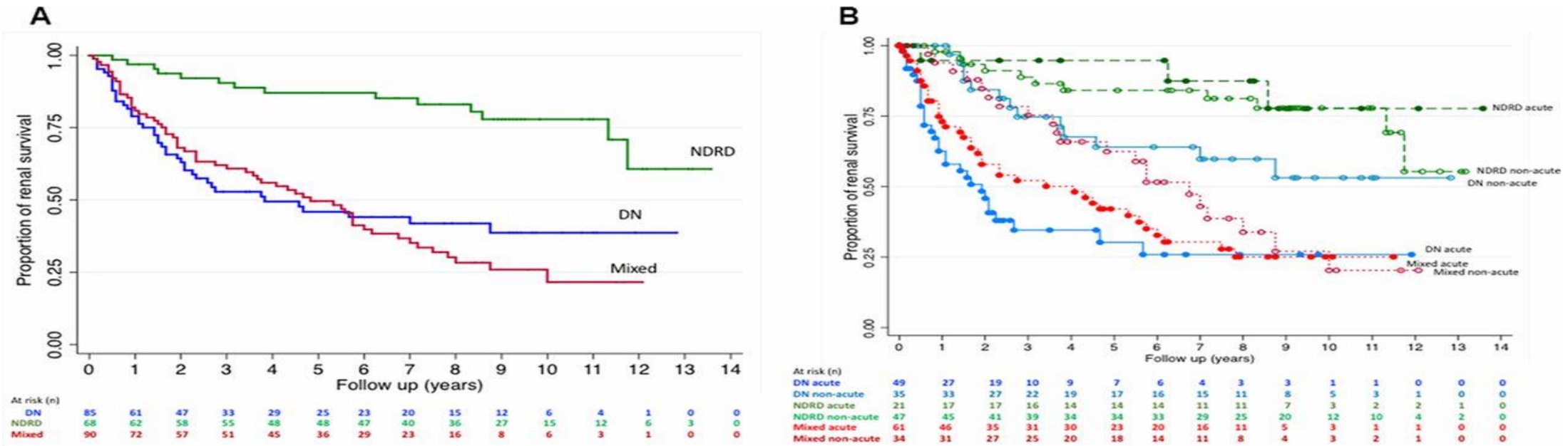
(A) Kaplan-Meier renal survival estimates of patients with diabetic nephropathy (DN), non-diabetic renal disease (NDRD) and mixed groups, adjusting for age, ethnicity, BMI, gender, proteinuria and eGFR at the time of biopsy.



Jasmine Tan et al. BMJ Open Diab Res Care 2017;5:e000412

BMJ Open Diabetes Research & Care

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How might the results of biopsies change the focus of research or clinical practice?

- Timely renal biopsy and nephrology referral can lead to change in treatment
- Provide an overview of the renal prognosis of the heterogeneous nephropathies in patients with type 2 diabetes
- Provide a platform for further research into the natural history of nephropathy in type 2 diabetes and to identify modifiable risk factors associated with acute kidney injury in those with diabetic nephropathy

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Prognosis/Outcome

- NDRD typically associated with CKD presentation (mostly FSGS) has a more benign natural history than DNP
- Renal histopathology led to a change in management of 1 in 8 patients (most commonly immunosuppressive therapy)
- The impact of treatment on outcome remains to be uncertain
- Overall survival less affected by the etiology of renal disease or the severity of diabetic lesions, probably because of high cardiovascular mortality

Jasmine Tan et al. BMJ Open Diab Res Care 2017;5:e000412

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Case Challenge #1 (3817)

- 74 year-old male with history of type 2 DM, hypertension, and stable CKD3 presents with
  - 2 grams of proteinuria/24 hours
- Biopsy performed
- What is your differential diagnosis?
  - Diabetic nephropathy, advanced
  - Diabetic nephropathy with superimposed glomerular disease
  - Something else (non-diabetic renal disease)
- Audience response

UCSF

Diagnosis

- Hypertensive nephrosclerosis with severe vascular changes in the background of mild (class 2a) diabetic glomerulosclerosis
- FSGS cannot be excluded

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Case challenge #2 (3819)

- 73 year-old Caucasian female with history of type 2 DM (10+ years), hypertension, and CKD3 presents with
  - 5gr of proteinuria/24 hours
  - rising serum creatinine
- Differential diagnosis
  - Diabetic nephropathy
  - Diabetic nephropathy with superimposed glomerular disease
  - Something else (non-diabetic renal disease)
- Audience response

UCSF

Diagnosis

- Mild diffuse diabetic nephropathy (class 2a) with focal segmental glomerulosclerosis (FSGS) (secondary vs primary?)

Case challenge #3 (30243)

- 47-year-old woman with history of type 1 DM, retinopathy, and hypertension presents with
  - weight gain, leg swelling
  - nephrotic syndrome
  - serum creatinine: 2.6.
- Differential diagnosis
  - Diabetic nephropathy
  - Diabetic nephropathy with superimposed glomerular disease
  - Something else (non-diabetic renal disease)
- Audience response

UCSF

Diagnosis, caveats

- Nodular DNP (class 3) with severe IFTA and diffuse effacement of the foot processes
- Consider secondary MCD: Search for triggers!

UCSF

Case challenge #4 (1589N1)

- 69-year-old male with history of type 2 DM and hypertension presents with
  - AKI (se creatinine 6.5; baseline 1.5, 6 months ago)
  - Sub-nephrotic range proteinuria (3g/24hours), microscopic hematuria
- Differential diagnosis
  - Diabetic nephropathy
  - Diabetic nephropathy with superimposed glomerular disease
  - Something else (non-diabetic renal disease)
- Audience response

UCSF

Diagnosis and interpretation

- Nodular DNP (class 3) with severe IFTA and scattered eosinophils in the interstitium
- Rule out allergic (drug-induced?) tubulointerstitial nephritis

Utility of renal biopsy in patients with diabetic nephropathy

- Exclude causes of proteinuria other than DNP
- Classify the severity of disease in those patients with “pure” DNP
- Classify DNP when it is complicated by another superimposed disease

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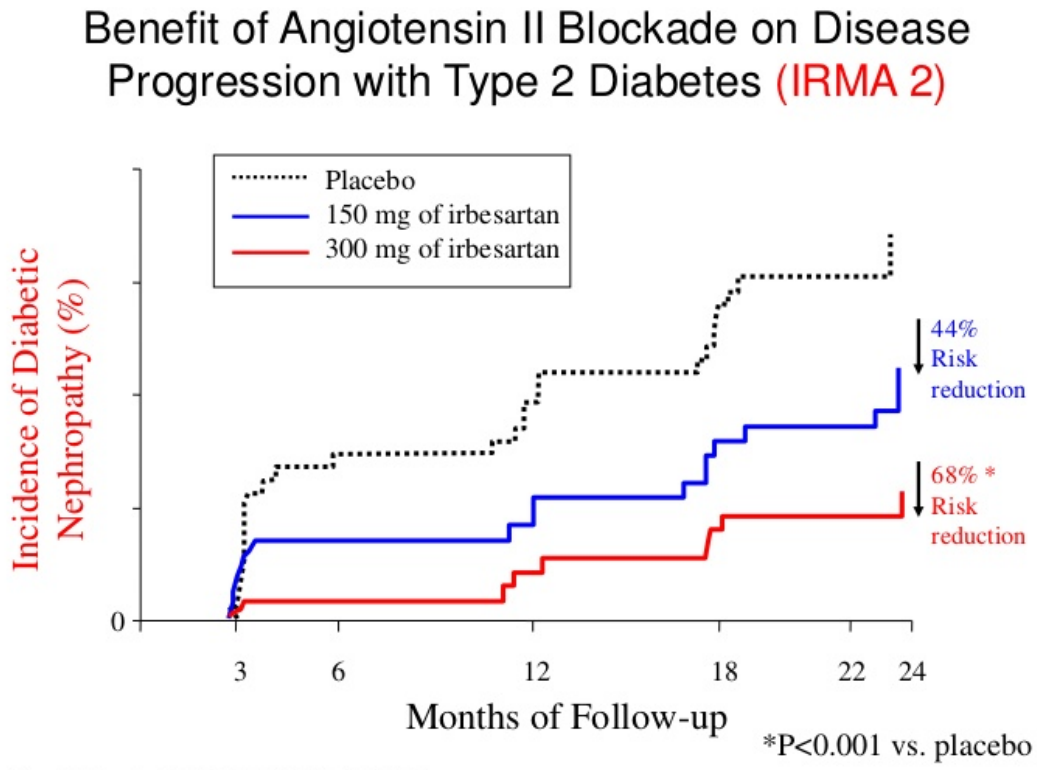
Management of diabetic renal disease



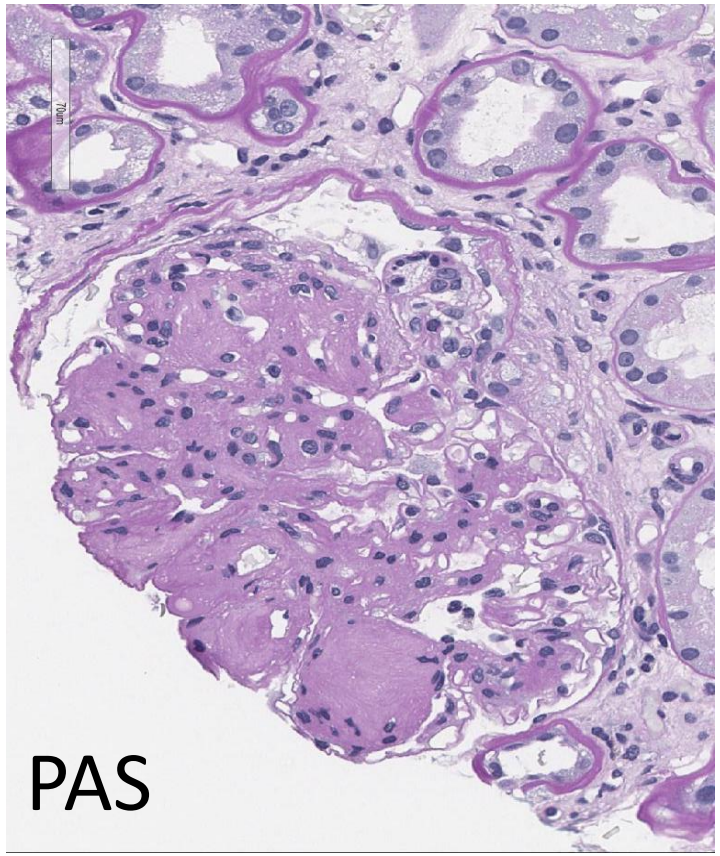
Parving, HH et al. NEJM 2001;345: 870-878

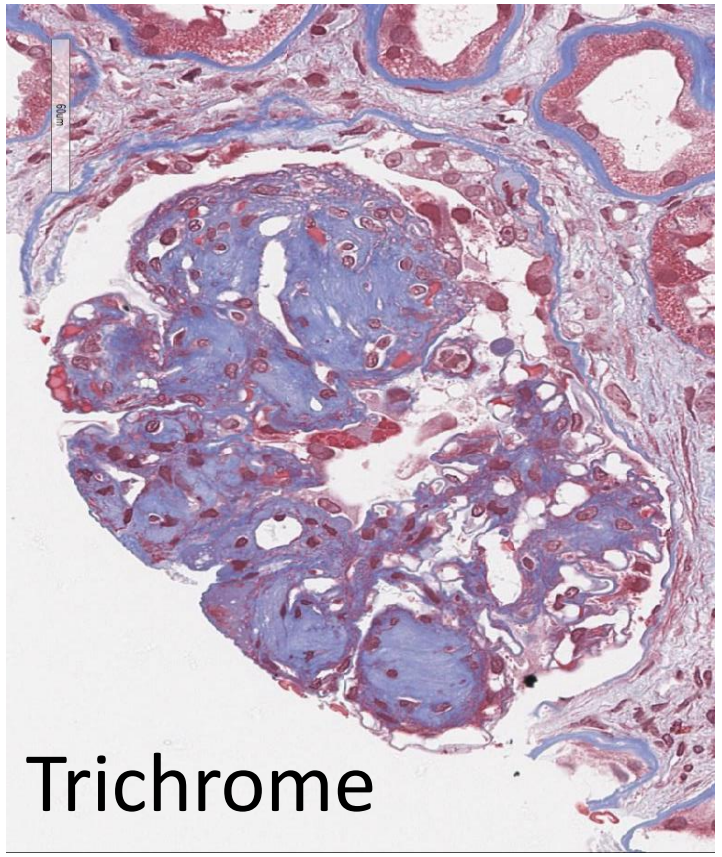
- Has largely been focused on remission of proteinuria through blood pressure lowering and the anti-proteinuric effects of ACE inhibitors and angiotensin II receptor blockers

Learning Objective 4

Not everything that shines is gold.
Mimickers and copy-cats.

The morphologic characteristics of DNP
Staining properties


PAS

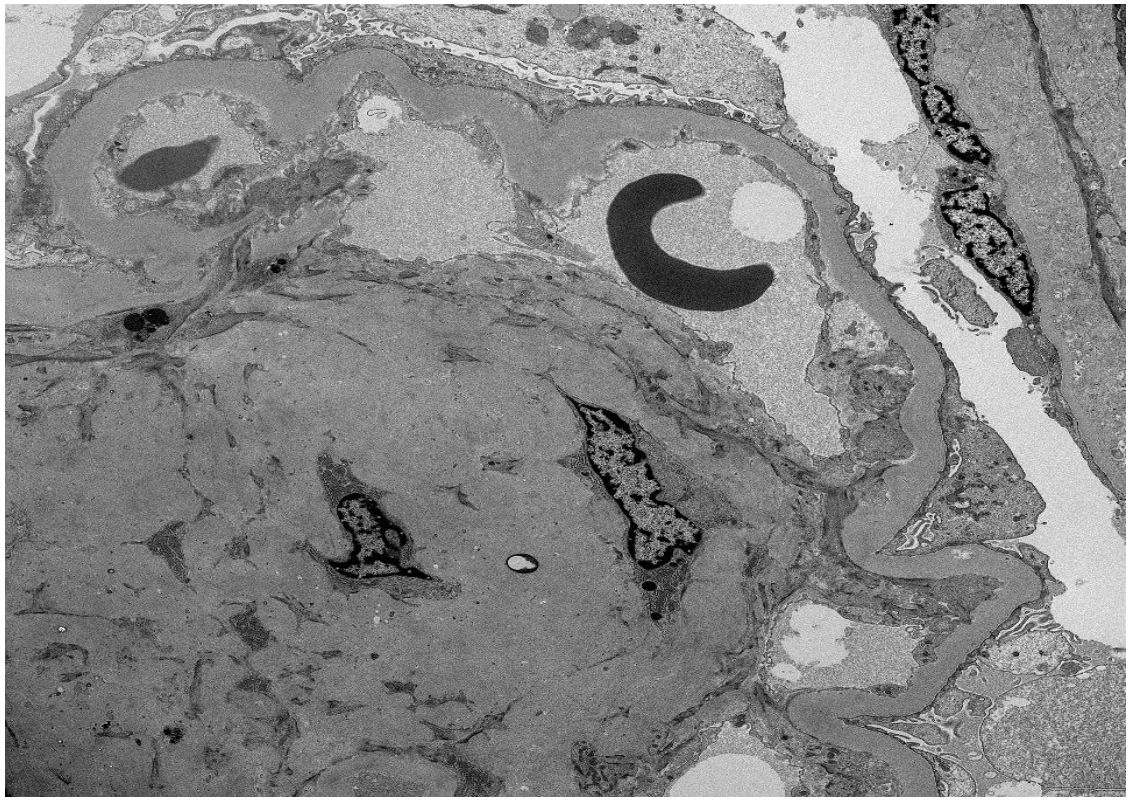

Trichrome

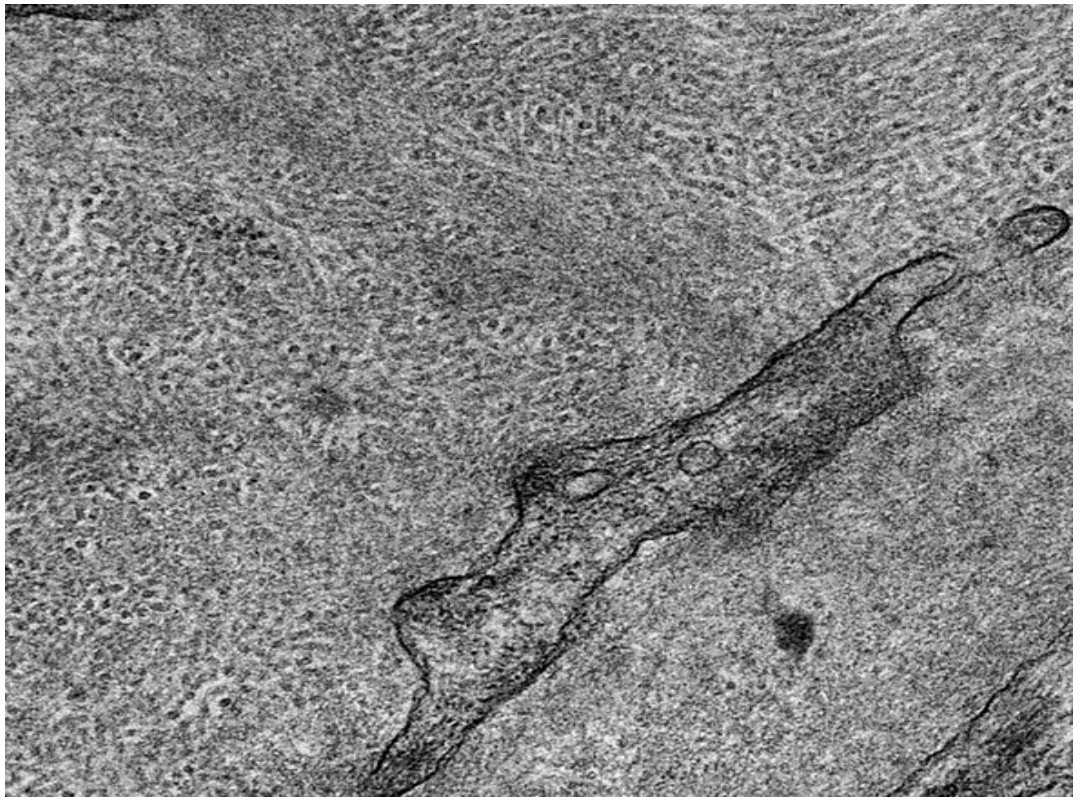
Silver

Morphologic differential diagnosis of nodular glomerulopathies

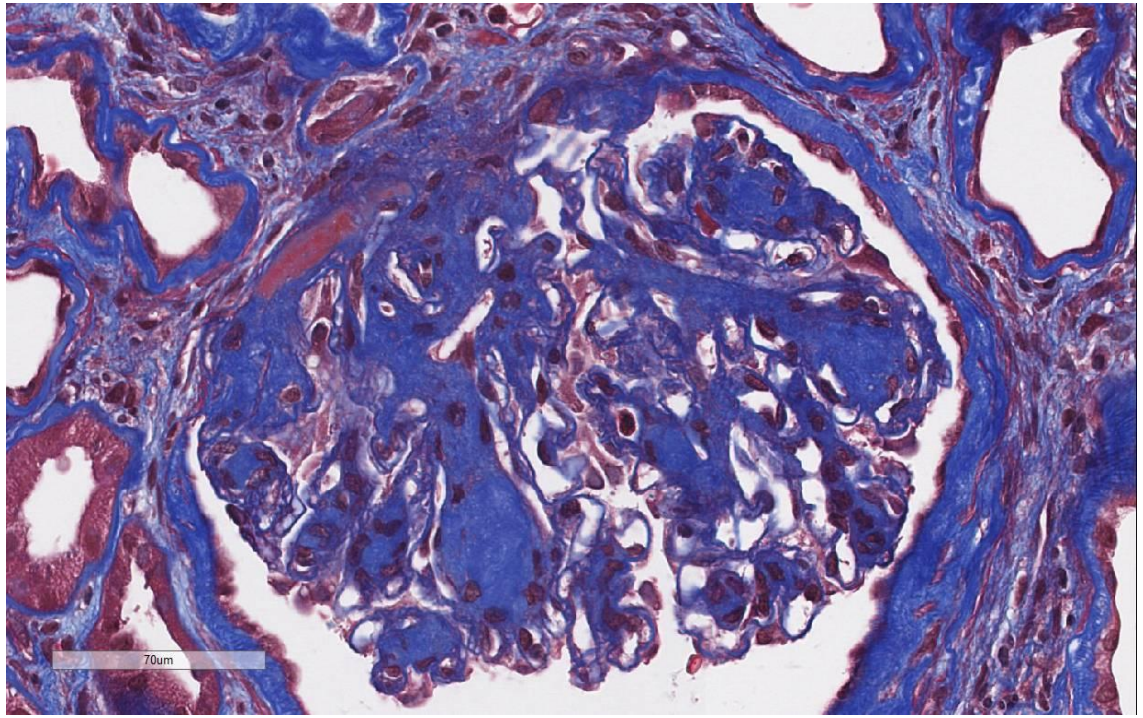
		DGS and INGS	MIDD	Amyloidosis	FI/IT	CFGP
LM	**H&E**	Eosinophilic	Eosinophilic	Pale/glassy	Pale/glassy	Pale
	PAS	**Positive**	Positive	Negative	Positive	Negative/weakly +
	Silver	**Argyrophilic**	Usually non-A	Usually non-A	Usually non-A	Usually non-A
	Trichrome	**Dark-blue**	Red-blue	Gray-purple	Gray-purple	Pale-blue
	Congo-red	Negative	Negative	Positive	Negative	Negative
IF		IgG & albumin, linear; GBM/TBM	κ or λ, linear, and/or single HC; GBM/TBM	κ or λ, smudgy; mesangial, peripheral (AL type); negative (AA, other)	IgG, C3, κ & λ (FI); IgG, C3, κ or λ or κ & λ (IT); smudgy	Negative
EM		GBM thickening and mesangial matrix accumulation	Punctate deposits, GBM/TBM	Randomly oriented fibrils (8-12 nm)	Fibrillary deposits (12-30 nm) microtubular deposits (>30 nm)	Banding collagen fibers

Electron microscopy

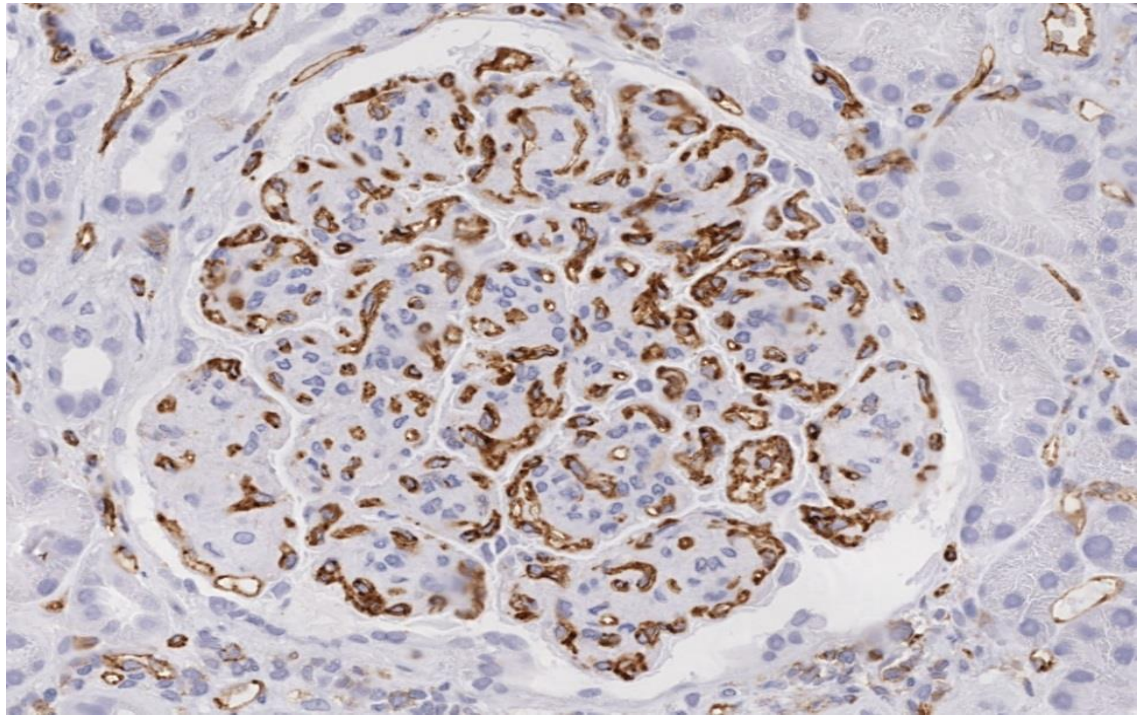




Idiopathic nodular glomerulosclerosis (INGS)

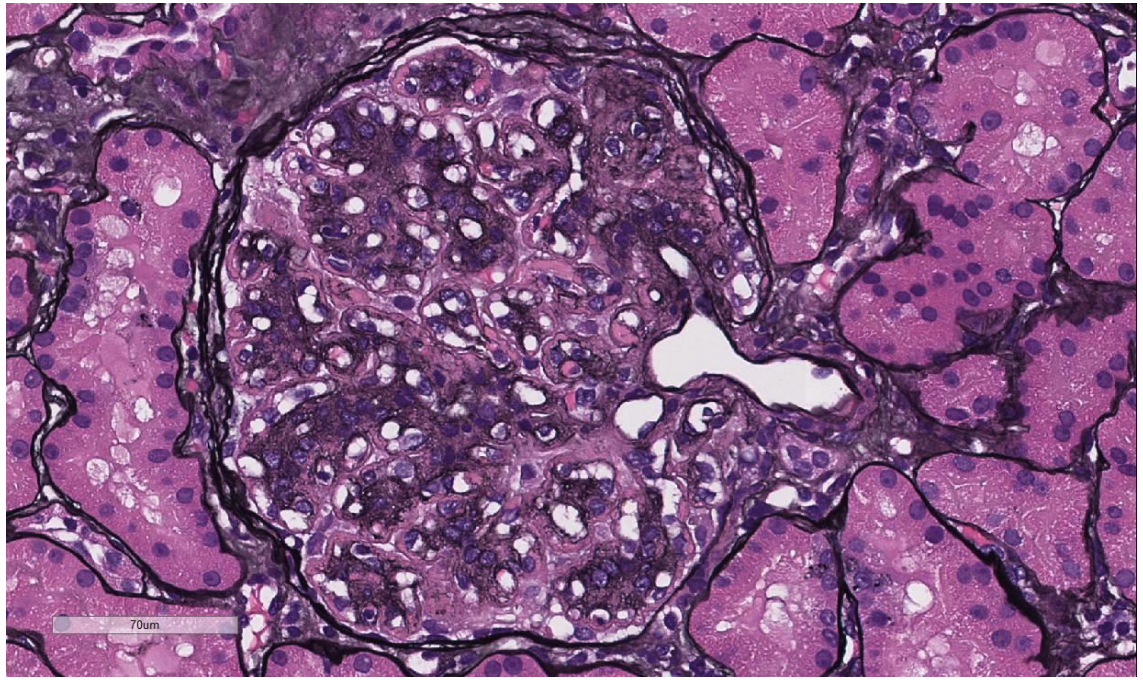


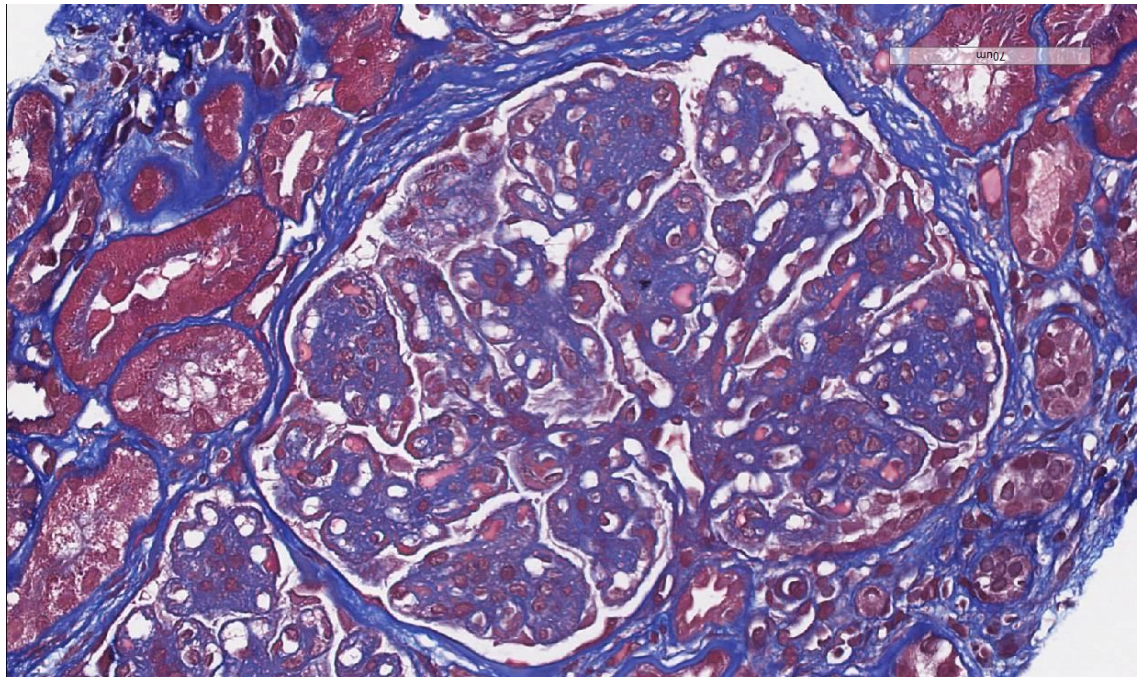
CD34



History is smoking in older white males.

Monoclonal immunoglobulin deposition disease (MIDD)





- Usually in the background of multiple myeloma or MGUS
- Usually without concurrent amyloidosis
- Both in native and transplant kidneys

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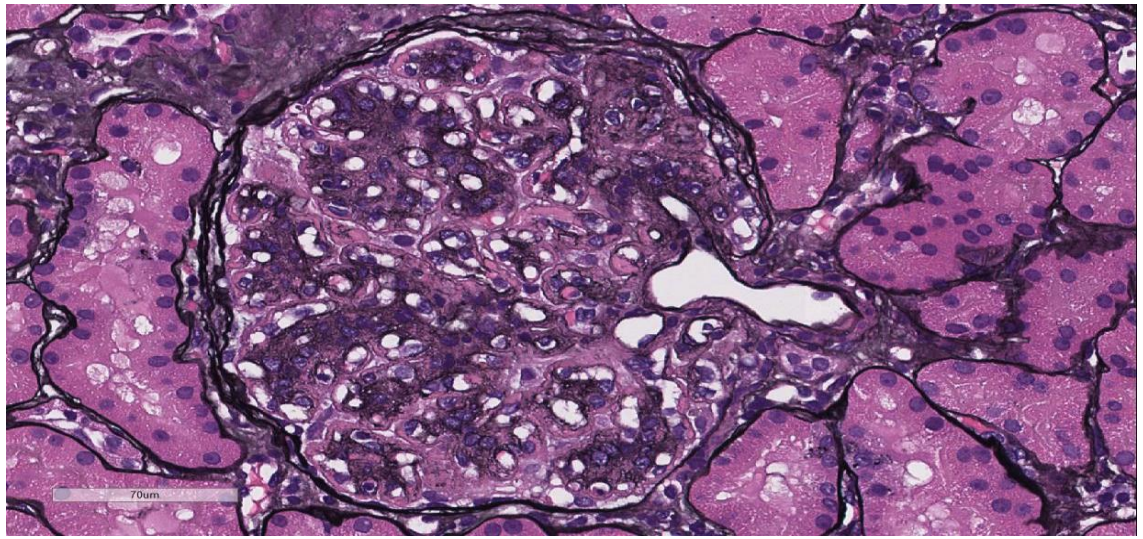
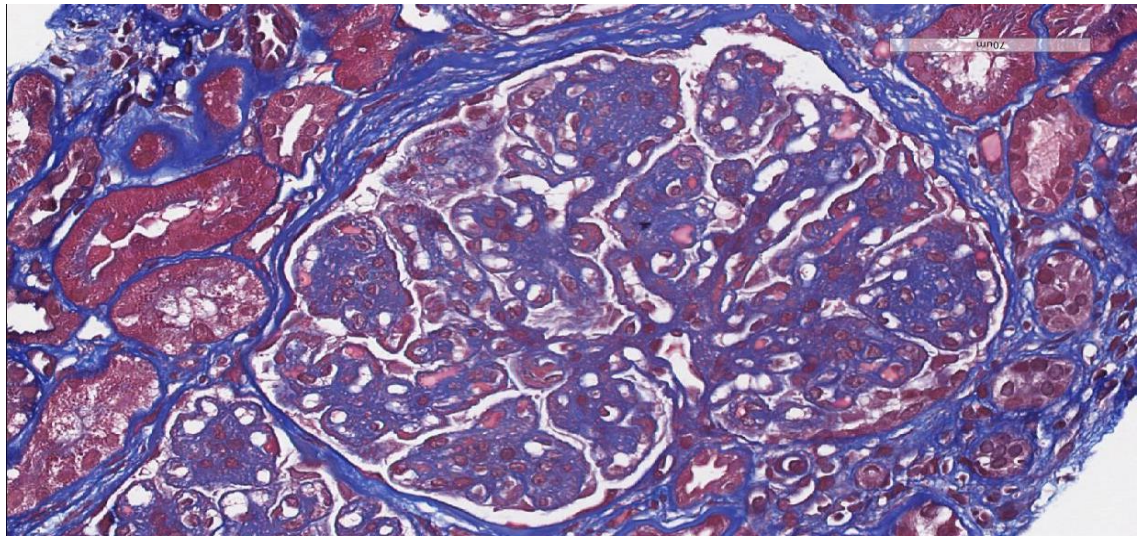
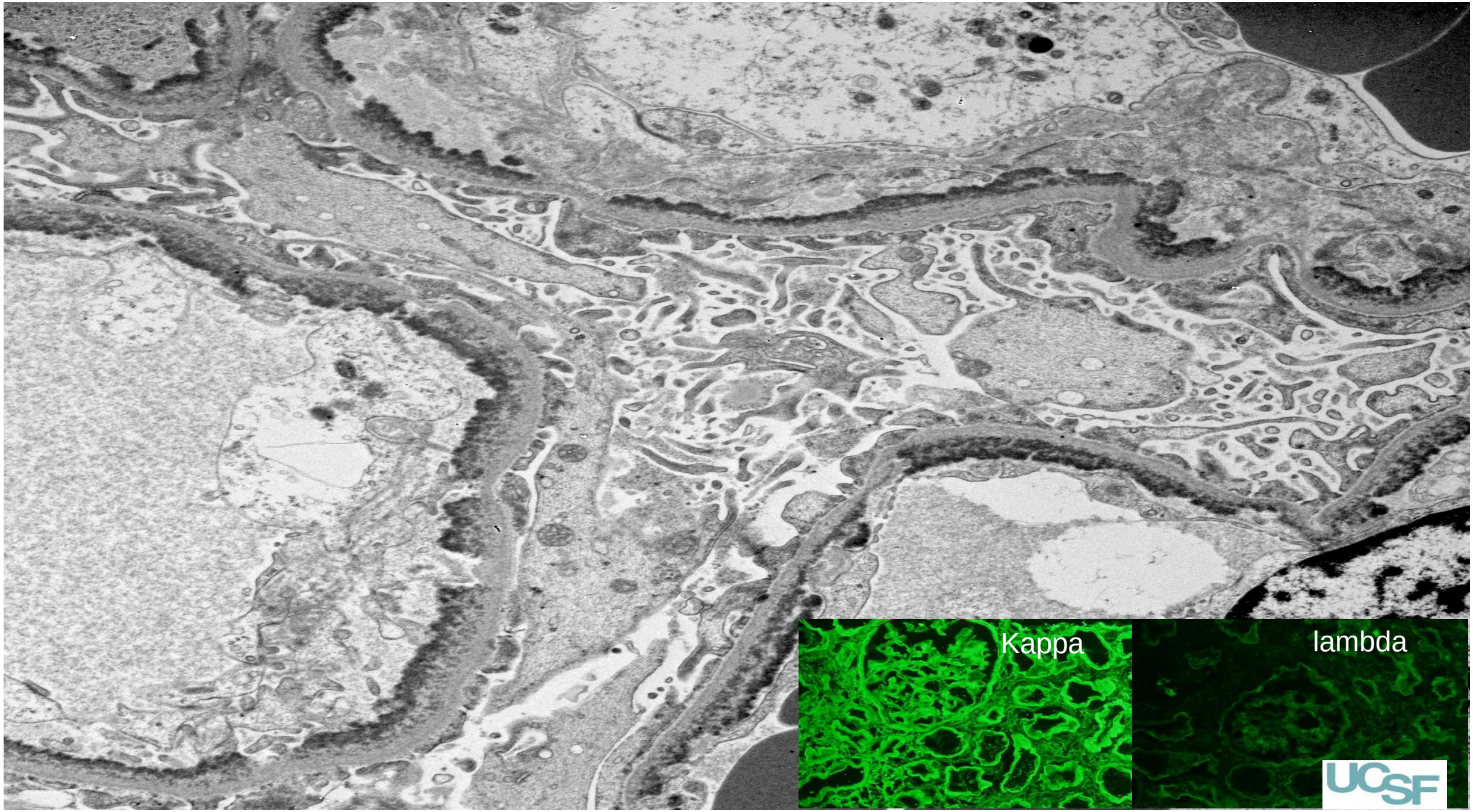
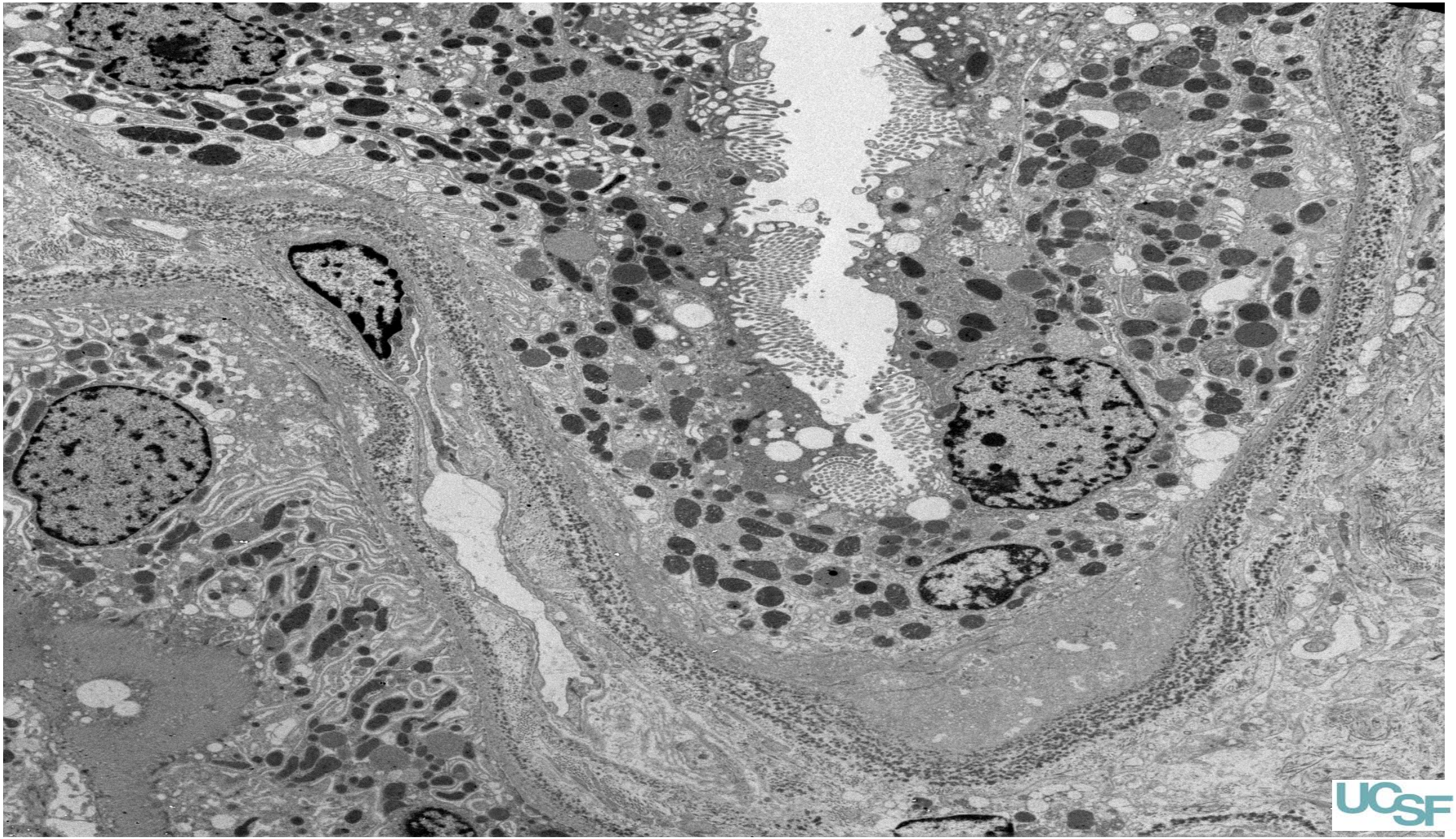
Monoclonal immunoglobulin deposition disease (MIDD)





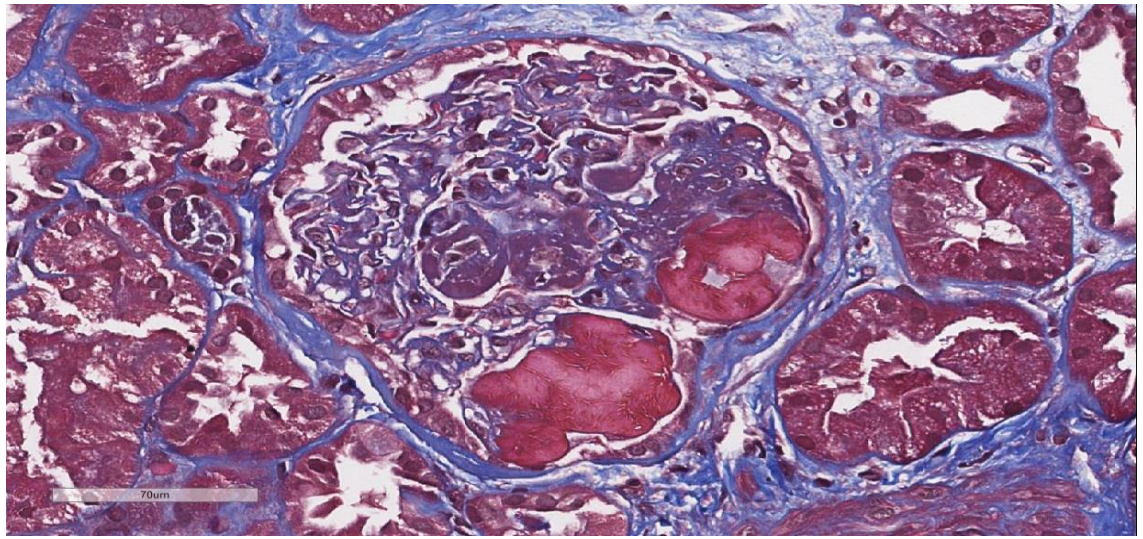
		DGS and INGS	MIDD	AM	FI/IT	CFGP
LM	**H&E**	Eosinophilic	Eosinophilic	Pale/glassy	Pale/glassy	Pale
	PAS	Positive	Positive	Negative	Positive	Negative/weakly +
	Silver	Argyrophilic	**Usually non-A**	Usually non-A	Usually non-A	Usually non-A
	Trichrome	Dark-blue	**Red-blue**	Gray-purple	Gray-purple	Pale-blue

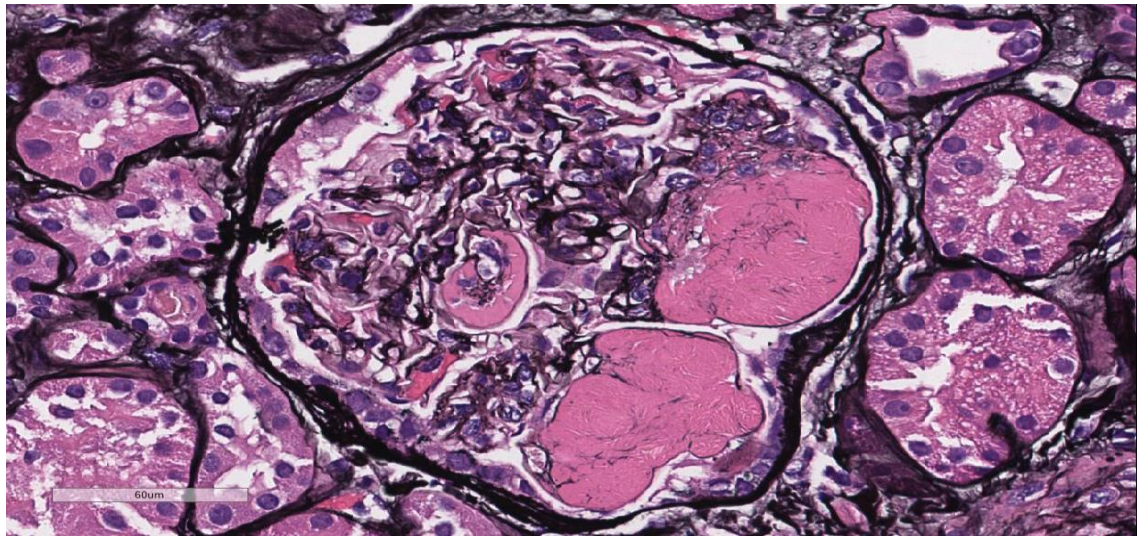

Kappa
lambda
UCSF

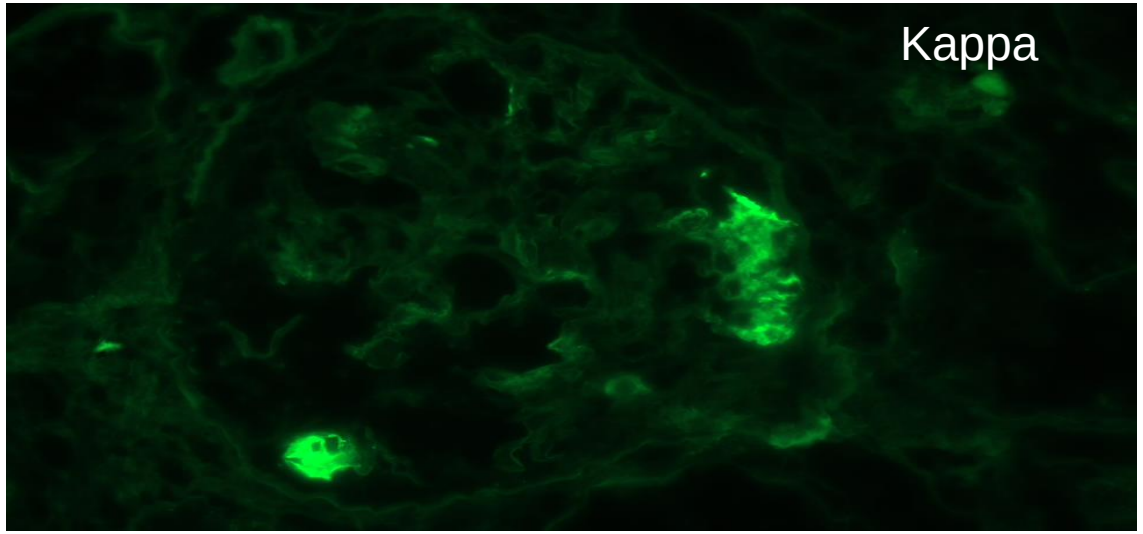


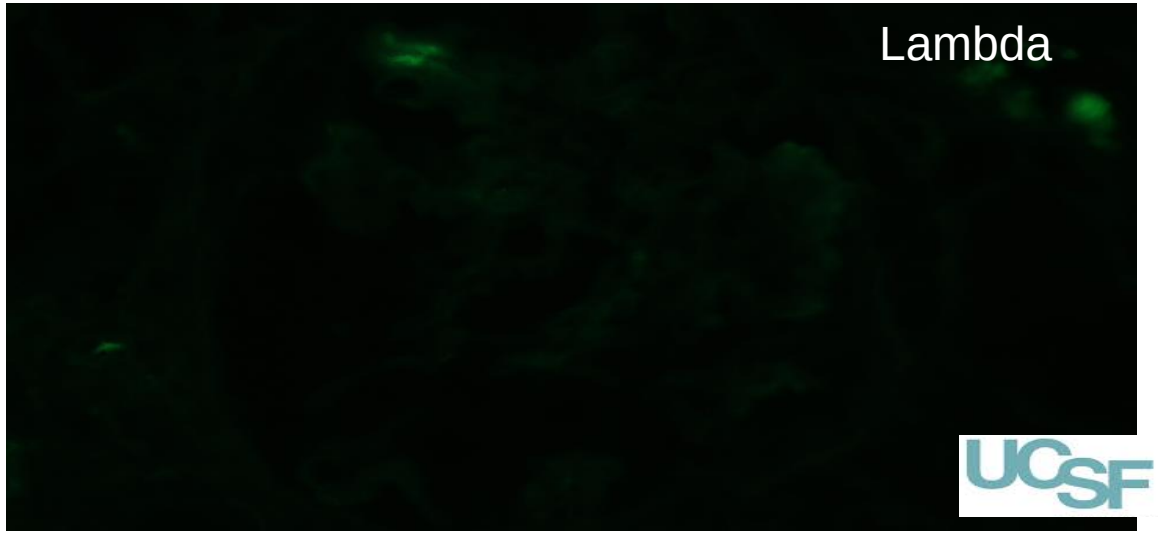
The many faces of MIDD

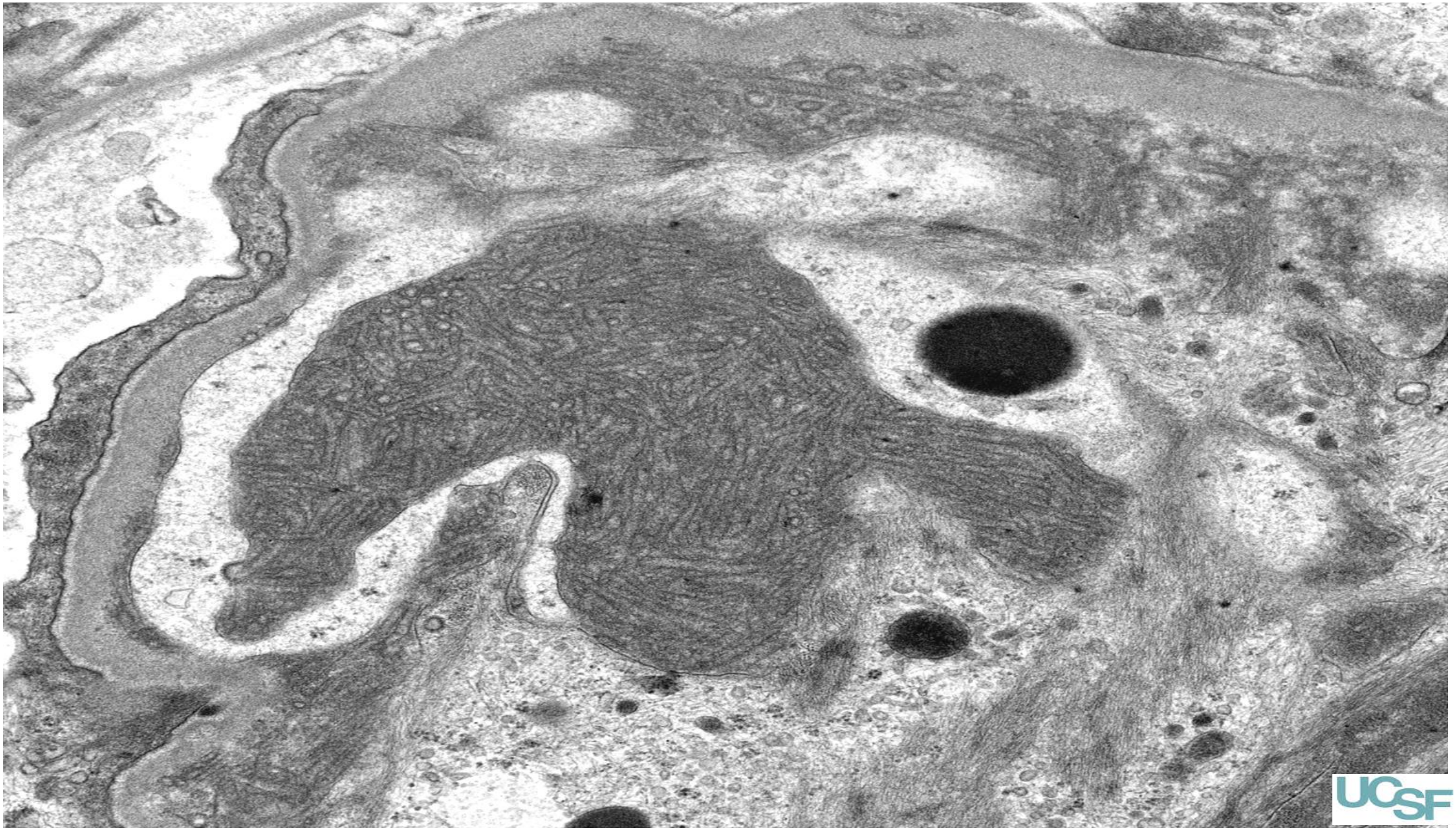
Seven years post transplant; original disease FSGS



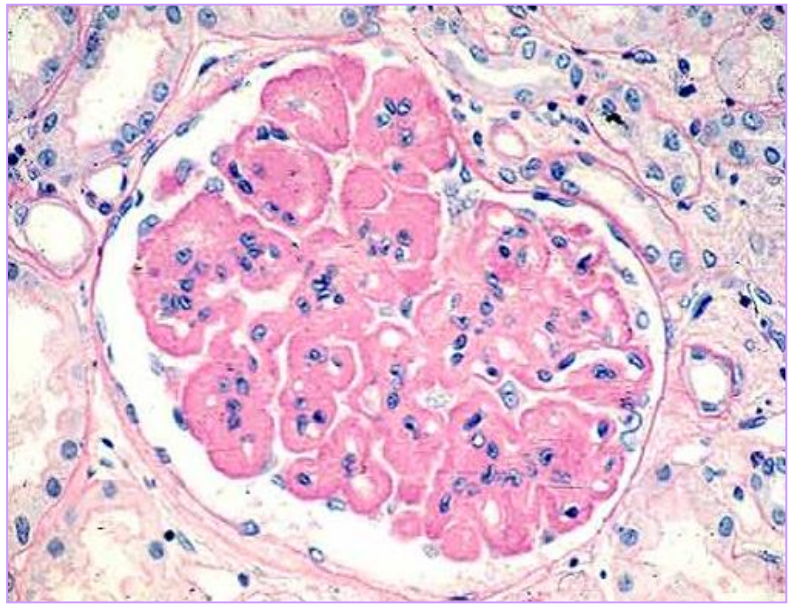




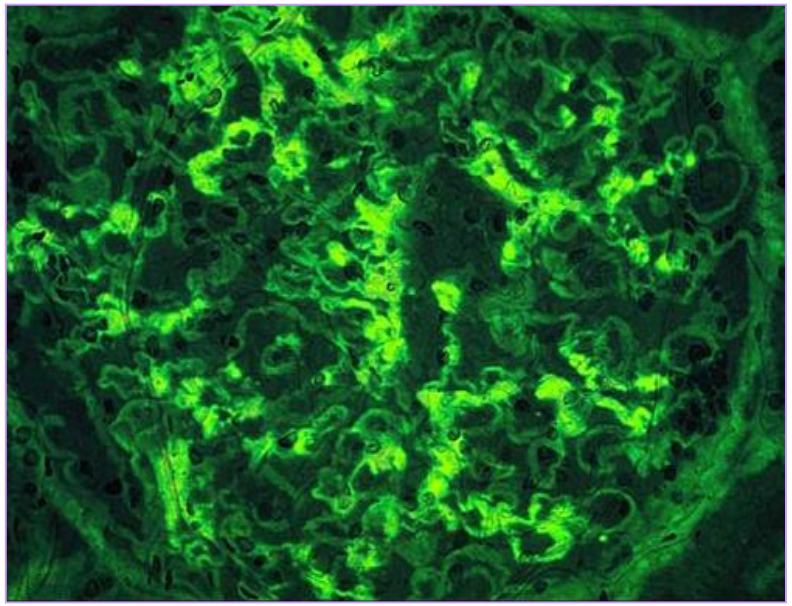




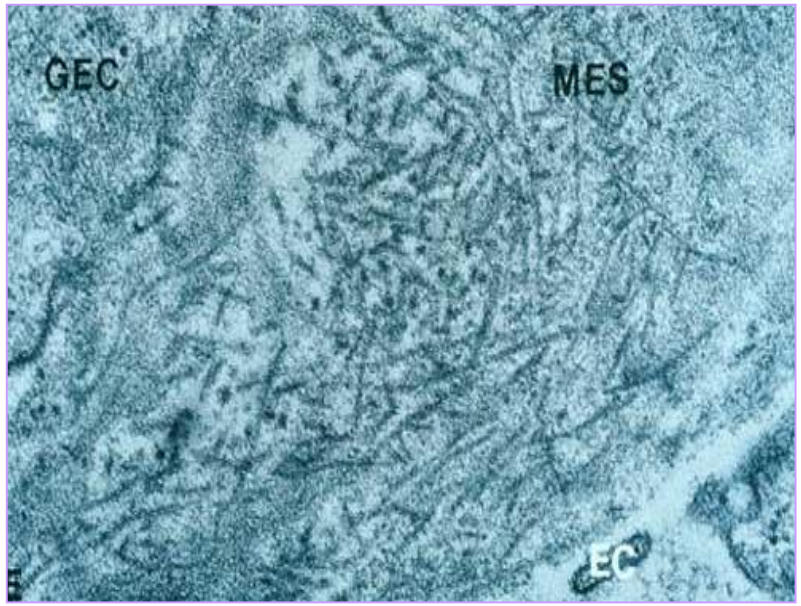
Fibrillary/immunotactoid GN



Congo-red negative fibrillary GN



Coarse granular mesangial IgG & C3



EM: 12-16 nm randomly oriented fibrils

Rosenmabn & Eliakim Nephron 18:301-303, 1977

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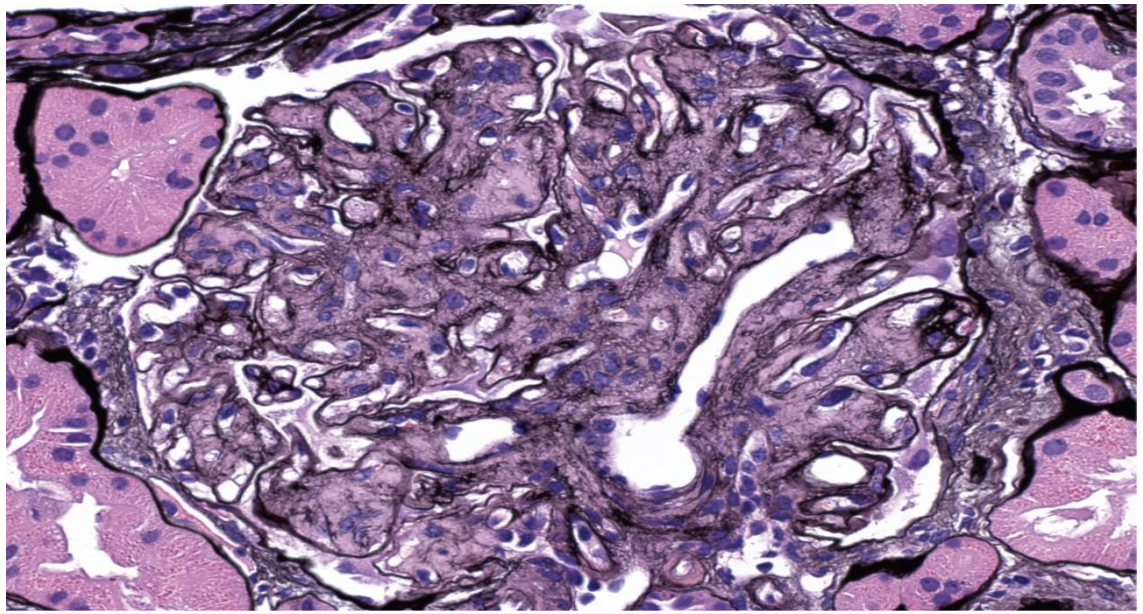
Fibrillary/immunotactoid GN



- **IF:** IgG, C3, κ & λ (FI); IgG, C3, κ or λ or κ & λ (IT); smudgy
- **EM:** fibrillary or microtubular deposits

		DGS and INGS	MIDD	AM	FI/IT	CFGP
LM	**H&E**	Eosinophilic	Eosinophilic	Pale/glassy	Pale/glassy	Pale
	PAS	Positive	Positive	Negative	Positive	Negative/weakly +
	Silver	Argyrophilic	**Usually non-A**	Usually non-A	**Usually non-A**	Usually non-A
	Trichrome	Dark-blue	**Red-blue**	Gray-purple	Gray-purple	Pale-blue

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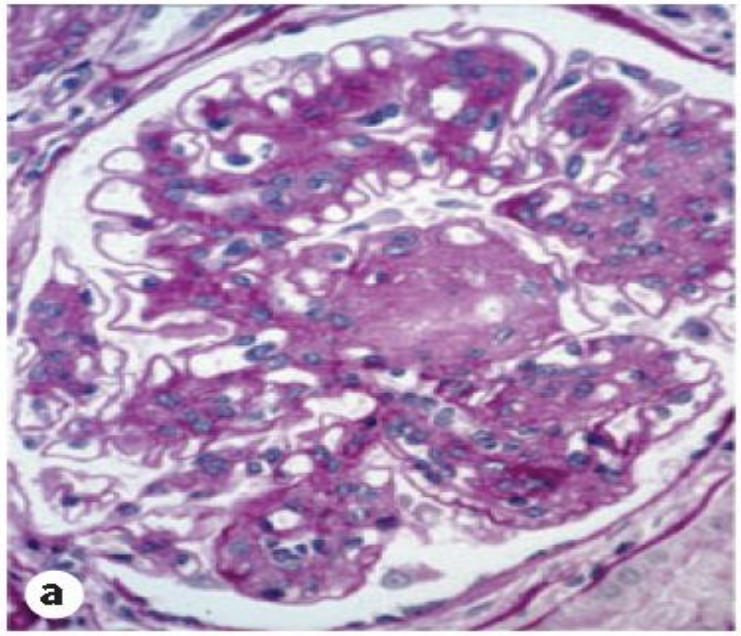
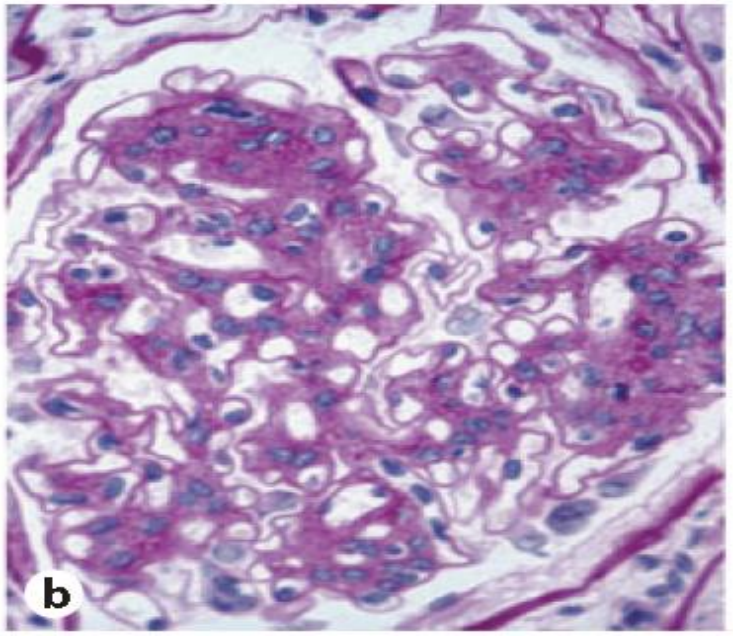
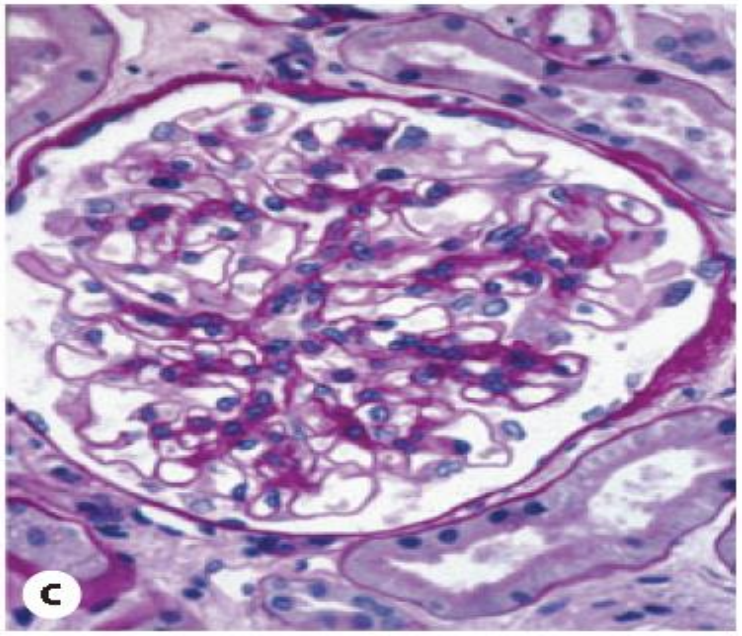
Reversibility of DNP after pancreas transplantation



baseline



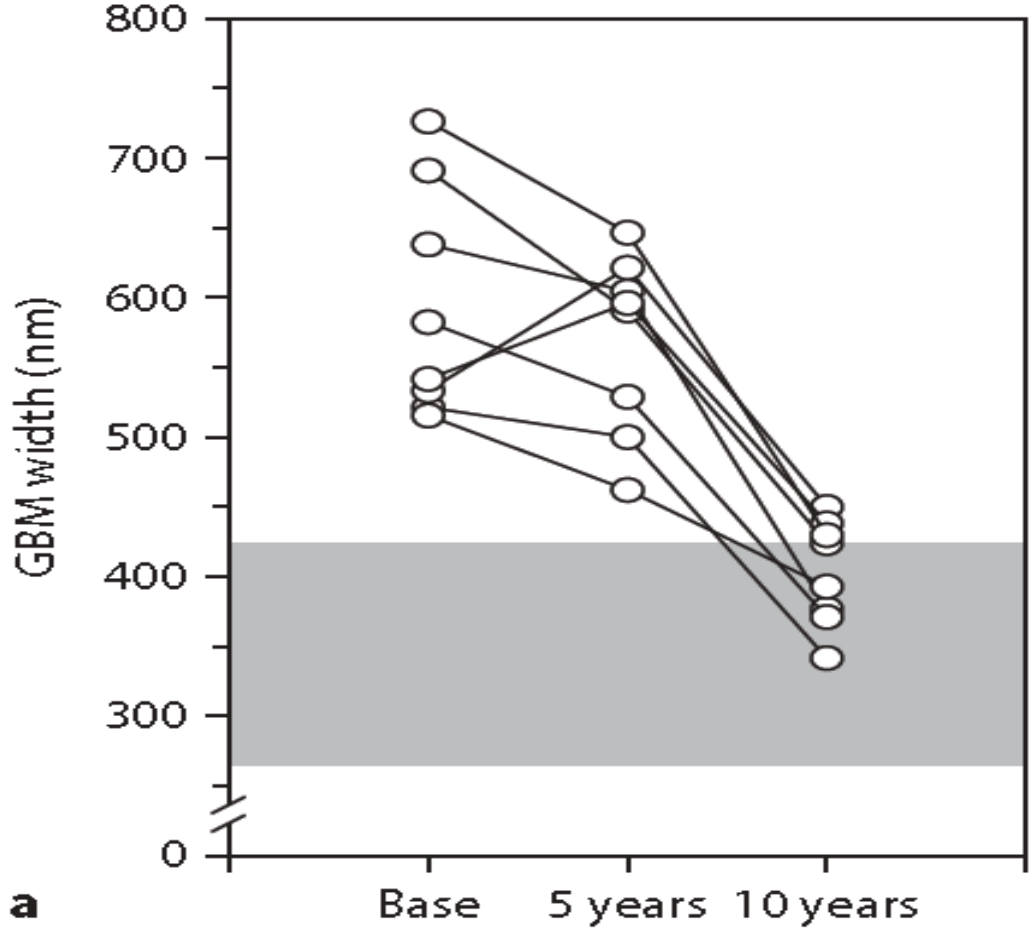
5 years after pancreas transplantation

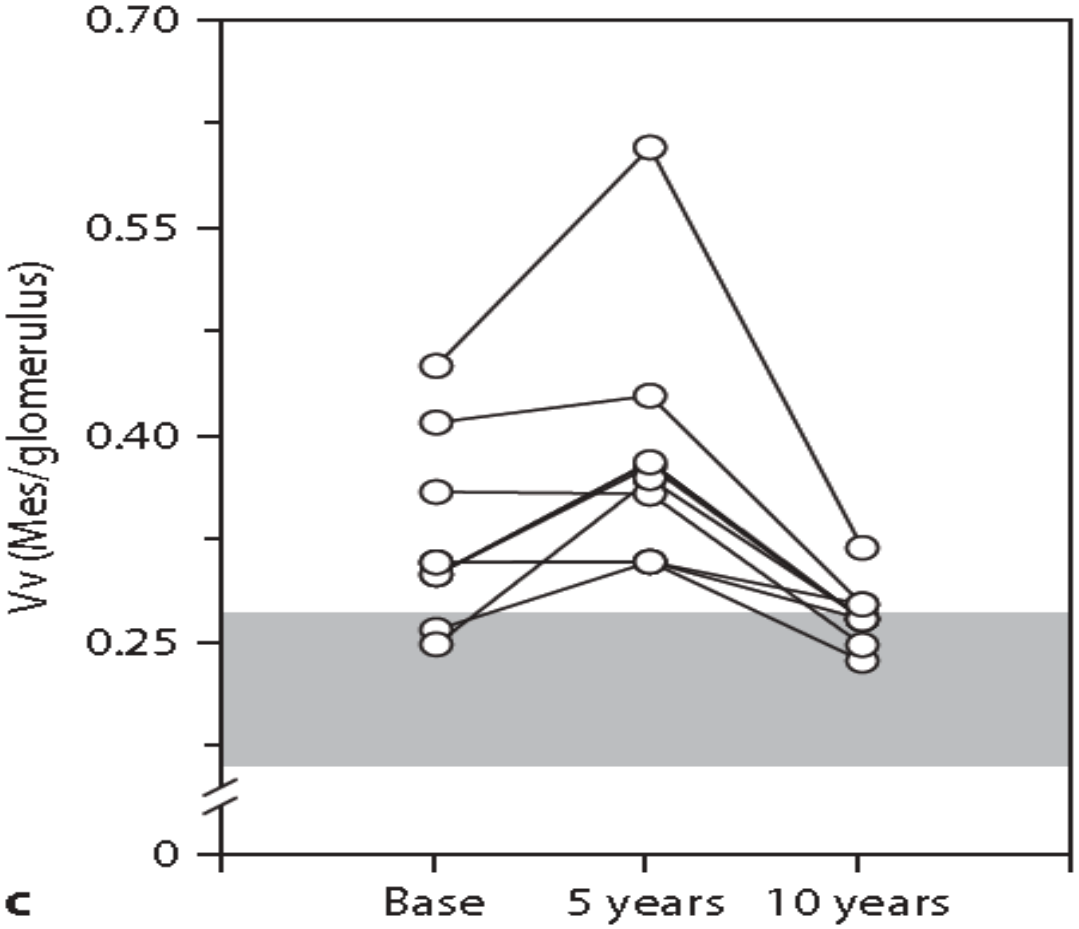


10 years after pancreas transplantation

N Engl J Med. 1998;339(2):69-75.

GBM thickness and fractional mesangial volume after pancreas Tx

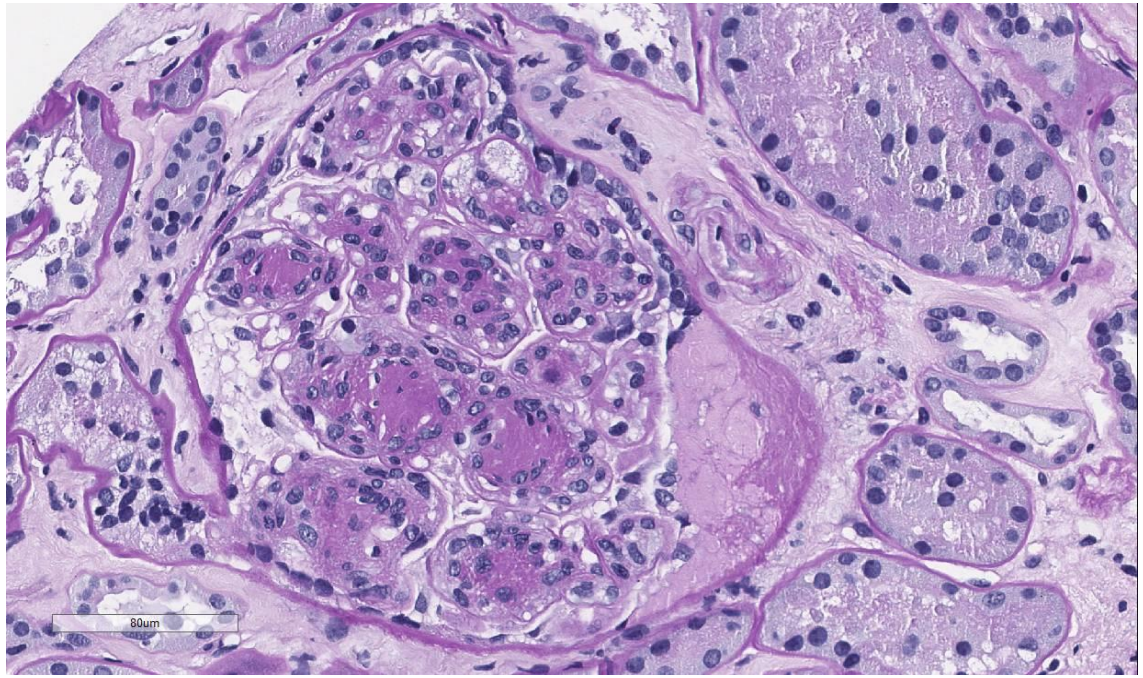




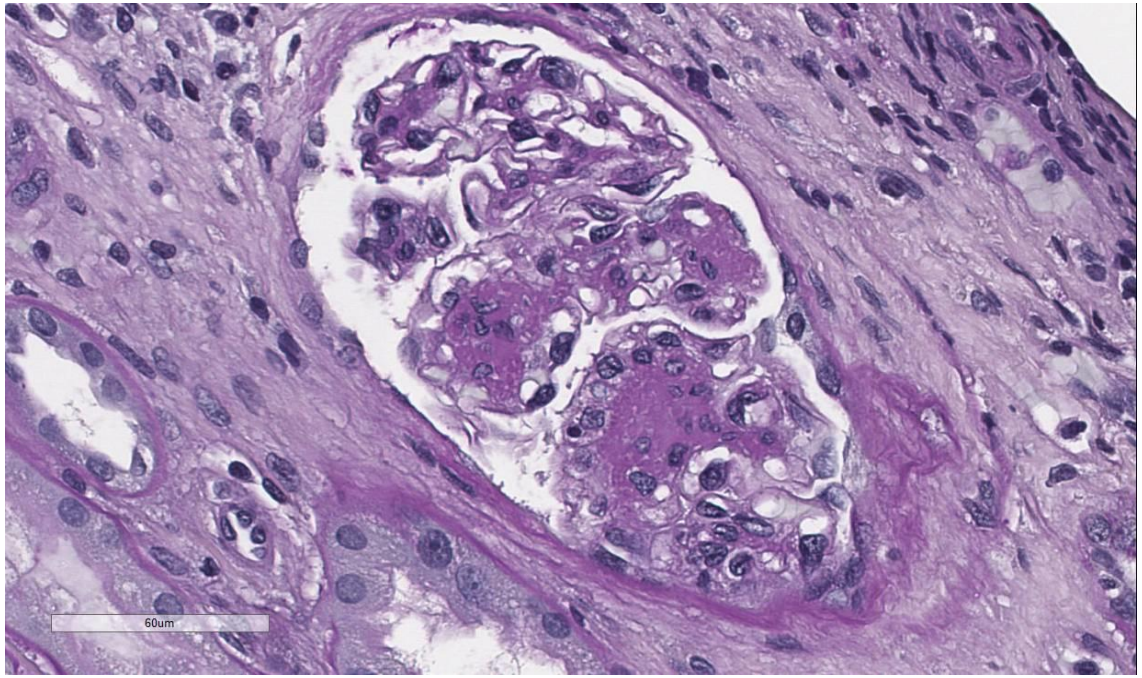
N Engl J Med. 1998;339(2):69-75.

Lack of reversal of DNP after Tx in a non-diabetic patient

3 years post-Tx



7 years post-Tx



Questions
& Answers

Thank You!

How Does NODAT Accelerate Graft Loss?

- No specific histologic phenotype has been described
- Recurrence of diabetic nephropathy is not common

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Impact of glucose metabolism abnormalities on histopathological changes in kidney transplant protocol biopsies

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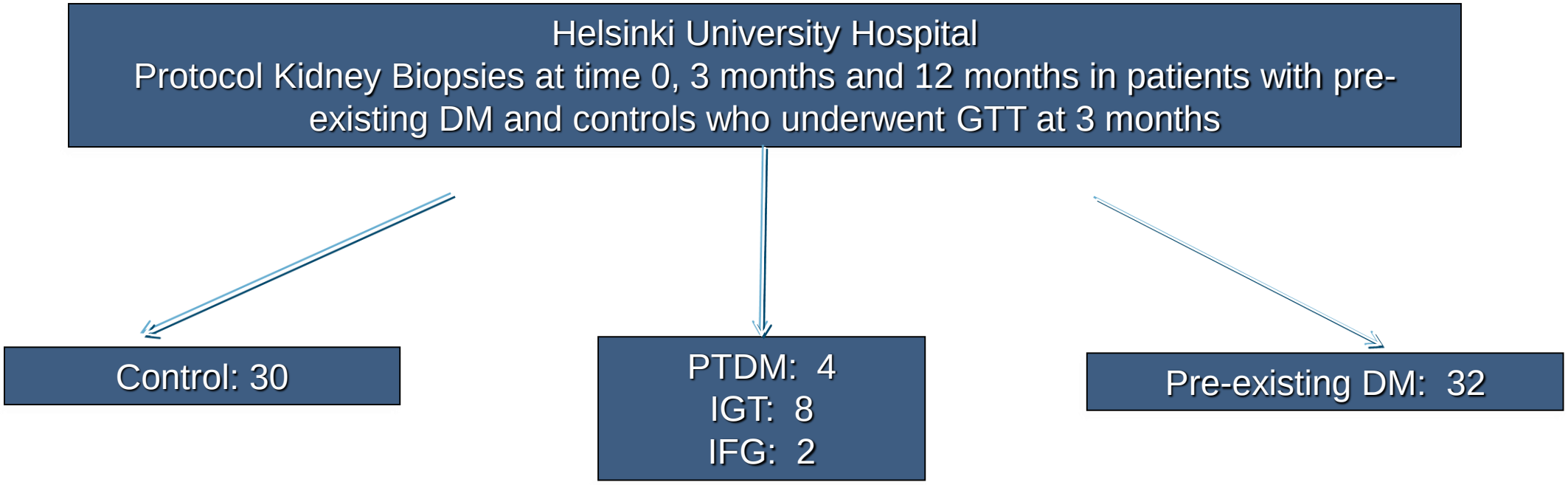
Helsinki University Hospital
Protocol Kidney Biopsies at time 0, 3 months and 12 months in patients with pre-existing DM and controls who underwent GTT at 3 months
Control: 30
PTDM: 4
IGT: 8
IFG: 2
Pre-existing DM: 32

Renal function (eGFR) estimated with Cockcroft- and Gault-equation (28), chronic allograft damage index (CADI) at 0, 3, 12 months, and changes in CADI (ΔCADI) between different time-points of biopsies in patients with normal glucose tolerance (controls); impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or post-transplant diabetes mellitus (PTDM); or pre-existing diabetes

	Controls (n=30)	IFG, IGT or PTDM (n=14)	Pre-existing diabetes (n=32)
CADI at baseline	0.3 ± 0.5	0.9 ± 1.0	0.5 ± 0.8
CADI at 3 months*	0.9 ± 1.1	2.2 ± 2.1	1.2 ± 1.1
CADI at 12 months	1.7 ± 1.6	2.9 ± 2.2	1.6 ± 1.4
ΔCADI 0-12 months	1.5 ± 1.6	2.1 ± 2.1	1.5 ± 1.2
eGFR at 12 months (ml/min)	74 ± 22	54 ± 12£	75 ± 23
eGFR at last follow-up (ml/min)	64 ± 23	52 ± 12	61 ± 26

All data expressed as mean ± SD.
*Biopsy at 3 months was available from 25 patients from the control group, 14 patients with IFG, IGT, or4 PTDM, and from 26 patients with pre-existing diabetes.
£P=0.006 between IFG, IGT or PTDM and controls and P=0.003 between IFG, IGT or PTDM and pre-existing diabetes (eGFR at 12 months).
All other differences are nonsignificant.

Summary

- Glucose abnormalities were associated with the progression of histopathological changes, especially in patients with already compromised kidneys, supporting the harmful role of NODAT to the kidney allograft.