Associazione Medici Endocrinologi

ITALIAN CHAPTER

3rd AME Diabetes Update

Diabete, Ipertensione e Nefropatia

Napoli, 16 - 17 marzo 2018

Hotel Royal Continental

Il danno renale in corso di Diabete Mellito tipo 2

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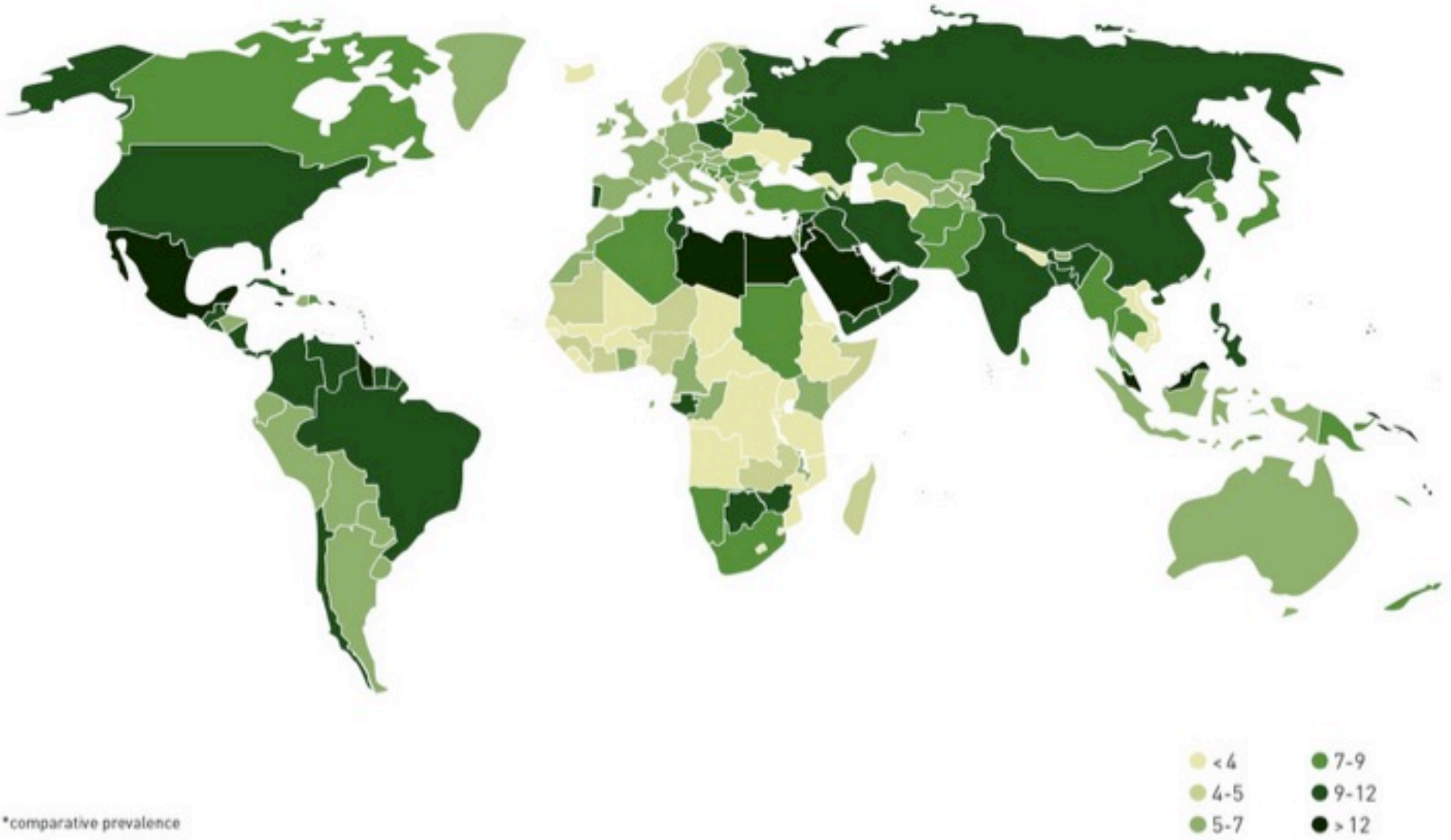
Leading European Nephrology

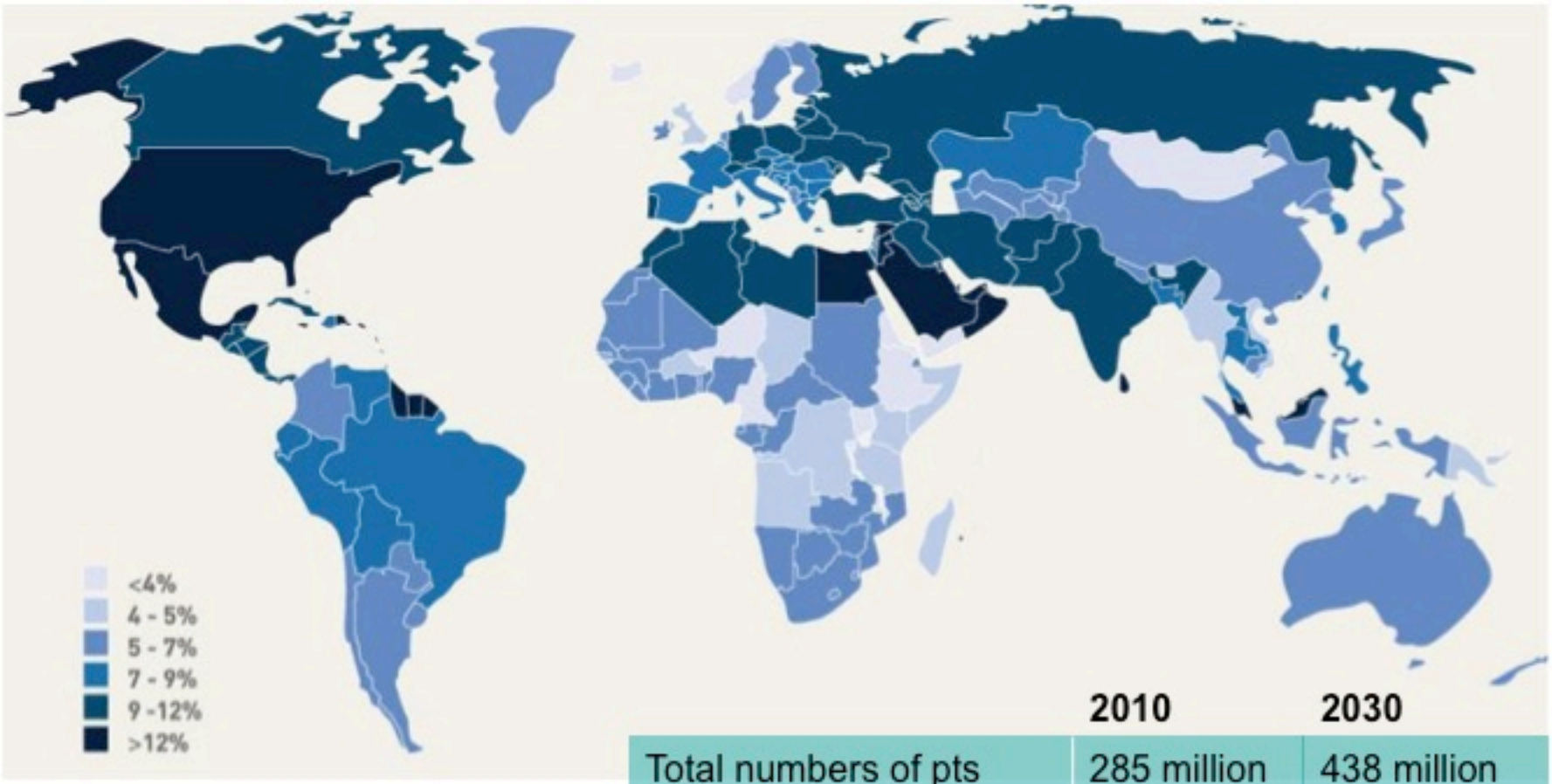
SIN reni Società Italiana Nefrologia

Prevalence (%) of diabetes in 2011 (20-79 years)



*comparative prevalence

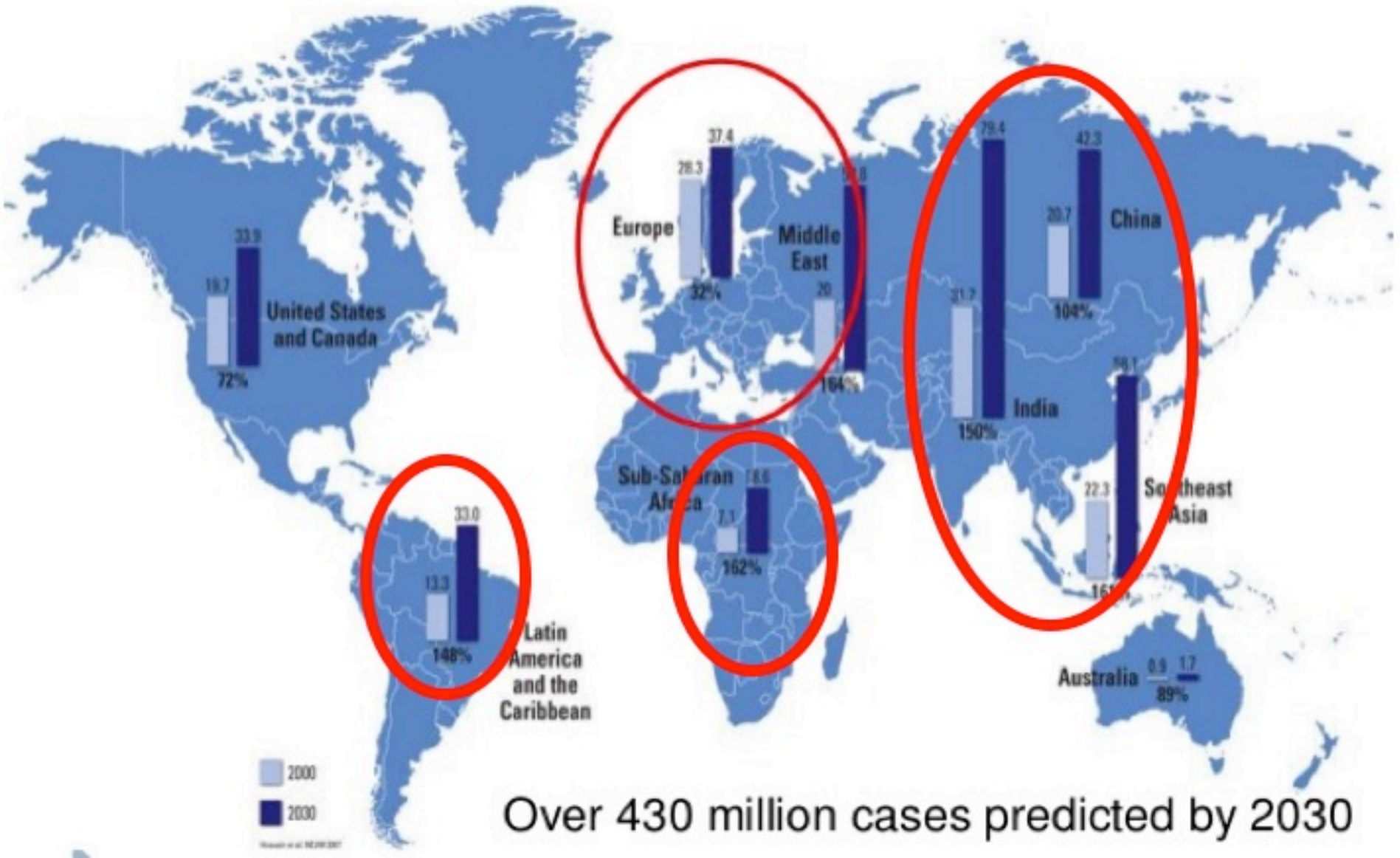
Prevalence (%) of diabetes in 2030 (20-79 years)



	2010	2030
Total numbers of pts with diabetes (age 20-79)	285 million	438 million
Prevalence of diabetes (age 20-79)	6.6 %	7.8 %

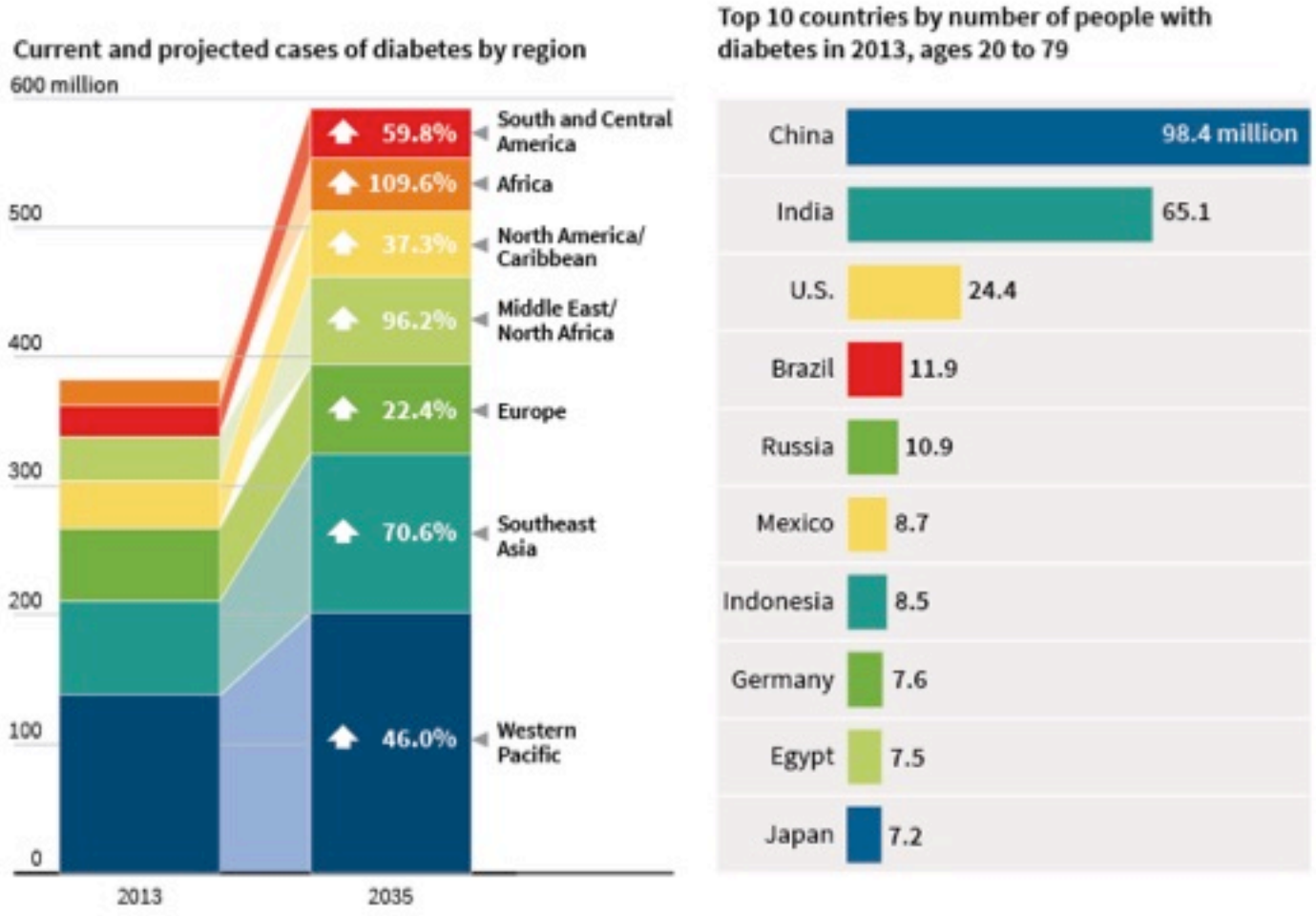
IDF diabetes atlas, 4th edition, 2010

Diabetes Prevalence in 2000 vs. 2030



Over 430 million cases predicted by 2030

World diabetes cases expected to jump 55 percent by 2035



Source: International Diabetes Federation

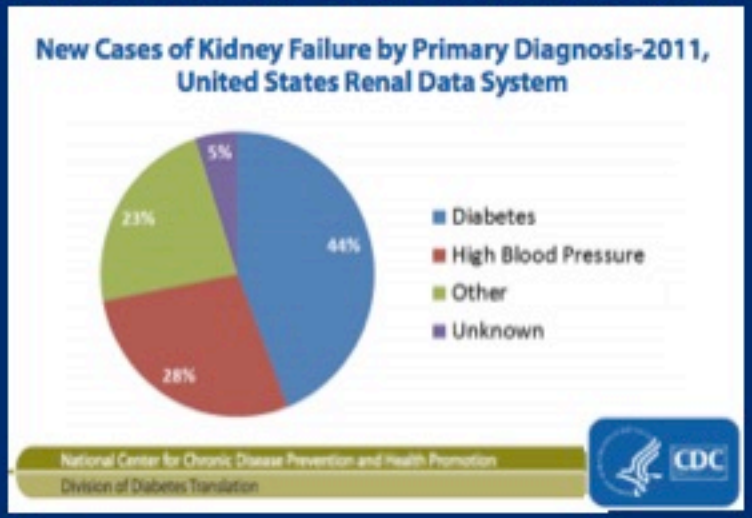
S. Cvijic, 12/11/2013

REUTERS

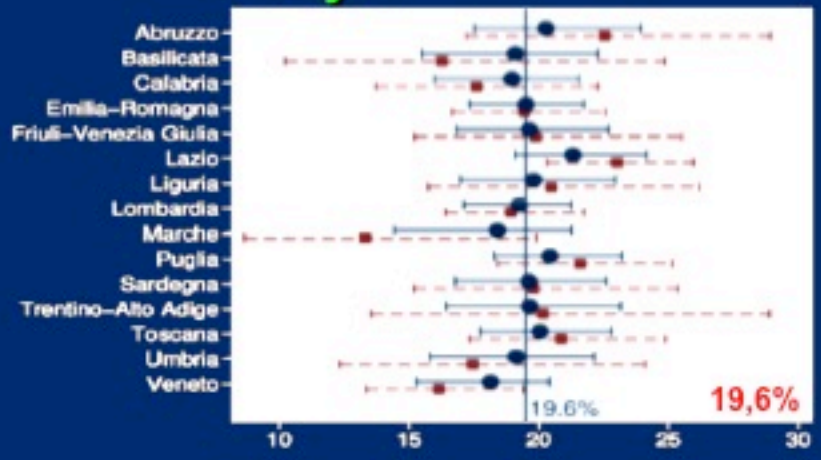
Diabetes and End Stage Renal Disease (ESRD)

World…

Incidence of ESRD due to diabetes



Italy…



Diabetic Nephropathy (DN)

Only 25-40% of diabetic patients develop DN.

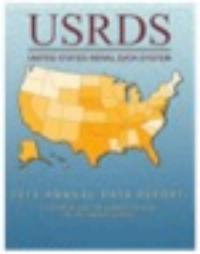
CLINICAL SIGNS

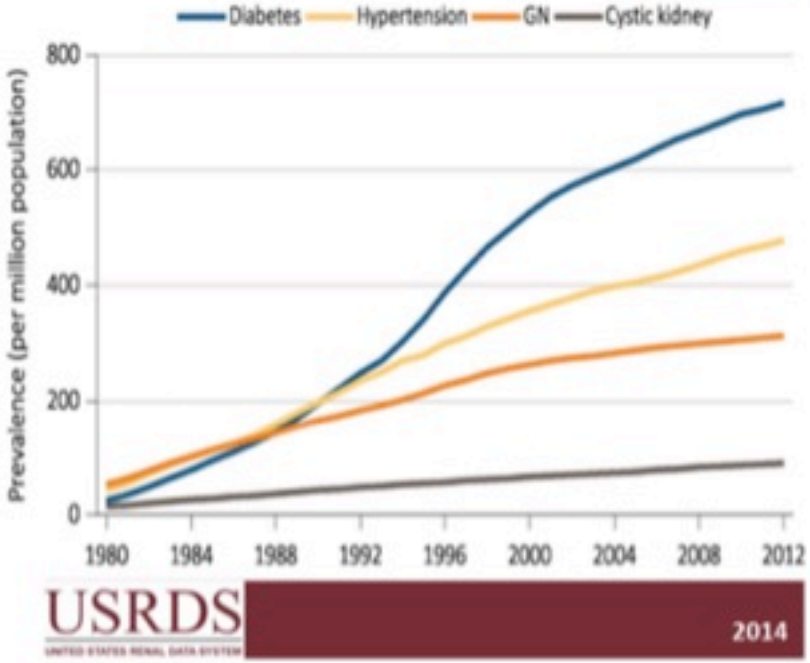
- Proteinuria
- Altered GFR

HISTOLOGICAL SIGNS

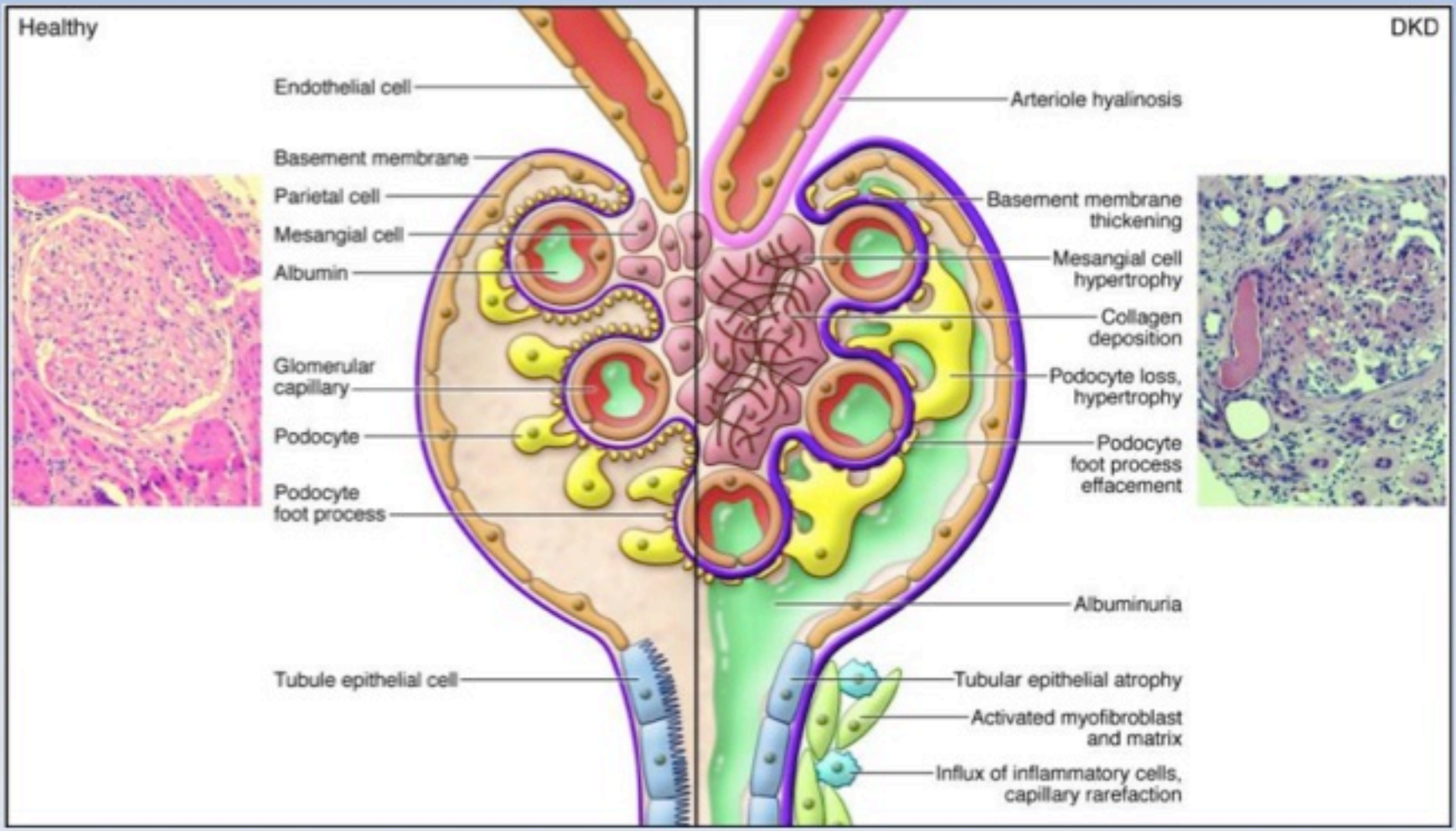
- Mesangial Proliferation
- Podocyte Loss
- GBM Thickening
- Nodular ECM accumulations

Prevalent ESRD Cases, by Primary Cause of ESRD, 1980-2012





Pathological lesions of DN



Reidy K, et al. J Clin Invest. 2014.

QUESTION

Renal Damage in a diabetic patient: is always a true diabetic nephropathy?

Pugliese et al. Cardiovascular Diabetology 2014, 13:59
http://www.cardiab.com/content/13/1/59

CARDIO VASCULAR DIABETOLOGY

ORIGINAL INVESTIGATION Open Access

Distribution of cardiovascular disease and retinopathy in patients with type 2 diabetes according to different classification systems for chronic kidney disease: a cross-sectional analysis of the renal insufficiency and cardiovascular events (RIACE) Italian multicenter study

Giuseppe Pugliese[1*], Anna Solini[2], Enzo Bonora[3], Emanuela Orsi[4], Gianpaolo Zerbini[5], Cecilia Fondelli[6], Gabriella Gruden[7], Franco Cavalot[8], Olga Lamacchia[9], Roberto Trevisan[10], Monica Vedovato[11], and Giuseppe Penno[2] for the RIACE Study Group

Patients stratification

		Cases			
N		A1	A2	A3	Total
G1	>90	62% 9900	22% 3,497	5% 738	4,662 (29.6)
G2	60-90				8,152 (51.7)
G3a	45-60	11% 1638			1,951 (12.4)
G3b	30-45				750 (4.8)
G4	15-30				229 (1.5)
G5	<15				29 (0.2)
Total		11,538 (73.2)	3,497 (22.2)	738 (4.7)	15,773 (100.0)

eGFR ml/min

<30 mg/g >30 <300 mg/g >300 mg/g

ALBUMINURIA

QUESTION

Renal Damage in a diabetic patient: is always a true diabetic nephropathy?

- Most nephrologists do not advocate renal biopsy in diabetic subjects, arguing that this procedure would simply confirm the presence of DN in the majority of patients

- There is no overall consensus on timing and indications, the decision to perform RB is usually based on personal opinions or single-center policies

- RB is an invasive procedure that is not completely free from complications.

Clinical Evaluation

KEY POINTS

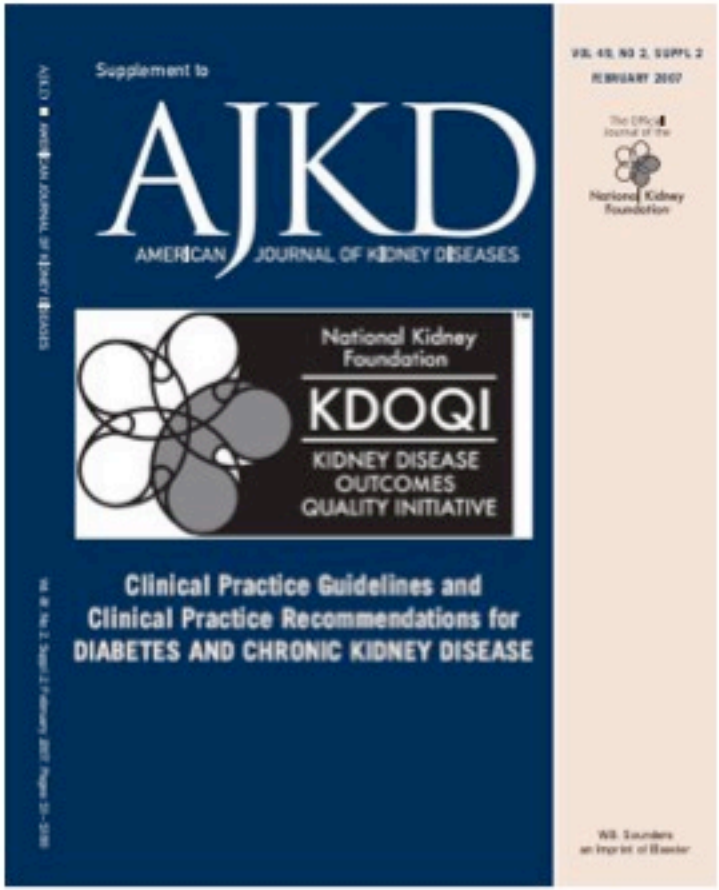
- The utility of renal biopsy in patients with diabetes is highly debated
- Diabetics with rapidly worsening renal disease are often 'clinically' labelled as having diabetic nephropathy (DN), whereas, in many cases, they are rather developing a **non-diabetic renal disease (NDRD) or mixed forms (DN + NDRD)**
- NDRD are highly prevalent in patients with diabetes. Clinical judgment alone can lead to wrong diagnoses and delay the establishment of adequate therapies.

Mazzucco G et al. *Different patterns of renal damage in type 2 diabetes mellitus: a multicentric study on 393 biopsies.*
Am J Kidney Dis 2002;39:713-720

Fiorentino M et al. *Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies.* Nephrol Dial Transplant 2017;32:97-110

DIABETES AND RENAL DAMAGE

Hematuria, Proteinuria, rising in serum creatinine in diabetic patients are **NOT ALWAYS** due to diabetic nephropathy and even they may not be due to diabetes mellitus.



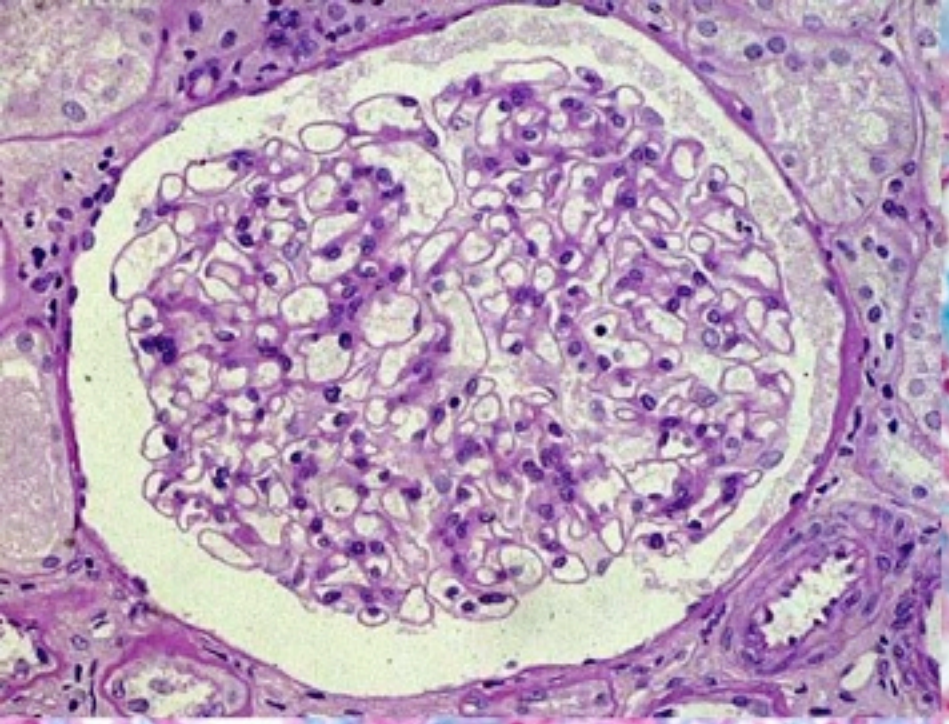
Terminology for the Kidney Disease of Diabetes

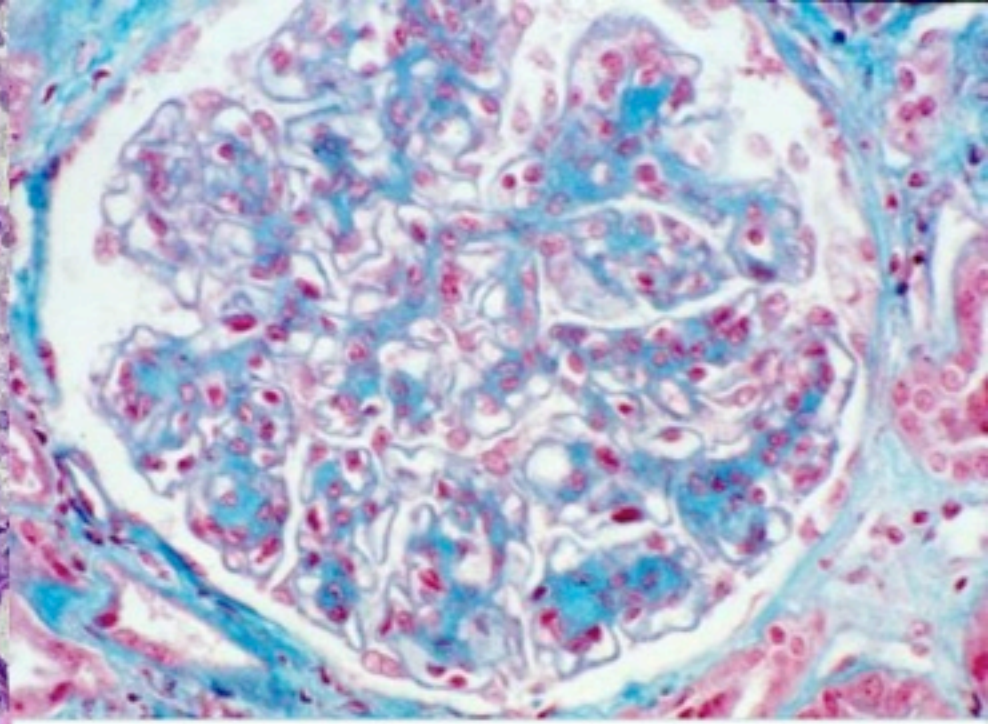
«The term diabetic nephropathy should be replaced by diabetic kidney disease (DKD). The term diabetic nephropathy should be reserved to biopsy-proven kidney disease caused by diabetes».

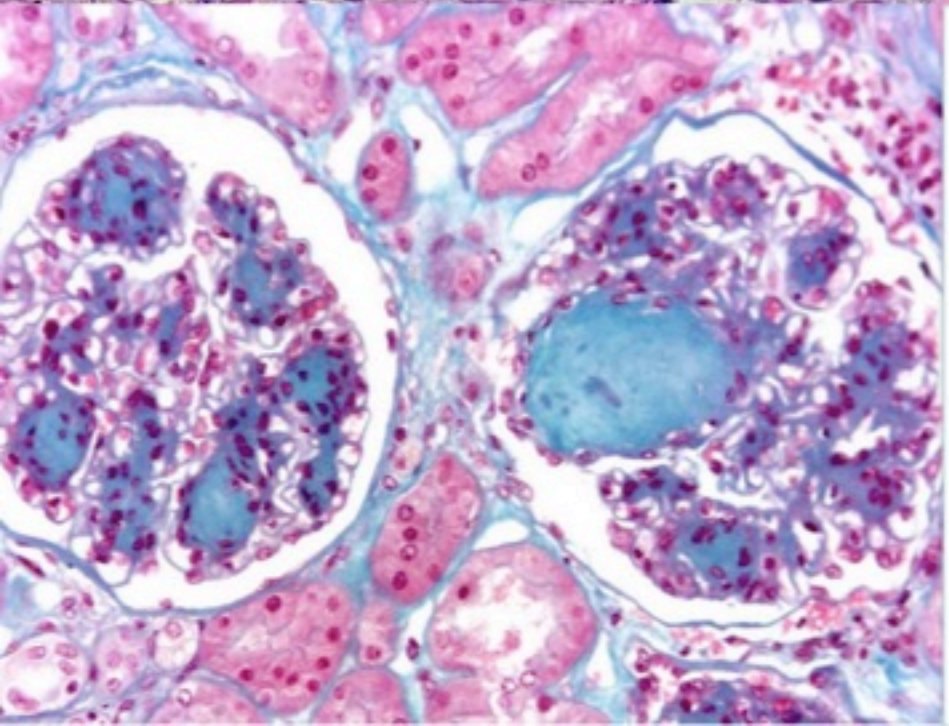
Histopatological Characteristics of renal damage in Diabetes

CLASSIFICATION	HISTOLOGY	PREVALENCE
• Class 1 →	Diabetic glomerulosclerosis	(39,6%)
• Class 2 →	Vascular (arterioarteriolosclerotic) and ischemic glomerular changes	(15,2%)
• Class 3a →	Glomerular diseases superimposed on diabetic glomerulosclerosis	(45,03%)
• Class 3b →	Other glomerulonephritis without the presence of diabetic lesions	

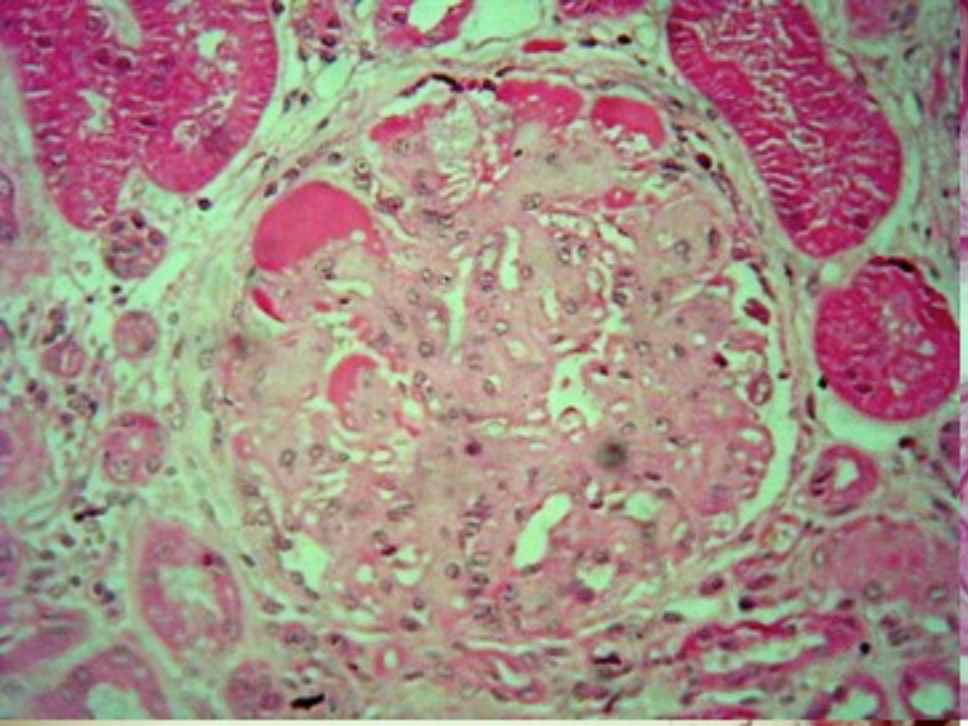
Mazzucco G et al, *Am J Kidney Dis* 2002; 39: 713-716

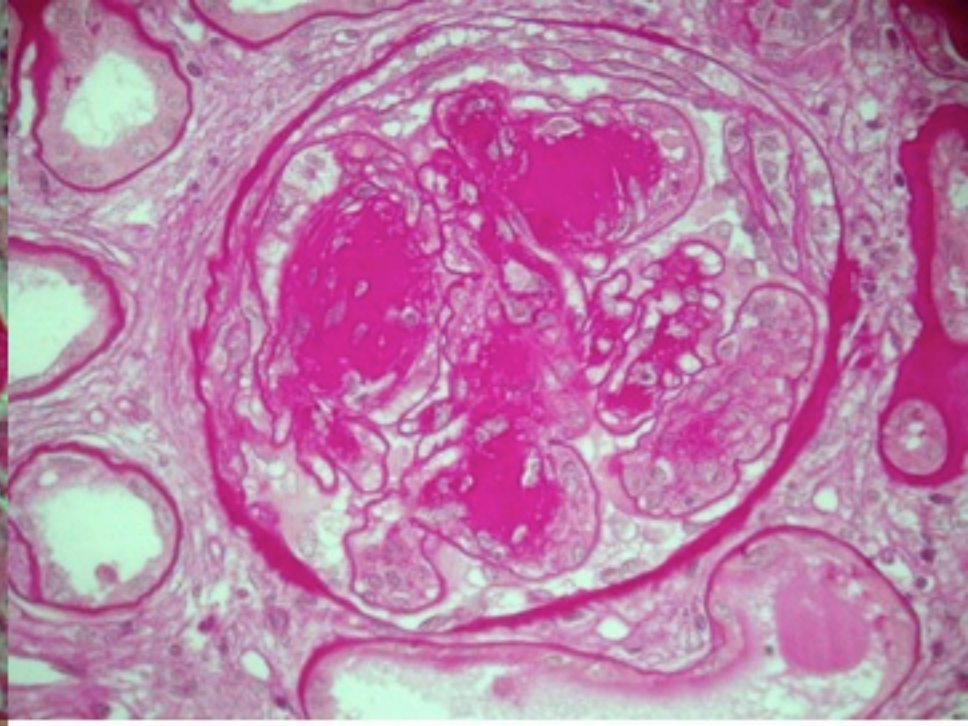


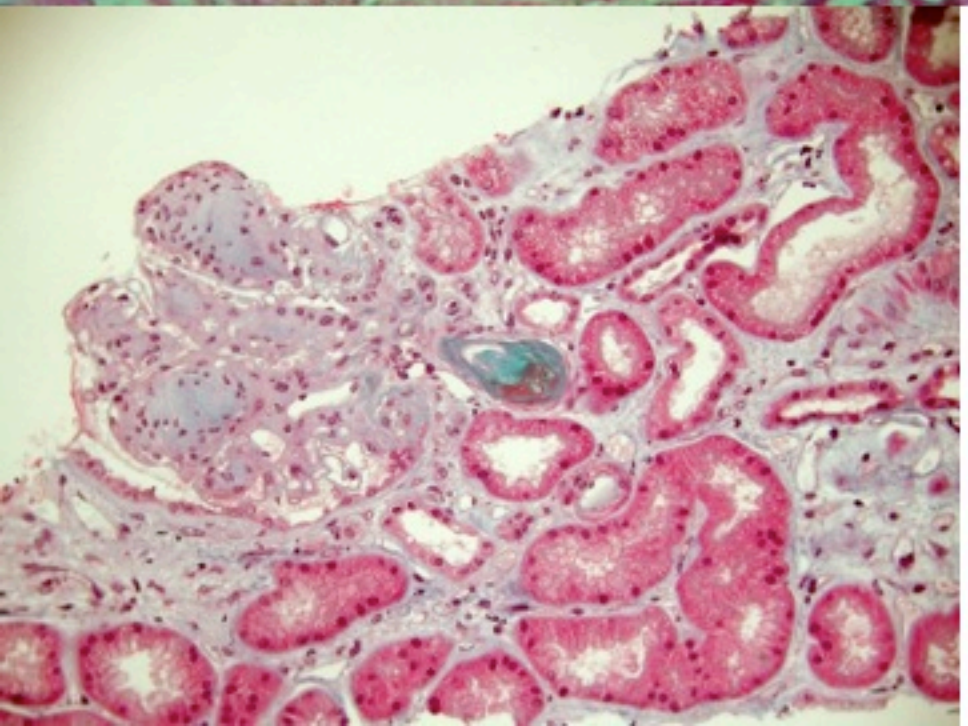




Class 1
(Kimmelstiel
Wilson lesions)







Class 1

- ✓ Glomerular hypertrophy
- ✓ Mesangial expansion (fibrosis)
- ✓ Sclerosis
- ✓ Nodular appearance
- ✓ Fibrin caps
- ✓ Fibrin necrosis on the afferent artheriola
- ✓ IFTA

Patients stratification

	Cases			
N	A1	A2	A3	Total
G1 >90	3,610 (22.9)			4,662 (29.6)
G2 60-90	6,255 (39.7)			8,152 (51.7)
G3a 45-60	1,253 (7.9)	**22%**	**5%**	1,951 (12.4)
G3b 30-45	351 (2.2)	**3,497**	**738**	750 (4.8)
G4 15-30	60 (0.4)			229 (1.5)
G5 <15	9 (0.06)			29 (0.2)
Total	11,538 (73.2)	3,497 (22.2)	738 (4.7)	15,773 (100.0)

eGFR ml/min

<30 mg/g | >30 <300 mg/g | >300 mg/g

ALBUMINURIA

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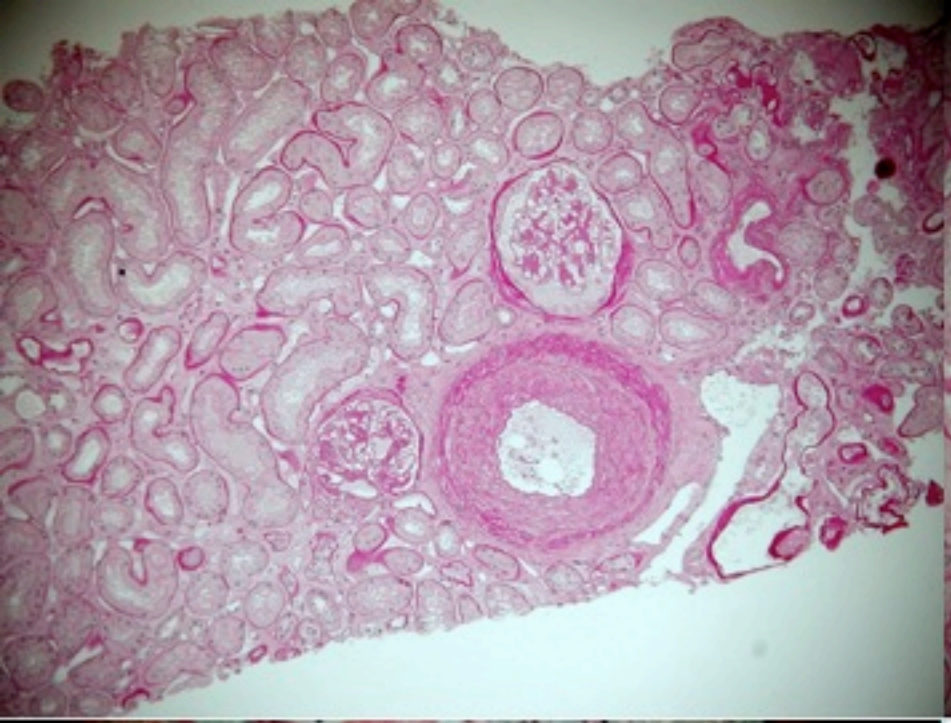
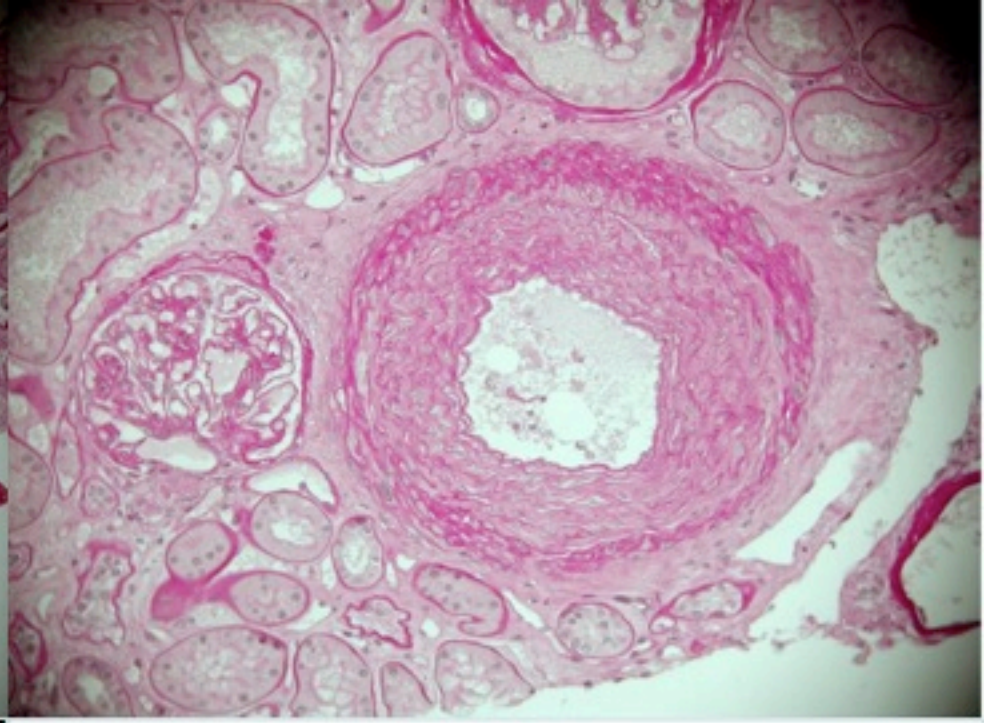
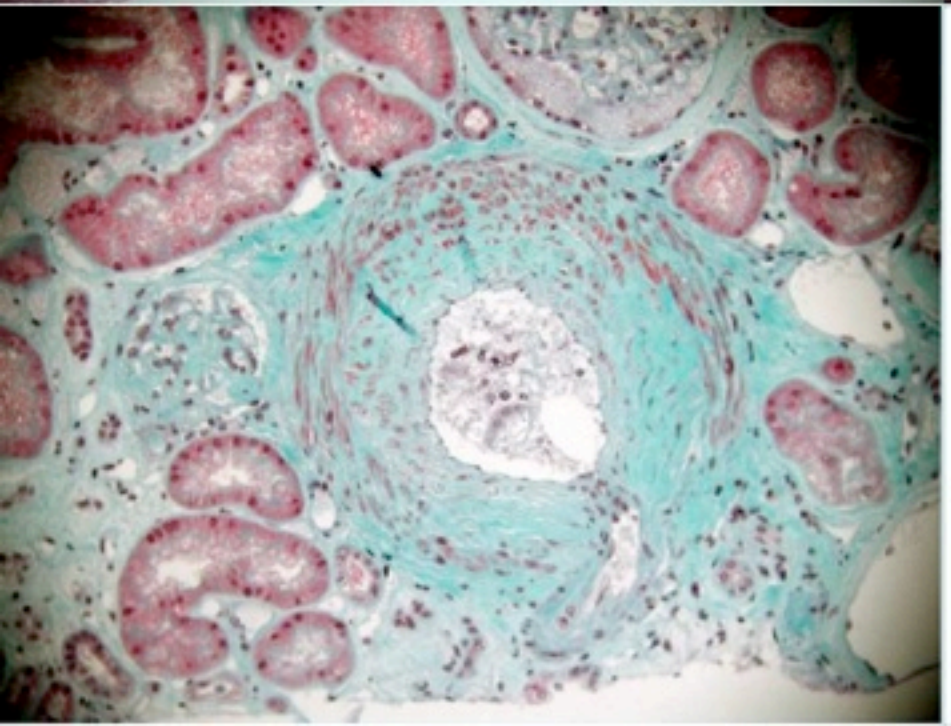






Class 2

- ✓ Vascular disease with macroangiopatic lesions
- ✓ Small and ischemic glomeruli
- ✓ Marked arteriosclerosis
- ✓ Chronic tubulointerstitial damage

Patients stratification

	Cases			
N	A1	A2	A3	Total
G1	3,610 (22.9)		120 (0.8)	4,662 (29.6)
G2	6,255 (39.7)		244 (1.6)	8,152 (51.7)
G3a		22% 3,497	136 (0.9)	1,951 (12.4)
G3b	11% 1638		136 (0.9)	750 (4.8)
G4			87 (0.6)	229 (1.5)
G5			15 (0.1)	29 (0.2)
Total	11,538 (73.2)	3,497 (22.2)	738 (4.7)	15,773 (100.0)

<30 mg/g >30 <300 mg/g >300 mg/g

ALBUMINURIA

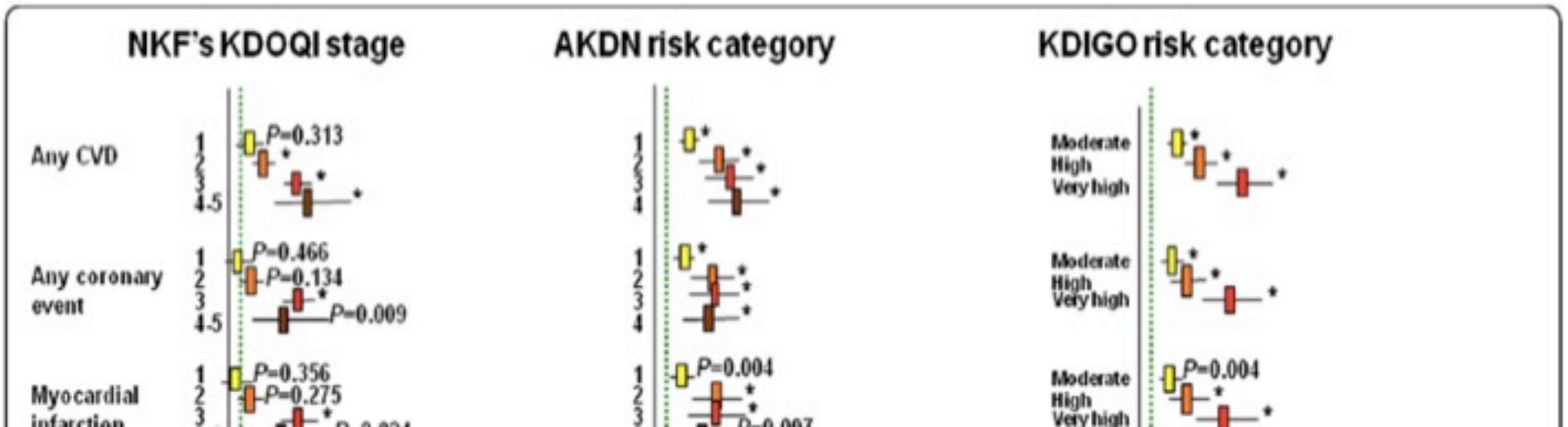
Table 1 Cases (% of total) and number of subjects (% of cases) with any CVD, any coronary event, AMI, any cerebrovascular event, stroke, any peripheral event, ulcer/gangrene, and non-advanced and advanced DR according to eGFR and albuminuria category

Cases				
N	A1	A2	A3	Total
G1	3,610 (22.9)	932 (5.9)	120 (0.8)	4,662 (29.6)
G2	6,255 (39.7)	1,653 (10.5)	244 (1.6)	8,152 (51.7)
G3a	1,253 (7.9)	562 (3.6)	136 (0.9)	1,951 (12.4)
G3b	351 (2.2)	263 (1.7)	136 (0.9)	750 (4.8)
G4	60 (0.4)	82 (0.5)	87 (0.6)	229 (1.5)
G5	9 (0.06)	5 (0.03)	15 (0.1)	29 (0.2)
Total	11,538 (73.2)	3,497 (22.2)	738 (4.7)	15,773 (100.0)

Any CVD				
n	A1	A2	A3	Total
G1	539 (14.9)	197 (21.1)	35 (29.2)	771 (16.5)
G2	1,218 (19.5)	480 (29.0)	82 (33.6)	1,780 (21.8)
G3a	373 (29.8)	220 (39.2)	67 (49.3)	660 (33.8)
G3b	129 (36.8)	135 (51.3)	61 (44.9)	325 (43.3)
G4	24 (40.0)	40 (48.8)	56 (64.4)	120 (52.4)
G5	2 (22.2)	3 (60.0)	4 (26.7)	9 (31.0)
Total	2,285 (19.8)	1,075 (30.7)	305 (41.3)	3,665 (23.2)

Any coronary event				
N	A1	A2	A3	Total
G1	369 (10.2)	122 (13.1)	17 (14.2)	508 (10.9)
G2	835 (13.4)	298 (18.0)	43 (17.6)	1,176 (14.4)
G3a	264 (21.1)	136 (24.2)	36 (26.5)	436 (22.4)
G3b	93 (26.5)	96 (36.5)	39 (28.7)	228 (30.4)
G4	16 (26.7)	23 (28.1)	23 (26.4)	62 (27.1)
G5	1 (11.1)	1 (20.0)	3 (20.0)	5 (17.2)

AMI				
n	A1	A2	A3	Total
G1	260 (7.2)	86 (9.2)	11 (9.2)	357 (7.7)
G2	614 (9.8)	218 (13.2)	31 (12.7)	863 (10.6)
G3a	189 (15.1)	105 (18.7)	22 (16.2)	316 (16.2)
G3b	68 (19.4)	73 (27.8)	31 (22.8)	172 (22.9)
G4	13 (21.7)	18 (22.0)	15 (17.2)	46 (20.1)
G5	1 (11.1)	1 (20.0)	2 (13.3)	4 (13.8)



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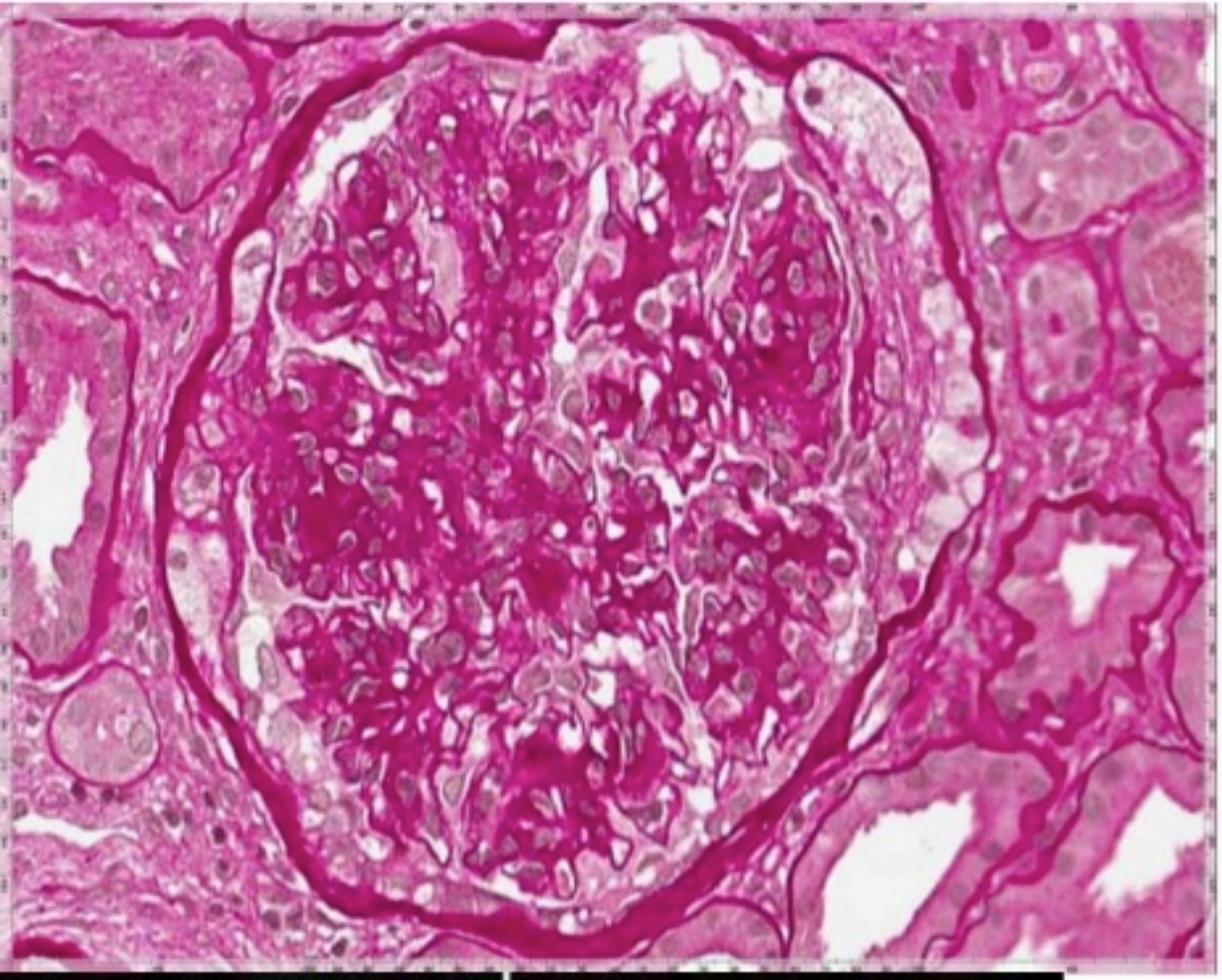
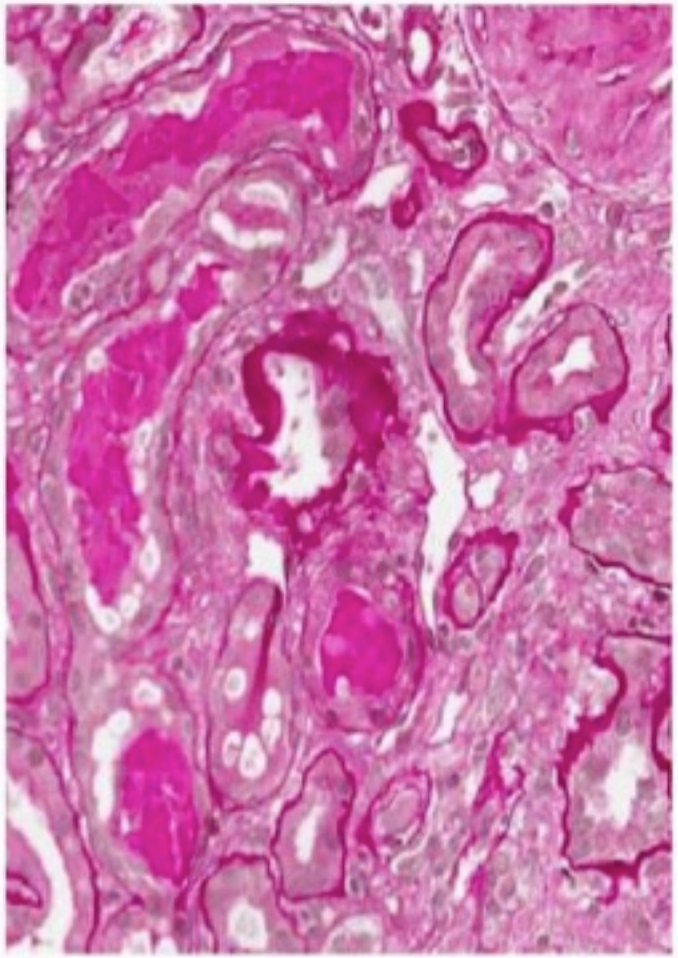
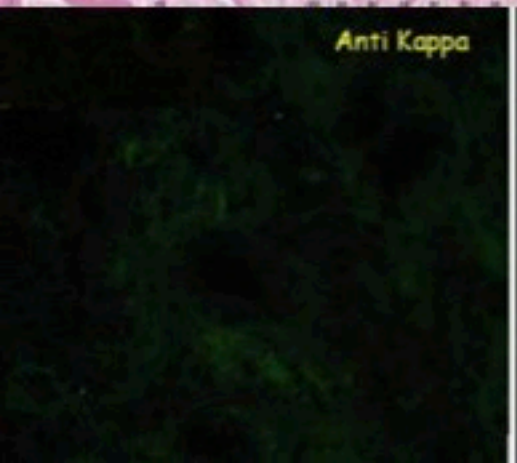
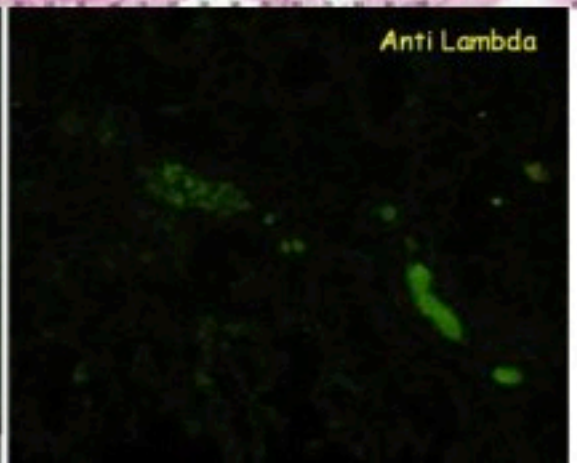




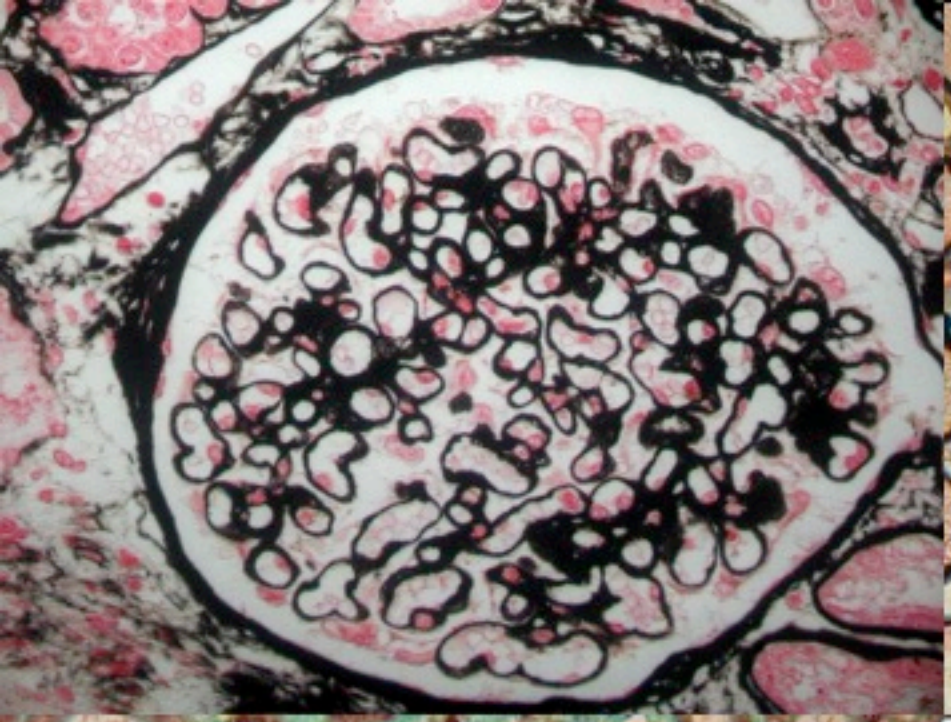


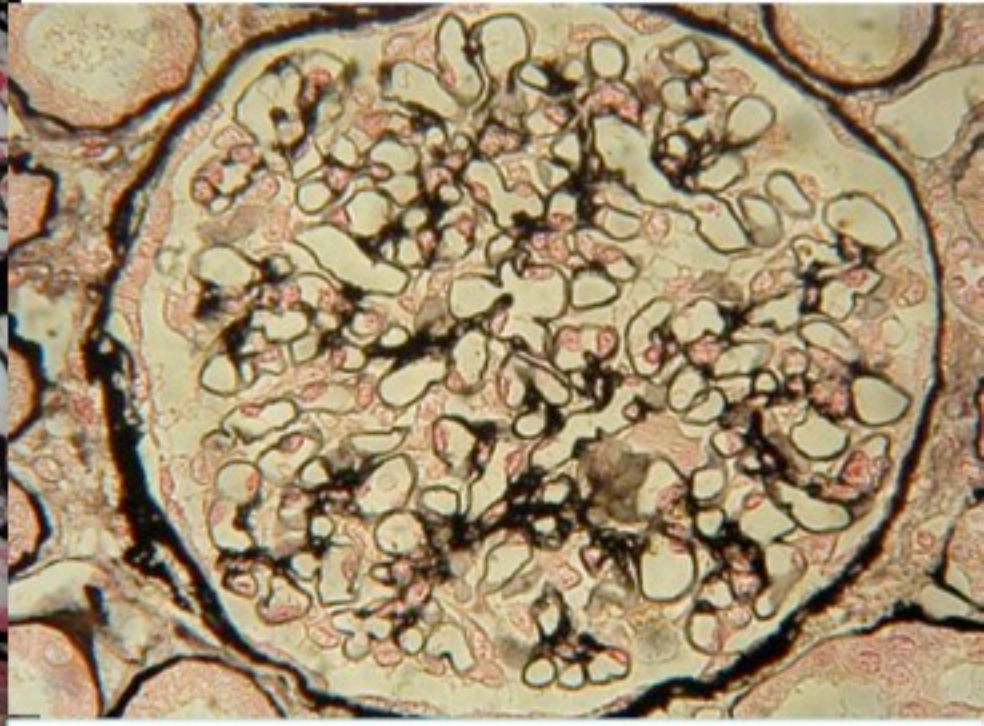


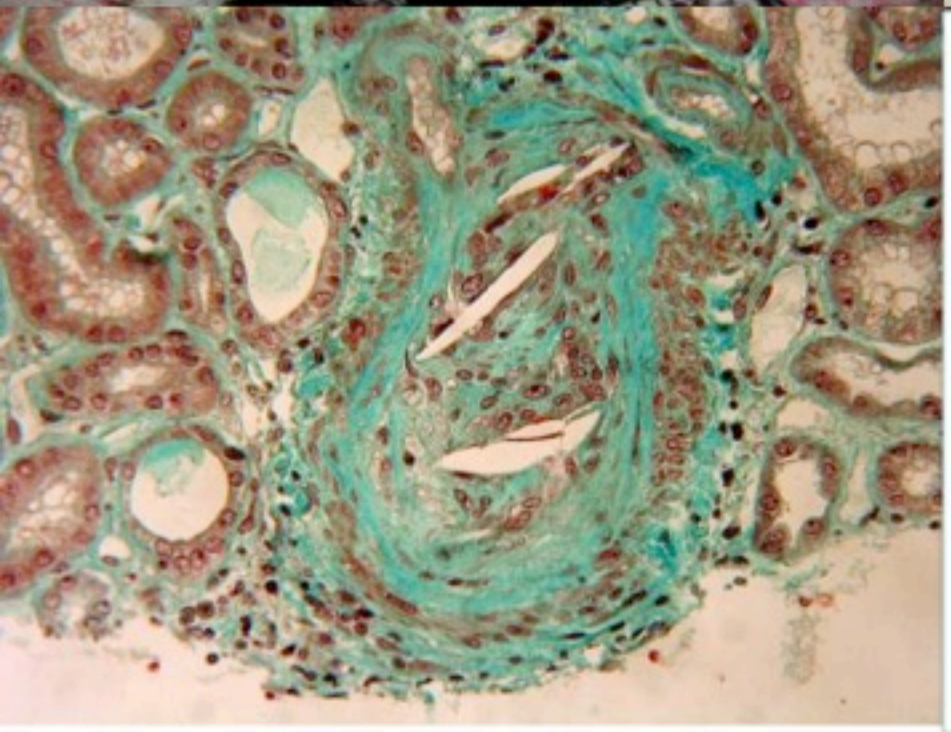
Classe 3a

- ✓ Another glomerular disease superimposed on well-developed diabetic glomerulo-sclerosis

DN + Cast Nephropathy







Class 3b

- ✓ Glomerular disease without clearly detectable or minimal lesions of diabetic nephropathy (membranous nphropathy, IgA nephropathy….)

Patients stratification

	Cases			
N	A1	A2	A3	Total
G1 >90	3,610 (22.9)	932 (5.9)		4,662 (29.6)
G2 60-90	6,255 (39.7)	1,653 (10.5)		8,152 (51.7)
G3a 45-60	1,253 (7.9)	562 (3.6)	5% 738	1,951 (12.4)
G3b 30-45	351 (2.2)	263 (1.7)		750 (4.8)
G4 15-30	60 (0.4)	82 (0.5)		229 (1.5)
G5 <15	9 (0.06)	5 (0.03)		29 (0.2)
Total	11,538 (73.2)	3,497 (22.2)	738 (4.7)	15,773 (100.0)

eGFR ml/min

<30 mg/g >30 <300 mg/g >300 mg/g

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PLOS | ONE

Identifying Parameters to Distinguish Non-Diabetic Renal Diseases from Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis

Shuang Liang, Xue-Guang Zhang, Guang-Yan Cai*, Han-Yu Zhu, Jian-Hui Zhou, Jie Wu, Pu Chen, Shu-peng Lin, Qiang Qiu, Xiang-Mei Chen*

Department of Nephrology, State Key Laboratory of Kidney Diseases, Chinese PLA General Hospital, Beijing, China

Abstract

Background: Renal injuries in patients with diabetes include diabetic nephropathy (DN) and non-diabetic renal diseases (NDRD). The value of a clinical diagnosis of DN and NDRD remains inconclusive. We conducted a meta-analysis of the literature to identify predictive factors of NDRD and to compare the clinical characteristics of DN and NDRD for differential diagnosis.

Methods: We searched PubMed (1990 to January 2012), Embase (1990 to February 2009), and CNKI (1990 to January 2012) to identify studies that enrolled patients with DN and NDRD. Then, the quality of the studies was assessed, and data were extracted. The results were summarized as odds ratios (ORs) for dichotomous outcomes and weighted mean differences (WMDs) for continuous outcomes.

Results: Twenty-six relevant studies with 2,322 patients were included. The meta-analysis showed that the absence of diabetic retinopathy (DR) predicts NDRD (OR, 0.15; 95% confidence interval [CI], 0.09–0.26, $p<0.00001$). A shorter duration of diabetes mellitus (DM) also predicted NDRD (weighted mean difference, −34.67; 95% CI, −45.23–−24.11, $p<0.00001$). The levels of glycosylated hemoglobin (HbA1C%), blood pressure (BP), and total cholesterol were lower in patients with NDRD, whereas triglycerides and body mass index were higher. Other clinical parameters, including age, 24-h urinary protein excretion, serum creatinine, creatinine clearance, blood urea nitrogen, and glomerular filtration rate were not different between patients with NDRD and DN.

Conclusions: We identified that the absence of DR, shorter duration of DM, lower HbA1C, and lower BP may help to distinguish NDRD from DN in patients with diabetes. This could assist clinicians in making a safe and sound diagnosis and lead to more effective treatments.

NDT Advance Access published May 4, 2016

Nephrol Dial Transplant (2016) 0: 1–14
doi: 10.1093/ndt/gfw070

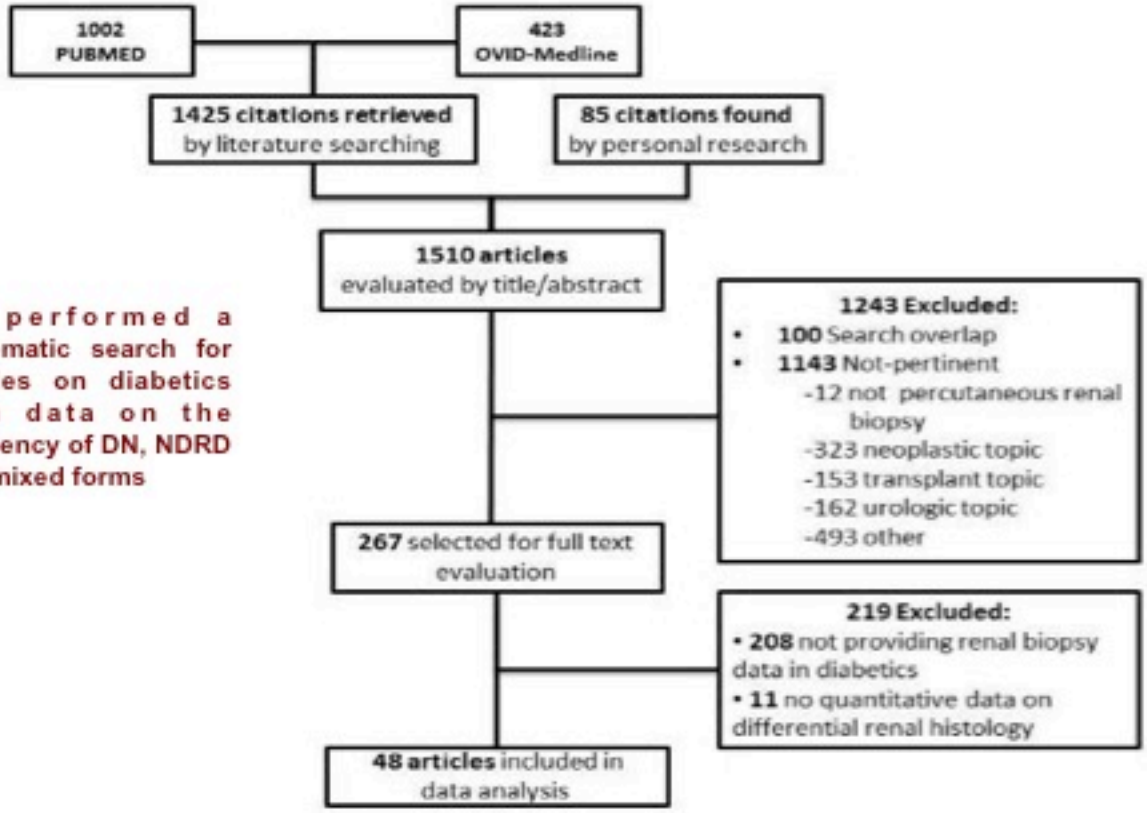
Original Article

Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies

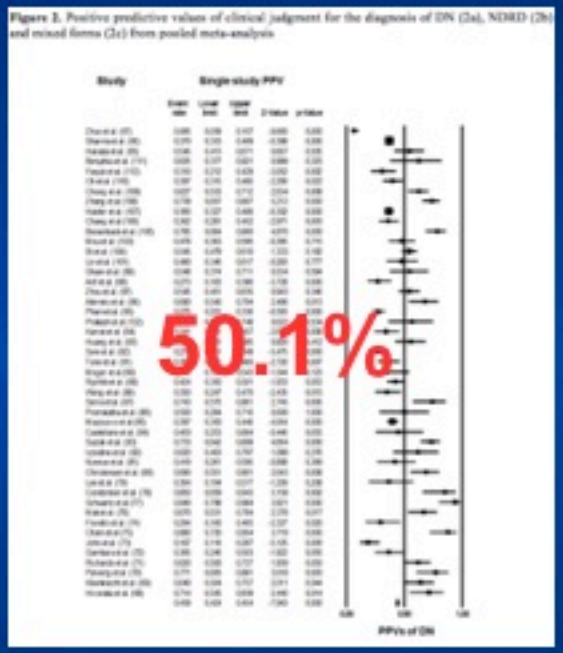
Marco Fiorentino[1], Davide Bolignano[2,3], Vladimir Tesar[4], Anna Pisano[2], Wim Van Biesen[5], Giovanni Tripepi[2], Graziella D'Arrigo[2] and Loreto Gesualdo[1]on behalf of the ERA-EDTA Immunonephrology Working Group

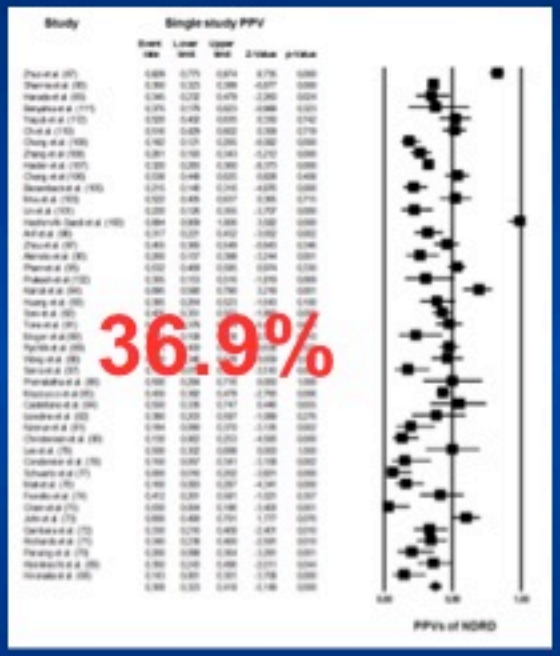
Flow of the study selection process

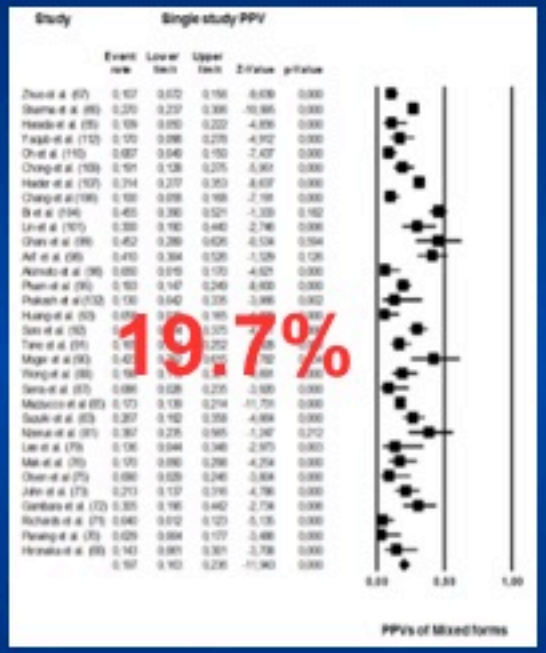
We performed a systematic search for studies on diabetics with data on the frequency of DN, NDRD and mixed forms



Positive predictive values of clinical judgment for the diagnosis of DN (2a), NDRD (2b) and mixed forms (2c) from pooled meta-analysis







Positive predictive values (PPVs) (pooled data) of clinical judgment for identifying DN, NDRD and mixed forms (as assessed by renal biopsy) were 50.1% (95% CI: 44.9 -55.3), 36.9% (95% CI: 32.3-41.8) and 19.7% (95% CI: 16.3-23.6), respectively

Meta-regression identified systolic pressure, HbA1c, diabetes duration and retinopathy as factors explaining heterogeneity for NDRD, creatinine and GFR for mixed forms and only serum creatinine for DN.

COMMENTS

Renal biopsy might be fundamental for clarifying the epidemiology of renal disease in diabetics and for planning proper therapeutic management.

Furthermore, although this procedure is invasive, the risk profile in diabetics is comparable to that of the general population.

Indeed, treatment approaches for DN and NDRD may diverge: for instance, IgA Nephropathy, FSGS, membranous glomerulonephritis and other primary and secondary glomerular diseases usually benefit from personalized treatments (e.g. immunosuppressive therapies) rather than from general approaches.

COMMENTS

The prognostic importance of renal biopsy is another aspect that should be seriously taken into consideration.

Diabetics with frank DN usually have worsen prognosis compared to NDRD and the severity of DN correlates with histological (glomerular and tubulo-interstitial damage) and clinical (eGFR, proteinuria) predictors of ESKD.

Nevertheless, NDRD may have better outcomes, particularly if these conditions are early identified and specific treatments are predisposed

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

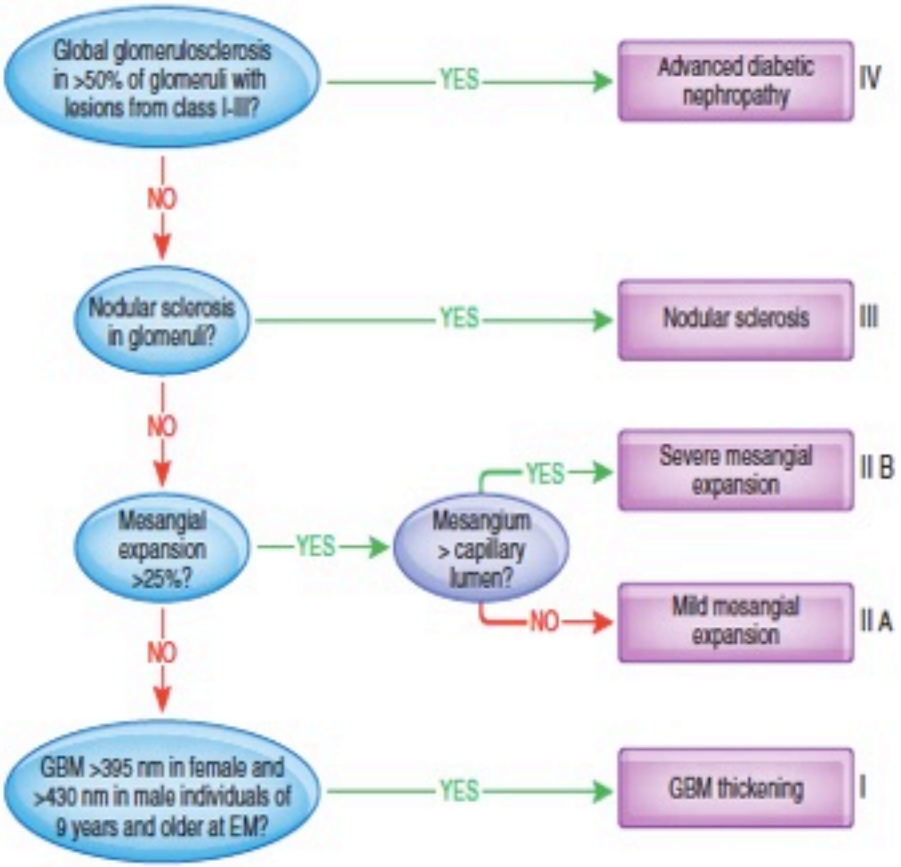
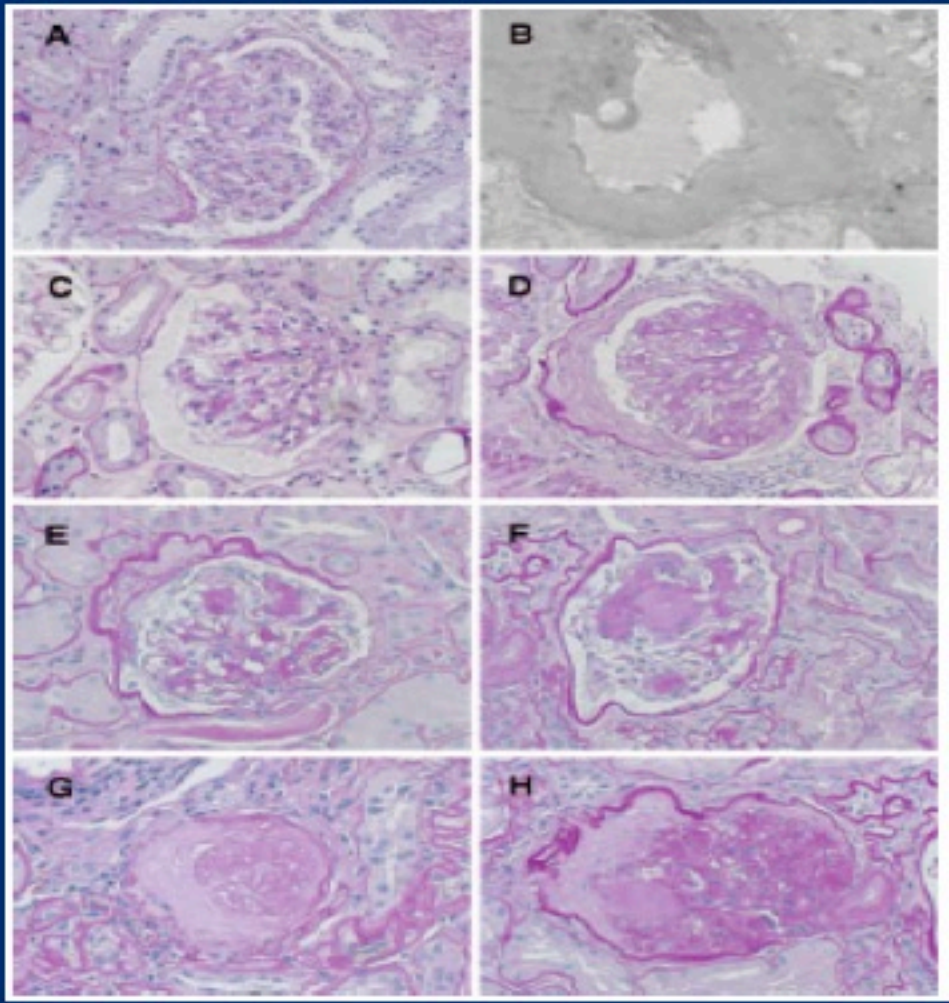


Figure 2. Flow chart for classifying DN.



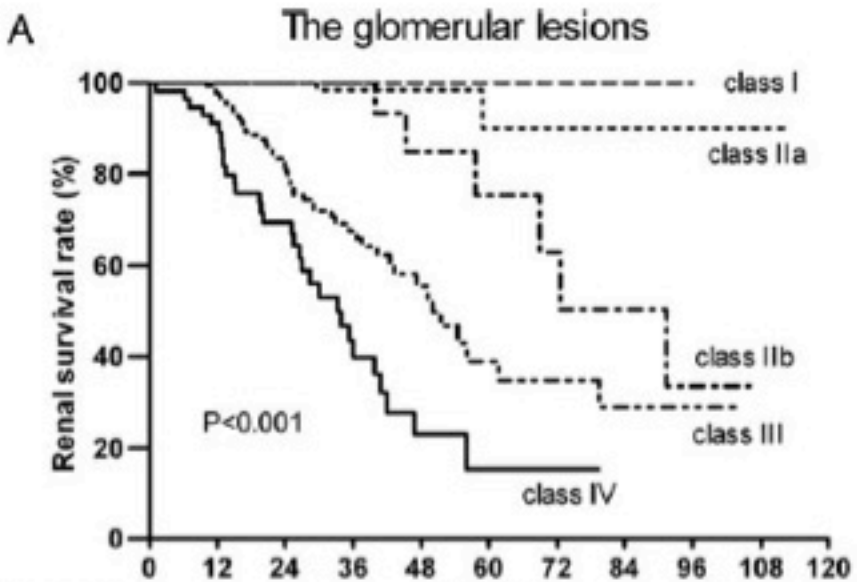
J Am Soc Nephrol 21: 556–563, 2010

Nephrol Dial Transplant (2015) 30: 257–266
doi: 10.1093/ndt/gfu250
Advance Access publication 25 July 2014

ORIGINAL ARTICLE

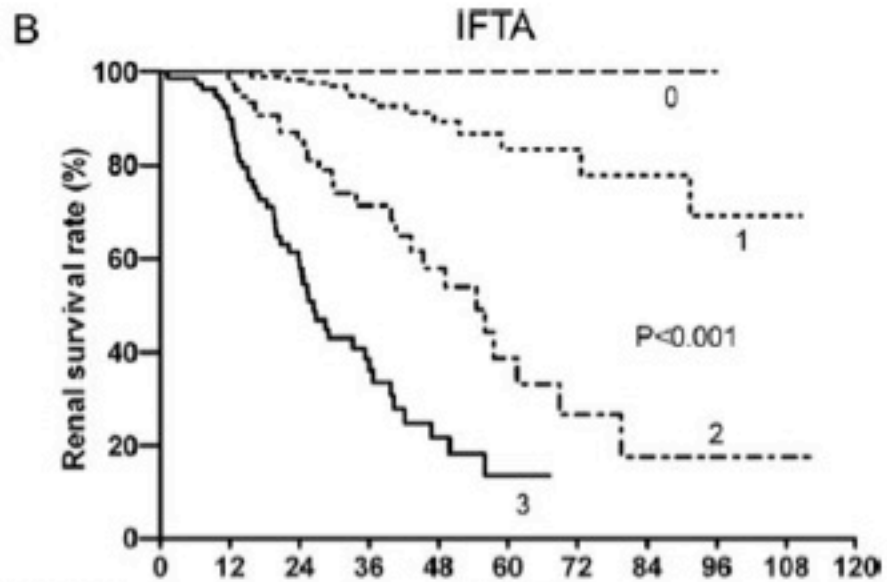
Renal histologic changes and the outcome in patients with diabetic nephropathy

Yu An*, Feng Xu*, Weibo Le, Yongchun Ge, Minlin Zhou, Hao Chen, Caihong Zeng, Haitao Zhang and Zhihong Liu



Patients at risk

class I	53	53	42	30	16	10	5	3	1	0
class IIa	87	87	73	49	23	10	5	4	4	2
class IIb	32	32	21	16	10	7	5	3	1	0
class III	168	167	87	41	21	9	6	4	3	0
class IV	56	51	28	13	5	2	1	0	0	0



Patients at risk

0	29	29	23	18	7	5	3	2	1	0
1	208	208	147	89	46	24	15	10	6	1
2	79	79	45	25	15	7	4	2	2	1
3	80	74	36	17	7	2	0	0	0	0

Renal lesions in patients with type 2 diabetes: a puzzle waiting to be solved

Loreto Gesualdo[1] and Salvatore Di Paolo[2]

+ Author Affiliations

Correspondence and offprint requests to: Loreto Gesualdo; E-mail: loreto.gesualdo@uniba.it

Received September 8, 2014.
Accepted November 4, 2014.

Three hundred sixty-six million people worldwide will be living with diabetes mellitus (DM) by 2030 ([1, 2]; http://www.idf.org/global-diabetes-plan-2011-2021). Prospectively, 75–150 million of these patients will develop a diabetic nephropathy (DN) or a non-diabetic renal disease (NDRD), either isolated or superimposed on DN [3, 4]. To date, the differential diagnosis between ND and NDRD remains a challenge that

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Nephrol. Dial. Transplant. (2015) 30 (2): 155-157.
doi: 10.1093/ndt/gfu372
First published online: December 10, 2014

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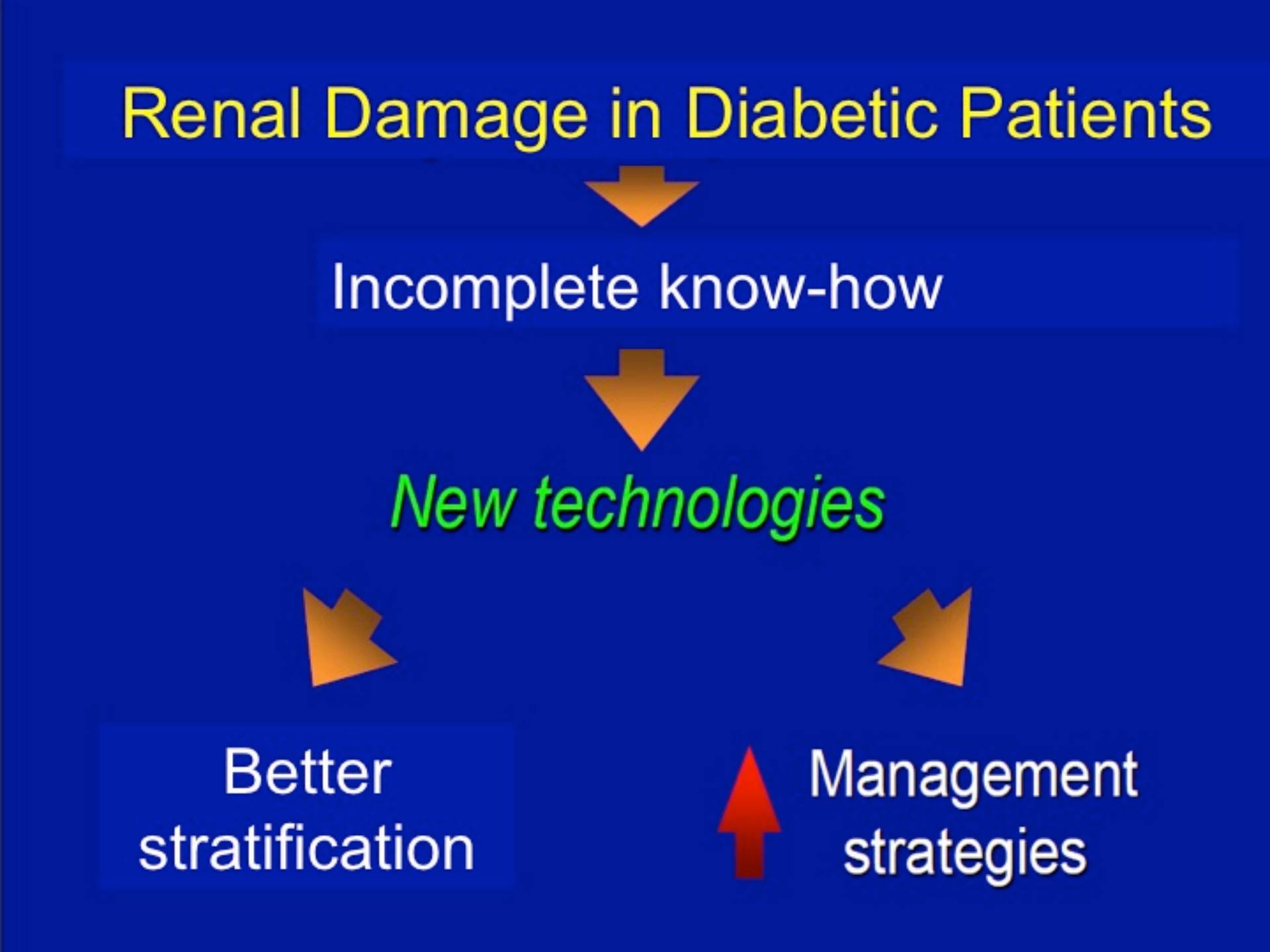
Current Issue

April 2015 30 (4)


Renal Damage in Diabetic Patients
Incomplete know-how
New technologies
Better stratification
Management strategies

How can we improve our diagnostic tools in diabetic patients?

capabilities of MRI

UNIVERSITY OF LEEDS

- Conventional investigative tools:
  - angiography (X-ray, CT); ultrasound; biopsy; nuclear medicine (GFR, renography)

- Qualitative MRI:
  - anatomy; angiography; urography
- Quantitative MRI:
  - renal blood flow (ASL/DCE)
  - glomerular filtration (DCE)

  - vessel flow (PCA); blood oxygenation (BOLD); (in)coherent water movement (diffusion)

Multiparametric MR measures

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

One stop study of renal function: ~ 40 min scan
Match data space


Coronal oblique

BOLD, TRUST

Oxygenation

ADC
D, D*, fp
DWI/DTI

Total blood flow,
fpD* mm²/s

Phase Contrast
Velocity cm/s
Area mm²
Flux ml/s

Structure

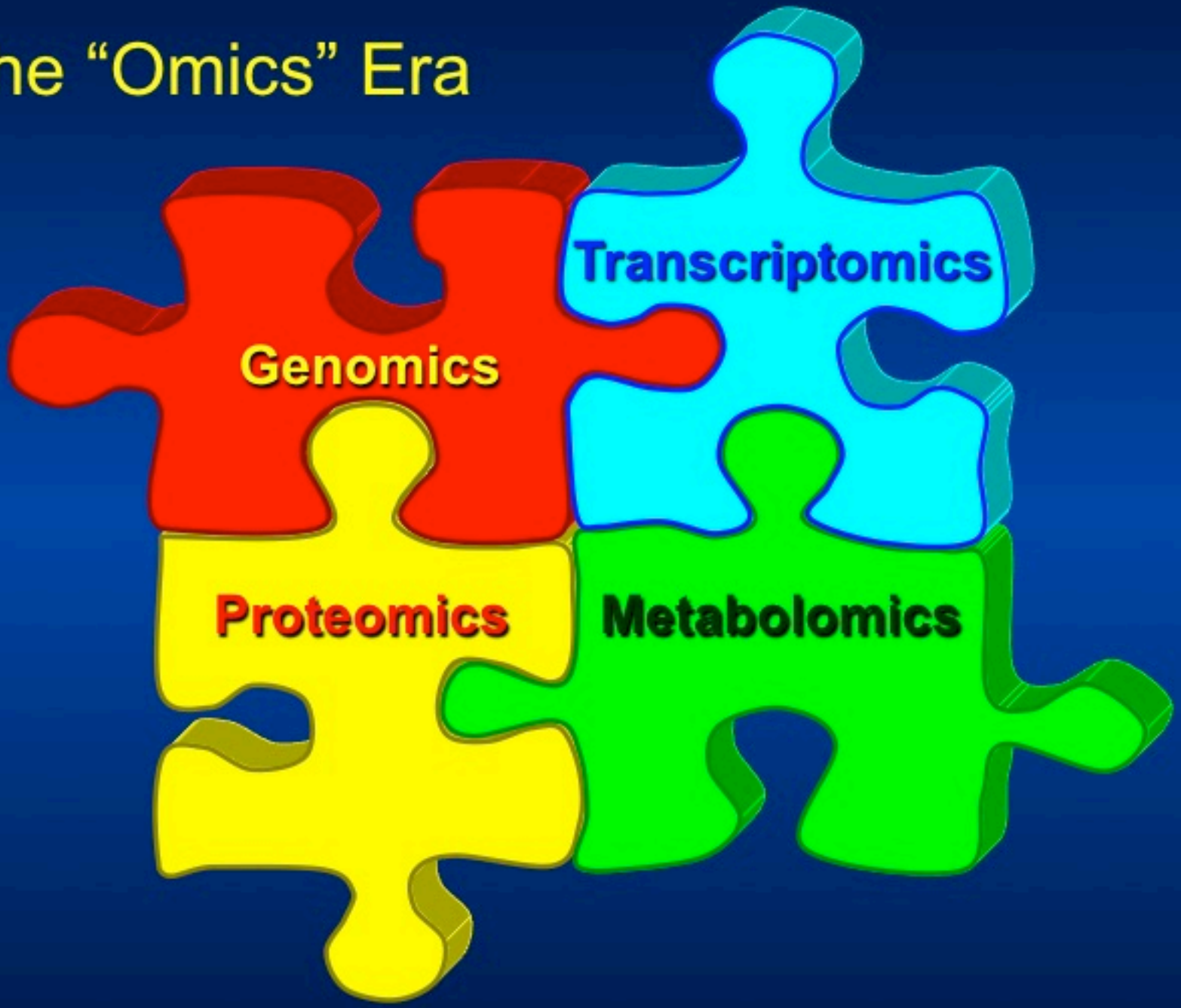
Haemodynamics

T1 ms → **Perfusion** ml/100g/min ← ASL

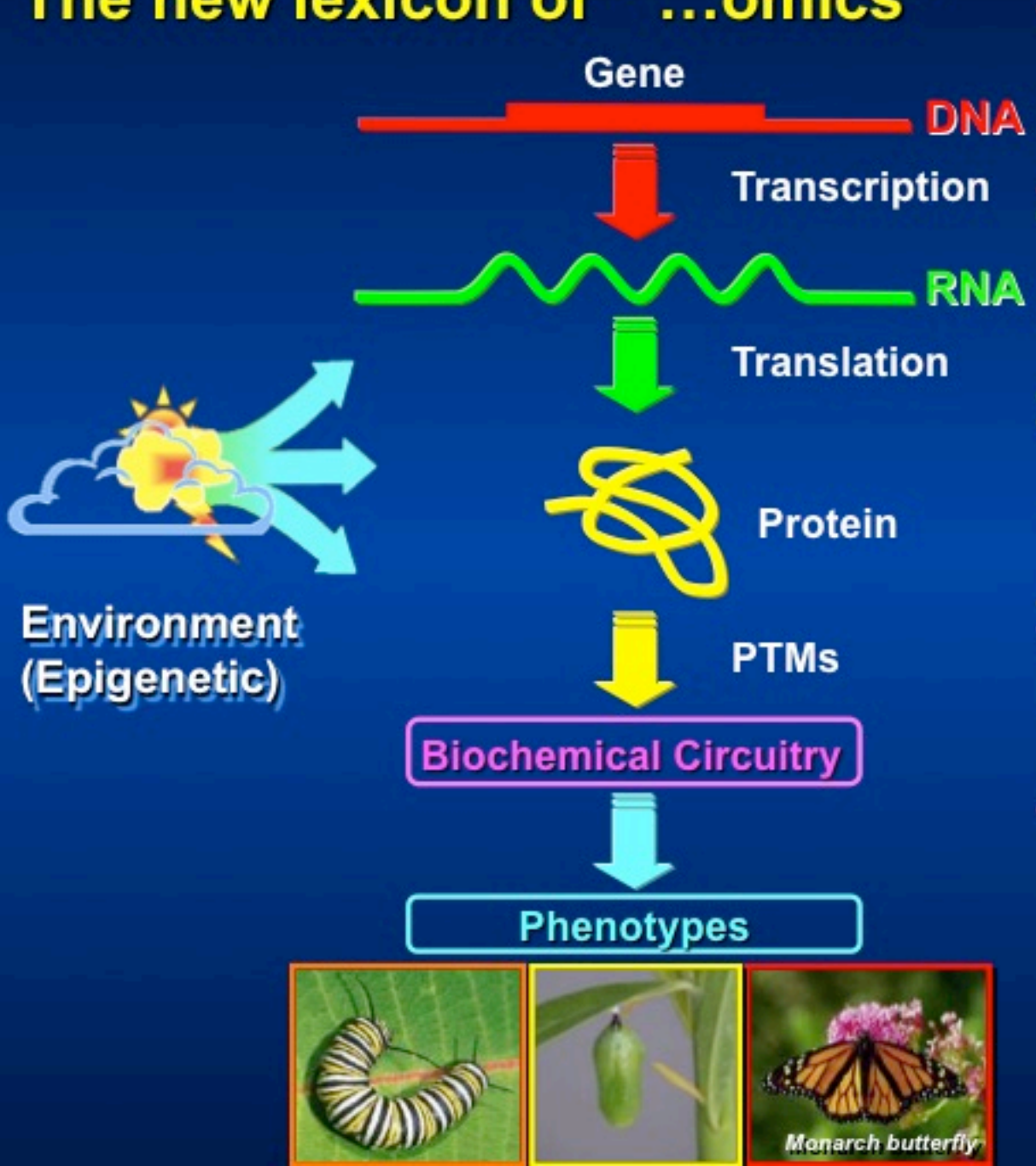
Volume
mm³

Total blood flow
ml/100g/min

The “Omics” Era

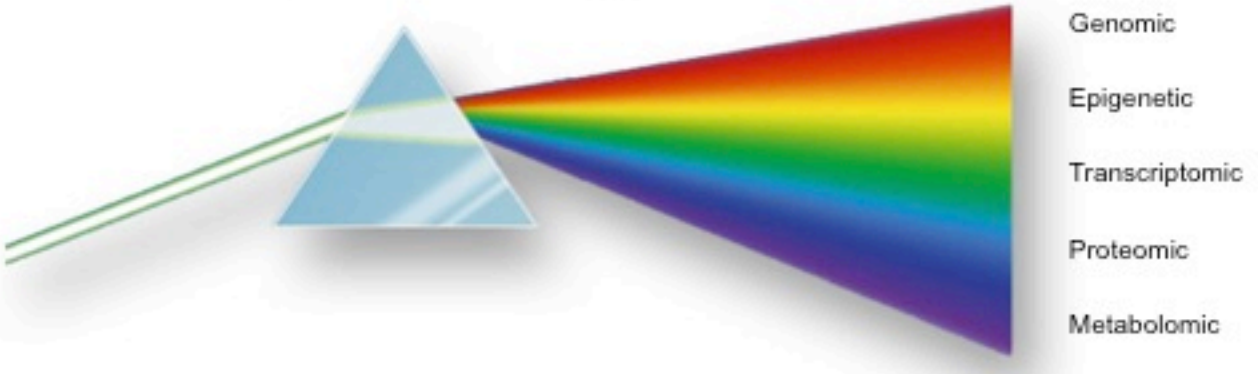


The new lexicon of "…omics"

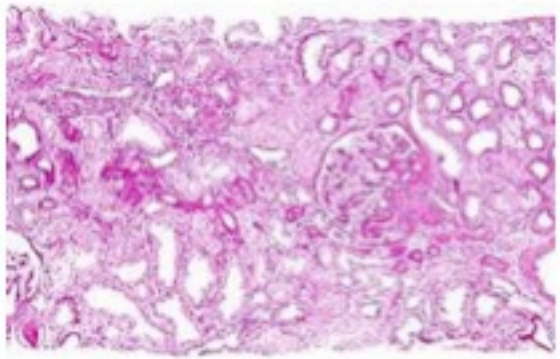


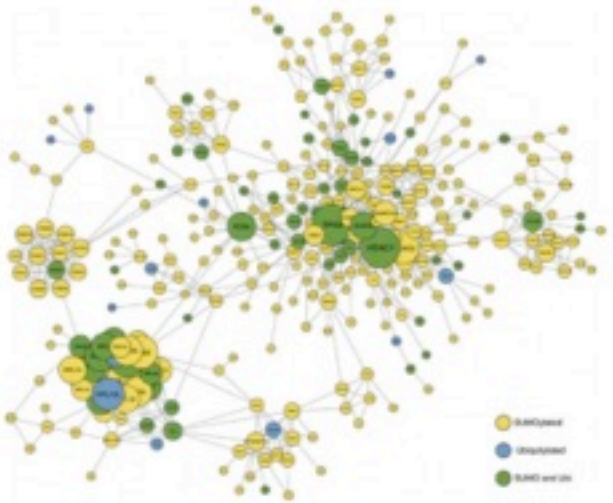
Define omic pattern

System biology



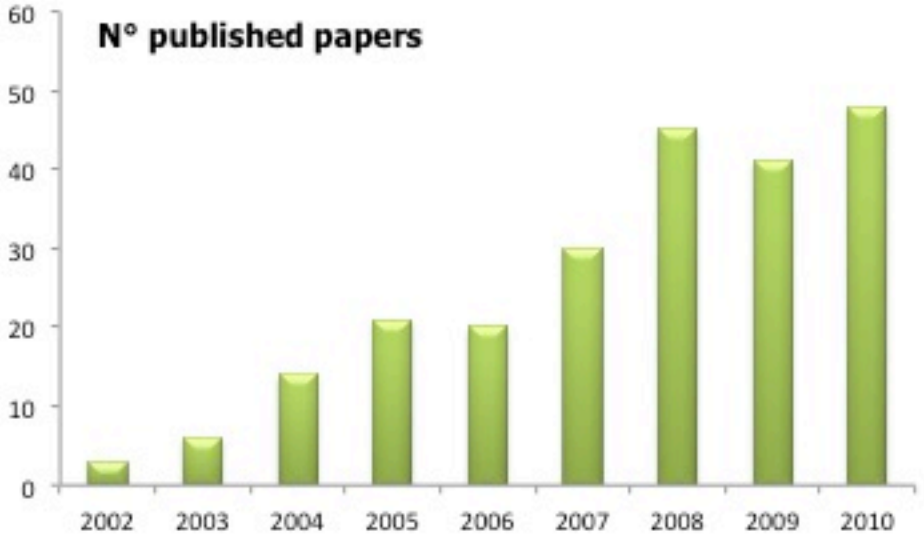
Clinical phenotye





Omics in Nephrology

Urine omics analysis for biomarker discovery for early diagnosis and for the progression of renal disease



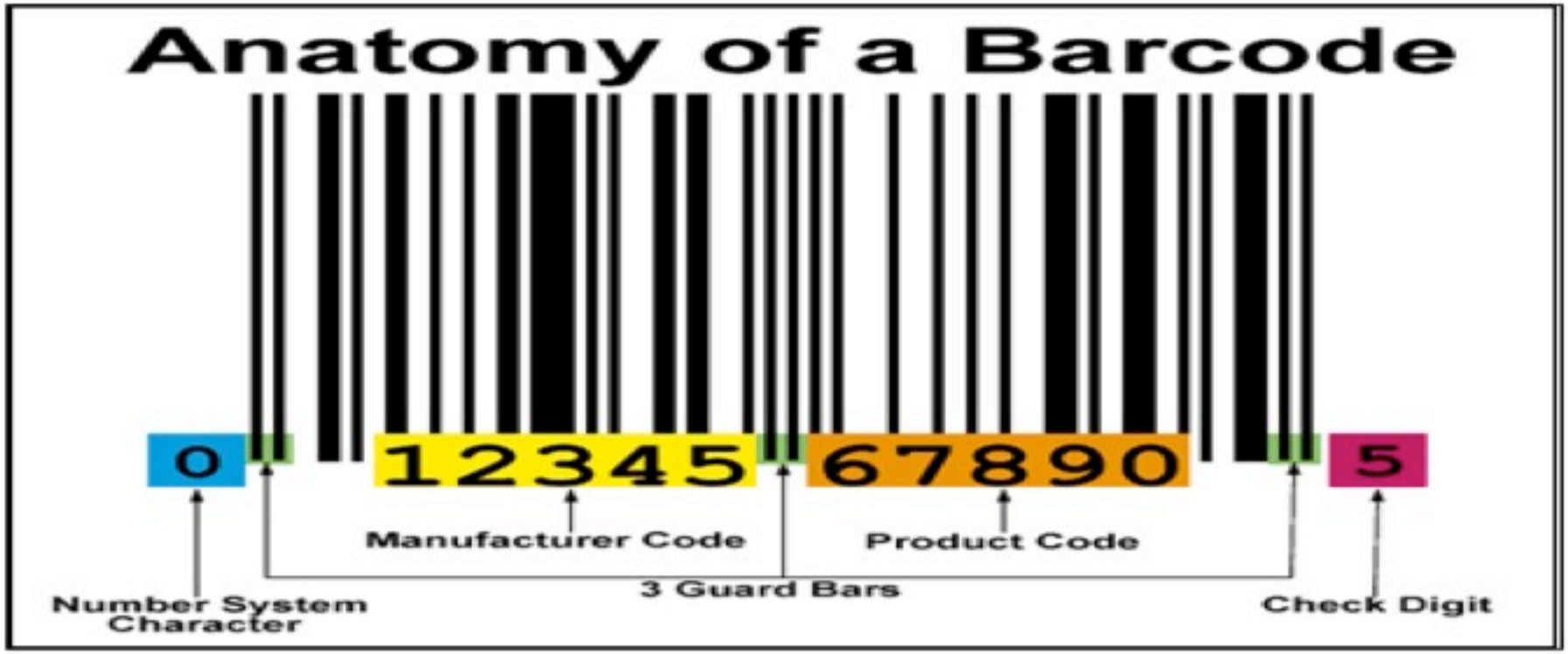
Urine: ideal source of biomarkers

-More stable and less complex of serum, easy to collect (not invasive), high content of renal proteins, miRNA and metabolites

Omics = High potential for multiple biomarkers discovery

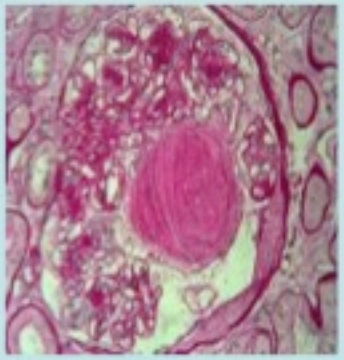
⇒ list of proteins/miRNA or a protein/miRNA profile able to classify and/or predicting the complex renal disease (rather of a single biomarker)

May omics allow successful differential diagnosis of renal damage in diabetic patients?

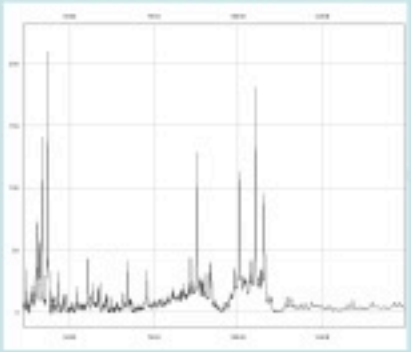


Urine: new uses for an old sample ?

Biopsy

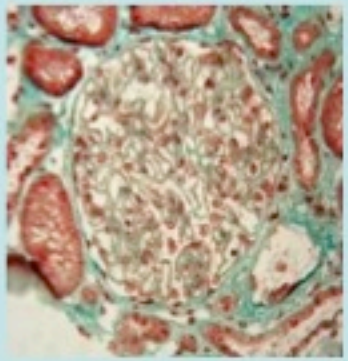


Urinary barcode

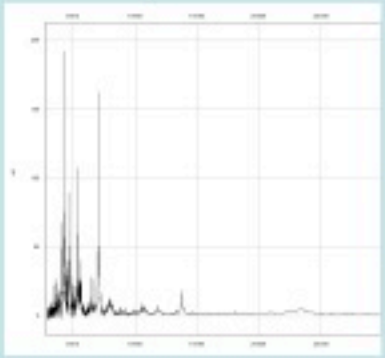


Diabetic Nephropathy

Biopsy

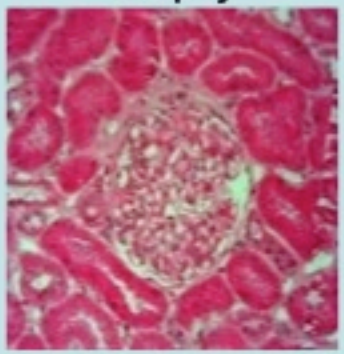


Urinary barcode



Membranous Nephropathy

Biopsy



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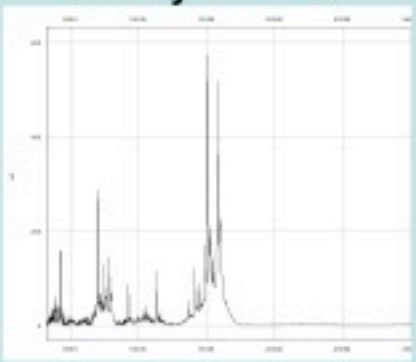
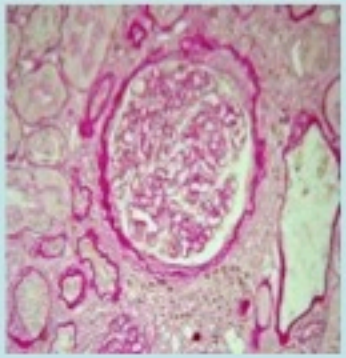


IgAN

Biopsy



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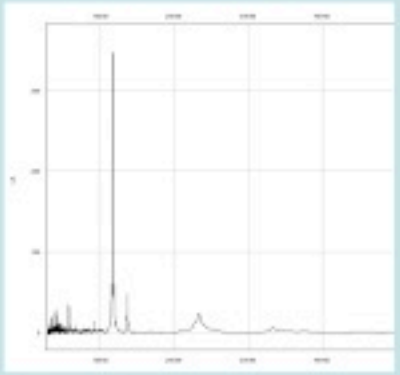


Nephroangiosclerosis

J Diabetes Res. 2016; 2016: 7934504.
Published online 2015 Dec 20. doi: 10.1155/2016/7934504
PMCID: PMC4698547

A Systems Biology Overview on Human Diabetic Nephropathy: From Genetic Susceptibility to Post-Transcriptional and Post-Translational Modifications

Francesca Conserva,[1,2] Loreto Gesualdo,[1,*] and Massimo Papale[3]

Author information ► Article notes ► Copyright and License information ►

J Nephrol (2014) 27:221–228
DOI 10.1007/s40620-014-0044-5

INVITED REVIEW

Proteomics and diabetic nephropathy: what have we learned from a decade of clinical proteomics studies?

Massimo Papale · Salvatore Di Paolo · Grazia Vocino · Maria Teresa Rocchetti · Loreto Gesualdo

REVIEW

JNEPHROL 2013; 26(5): 811-820
DOI: 10.5301/jn.5000262

The pathogenesis of diabetic nephropathy: focus on microRNAs and proteomics

Francesca Conserva, Paola Pontrelli, Matteo Accetturo, Loreto Gesualdo

Renal, Dialysis and Transplantation Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari - Italy

Overview of the urinary biomarkers of Diabetic Nephropathy

GLOMERULAR DAMAGE
- Albumin
- Transferrin

Podocyte Injury
- Nephrin
- Podocalyxin
- Podocin
- α-actinin-4,
- Synaptopodin
- Wilms' Tumor-1 (WT1)
- Vascular endothelial growth factor A (VEGF-A)

Glomerular endothelial Injury
- Glycosaminoglycan (GAG)

TUBULAR DAMAGE
- Cubilin and Megalin
- α1-microglobulin
- Retinol-binding protein (RBP)
- Neutrophil gelatinase-associated lipocalin (NGAL)
- Kidney injury molecule 1 (KIM-1)
- Cystatin C
- Glycosaminoglycan (GAG)

GLOMERULAR/TUBULAR BASEMENT MEMBRANE AND EXTRACELLULAR MATRIX PROTEINS
- Type IV collagen
- Type I collagen fragments
- Matrix metalloproteinase (MMP)-9
- Fibronectin
- TGF-β-induced protein h3 (βig-h3)

GROWTH FACTORS
- Transforming growth factor (TGF)-β1
- Connective tissue growth factor (CTGF)

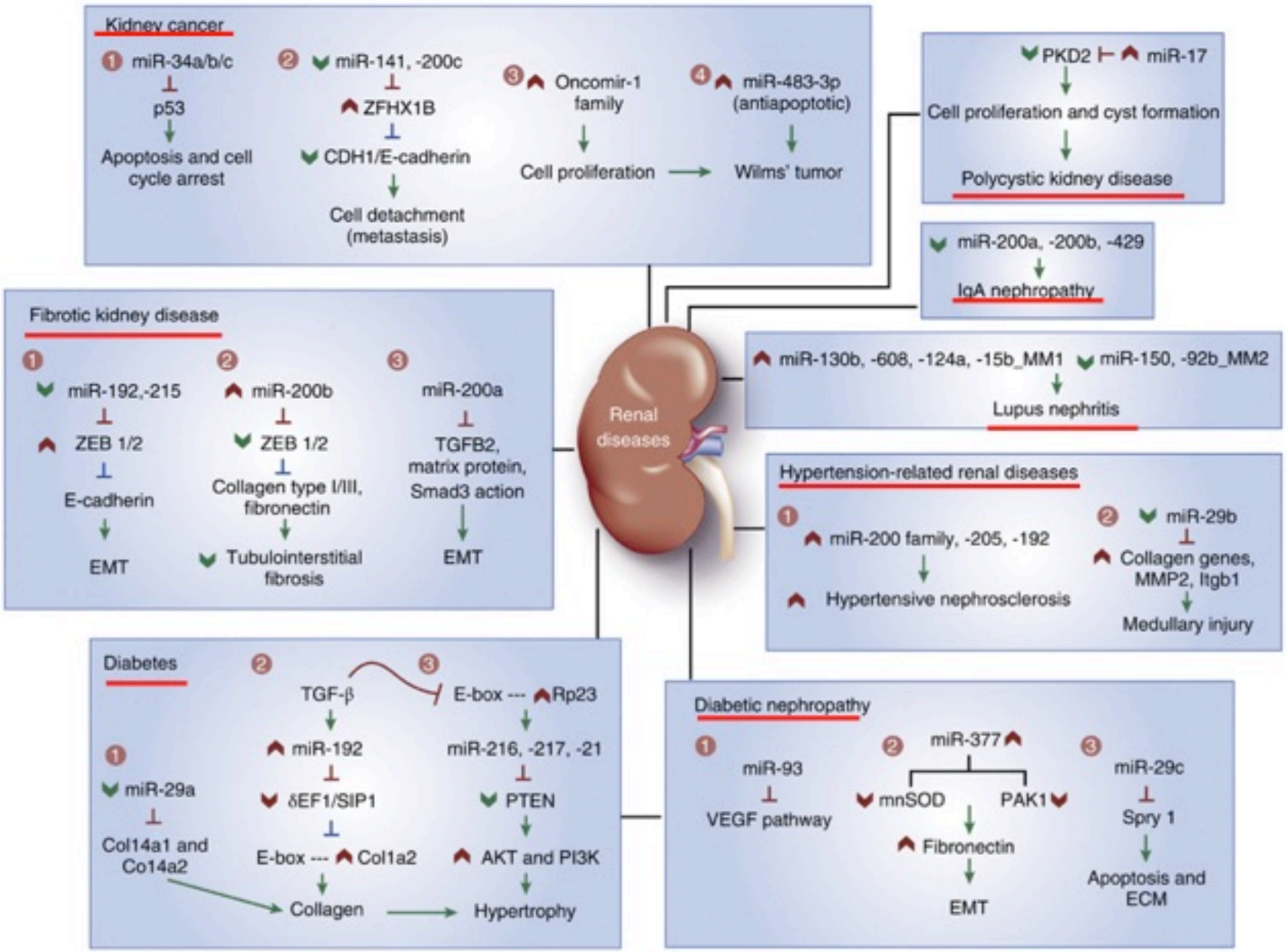
OXIDATIVE STRESS
- 8-Hydroxy-2′-deoxyguanosine (8-OHdG)
- 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG)

INFLAMMATION
- Tumor necrosis factor-α (TNF-α)

INTRARENAL RENIN-ANGIOTENSIN SYSTEM
- Renin

So-Young Lee at al. Pediatric Nephrol, 2014

miRNA in renal diseases



The "Classifier 273"

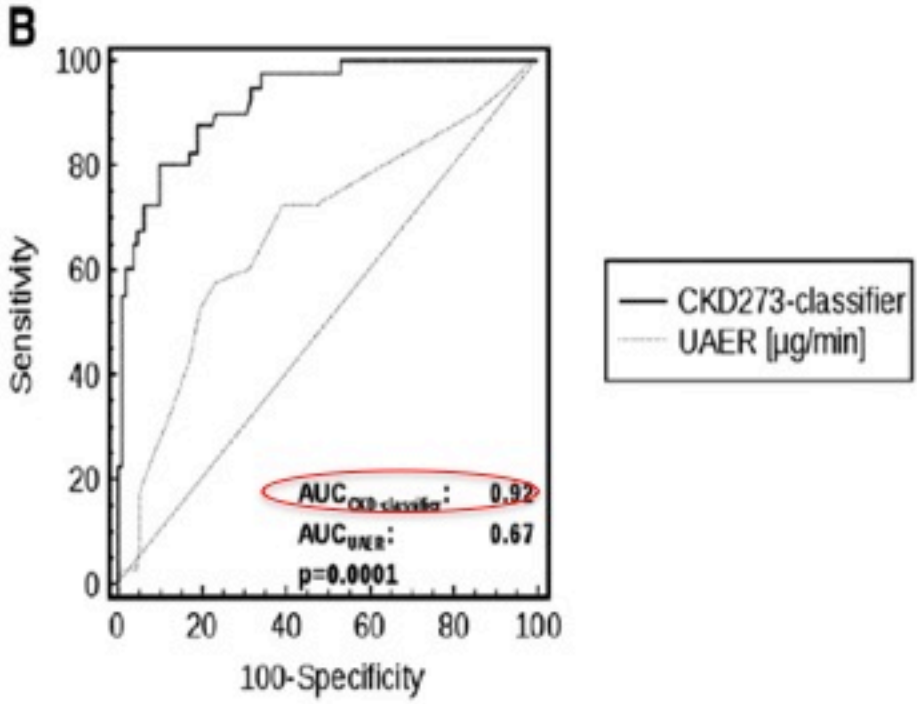
TABLE III
Source proteins and peptide distribution of CKD biomarkers

Protein	Swiss-Prot name	Number of fragments
Collagen α-1 (I) chain	CO1A1_HUMAN	126
Collagen α-1 (III) chain	CO3A1_HUMAN	55
α_1-Antitrypsin	A1AT_HUMAN	18
Collagen α-2 (I) chain	CO1A2_HUMAN	15
Uromodulin	UROM_HUMAN	11
Serum albumin	ALBU_HUMAN	9
Fibrinogen α chain	FIBA_HUMAN	5
Polymeric immunoglobulin receptor	PIGR_HUMAN	4
α_2-HS-glycoprotein	FETUA_HUMAN	3
Clusterin	CLUS_HUMAN	2
Collagen α-1 (II) chain	CO2A1_HUMAN	2
Membrane-associated progesterone receptor component 1	PGRC1_HUMAN	2
Osteopontin	OSTP_HUMAN	2
Sodium/potassium-transporting ATPase γ chain	ATNG_HUMAN	2
Transthyretin	TTHY_HUMAN	2
α_{1B}-Glycoprotein	A1BG_HUMAN	1
Antithrombin-III	ANT3_HUMAN	1
Apolipoprotein A-I	APOA1_HUMAN	1
β_2-Microglobulin	B2MG_HUMAN	1
CD99 antigen	CD99_HUMAN	1
Collagen α-1 (V)	CO5A1_HUMAN	1
Collagen α-1 (XVII) chain	COHA1_HUMAN	1
Collagen α-1 (XVIII) chain	COIA1_HUMAN	1
Collagen α-2 (VIII) chain	CO8A2_HUMAN	1
Cystatin-B	CYTB_HUMAN	1
Ig λ chain C regions	LAC_HUMAN	1
Neurosecretory protein VGF	VGF_HUMAN	1
Pro-SAAS	PCSK1_HUMAN	1
Prostaglandin-H_2 D-isomerase	PTGDS_HUMAN	1
Psoriasis susceptibility 1 candidate gene 2 protein	PS1C2_HUMAN	1

Adapted from Good et al. Mol. Cel. Prot. 2010

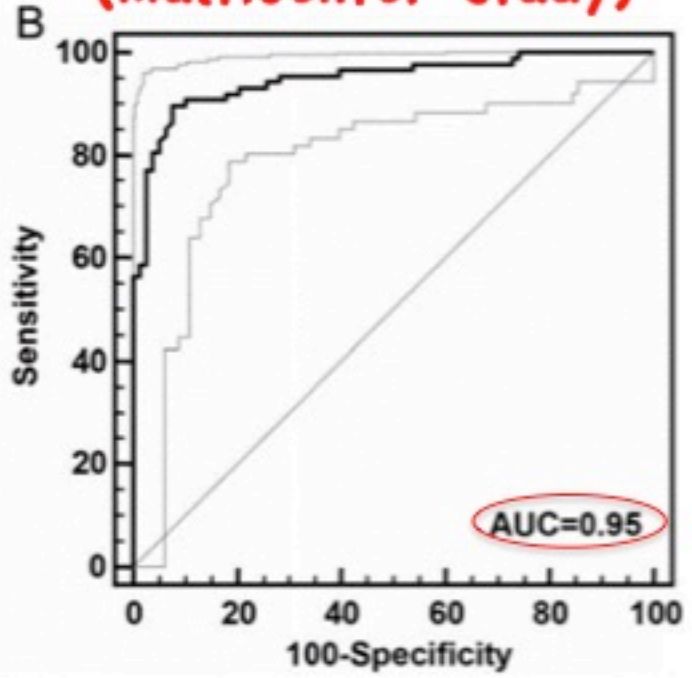
The "Classifier 273" predicts the worsening of the renal function better than albuminuria

Independent validation



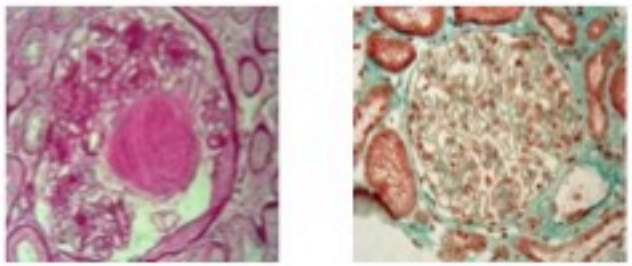
Zürbig P et al. Diabetes, 2012

Independent validation (multicenter study)

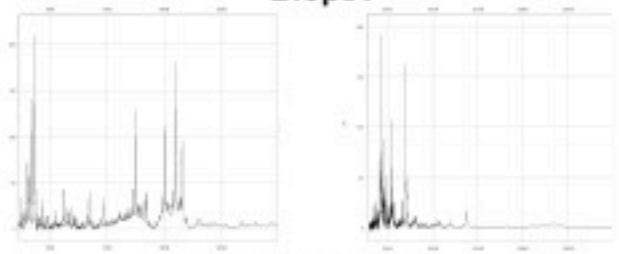


Siwi J et al. NDT, 2014

A



Biopsy



SELDI profiling

Pathophysiology/Complications

ORIGINAL ARTICLE

Urine Proteome Analysis May Allow Noninvasive Differential Diagnosis of Diabetic Nephropathy

Massimo Papale, phd[1]
Salvatore Di Paolo, md[2]
Riccardo Magistroni, md[3]
Olga Lamacchia, md[4]
Anna Maria Di Palma, md[5]
Angela De Mattia, md[3]
Maria Teresa Rocchetti, phd[1]
Luciana Furci, md[3]
Sonia Pasquali, md[6]
Salvatore De Cosmo, md[7]
Mauro Cignarelli, md[4]
Loreto Gesualdo, md[1,8]

Diabetes Care 33:2409–2415, 2010

B

Prediction Success (training set)

Actual Class	Total Cases	Percent Correct	DN N=37	nd-CKD N=35
DN	31	100.000	31	0
nd-CKD	41	85.366	6	35

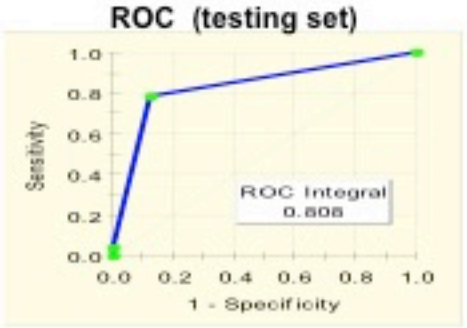
Prediction Success for DN (testing set)

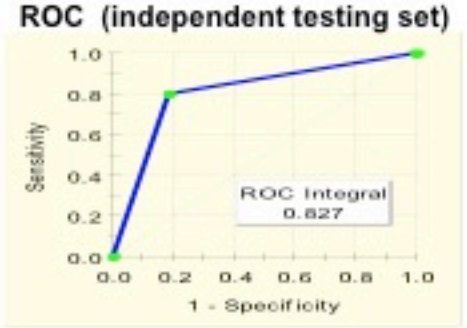
Actual Class	Total Cases	Percent Correct	DN N=20	nd-CKD N=19
DN	23	78.261	18	5
nd-CKD1	16	87.500	2	14

Prediction Success (independent testing set)

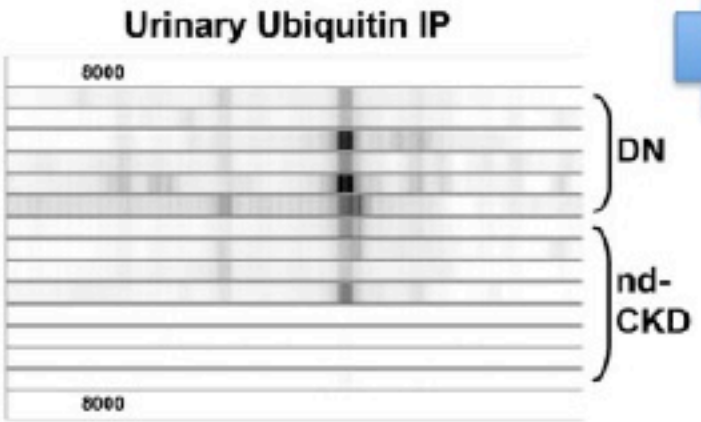
Actual Class	Total Cases	Percent Correct	DN N=11	nd-CKD N=10
DN	11	81.818	9	2
nd-CKD2	10	80.000	2	8

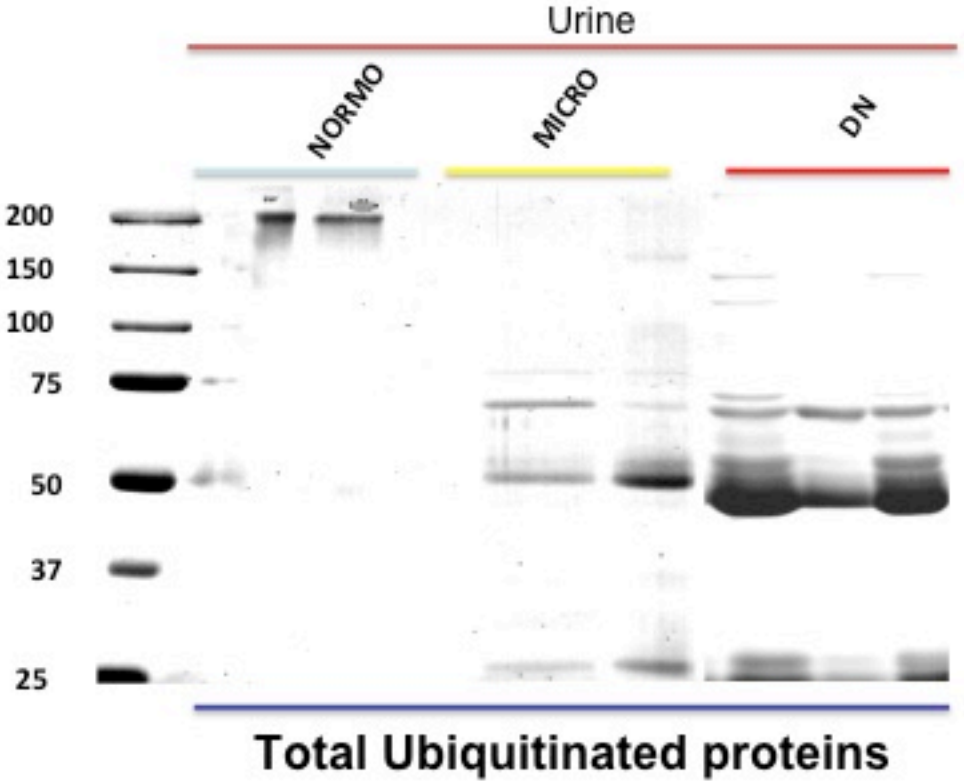
C





Increased free ubiquitin in DN may reflect impaired ubiquitination…

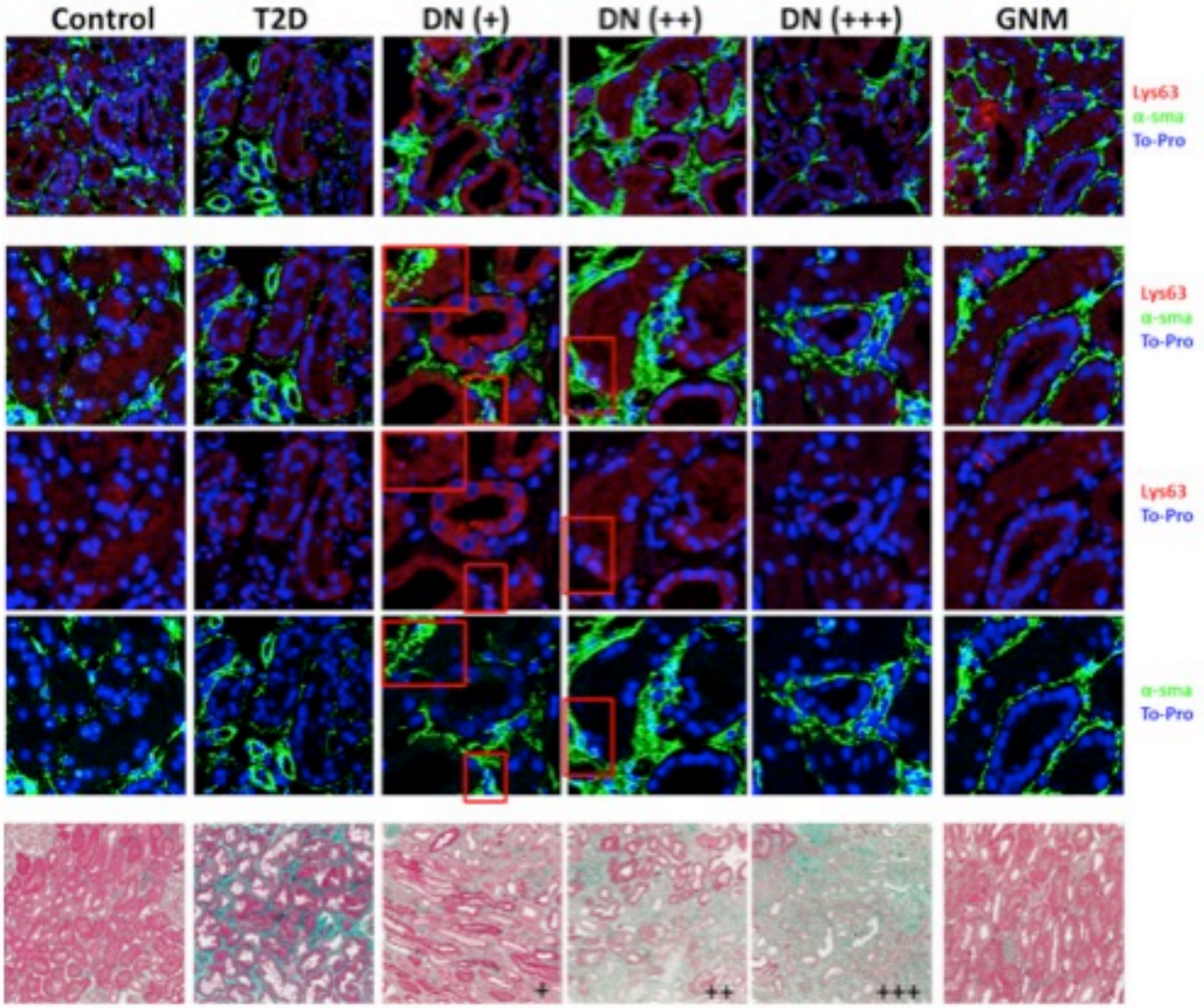




Papale M, Gesualdo L et al.
Diabetes Care, 2010

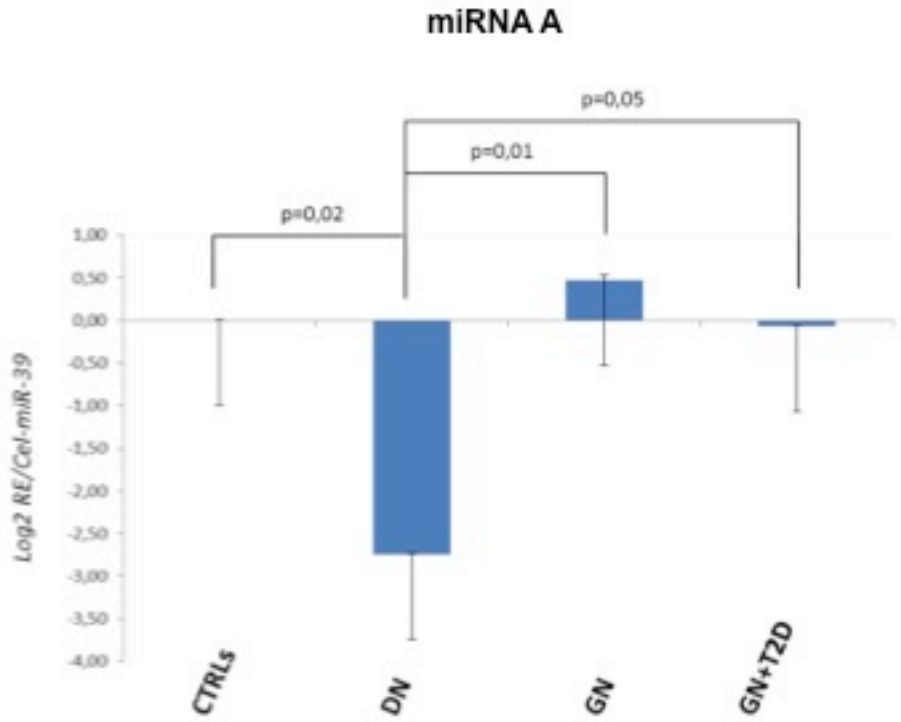
Papale M, Gesualdo L et al. submitted

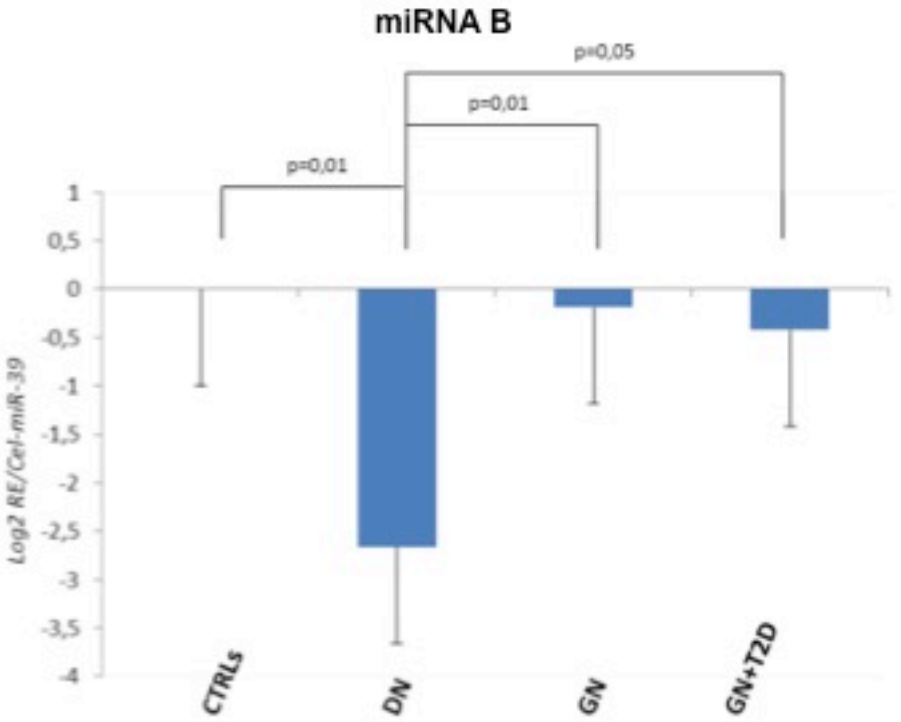
Lys63-Ubiquitination is linked to Fibrosis in DN



Pontrelli P et al. *Lysine 63 ubiquitination is involved in the progression of tubular damage in diabetic nephropathy.* FASEB J 2017;31:308-319

miRNA in Urinary Samples





Conserva, Barozzino et al., *in preparation*

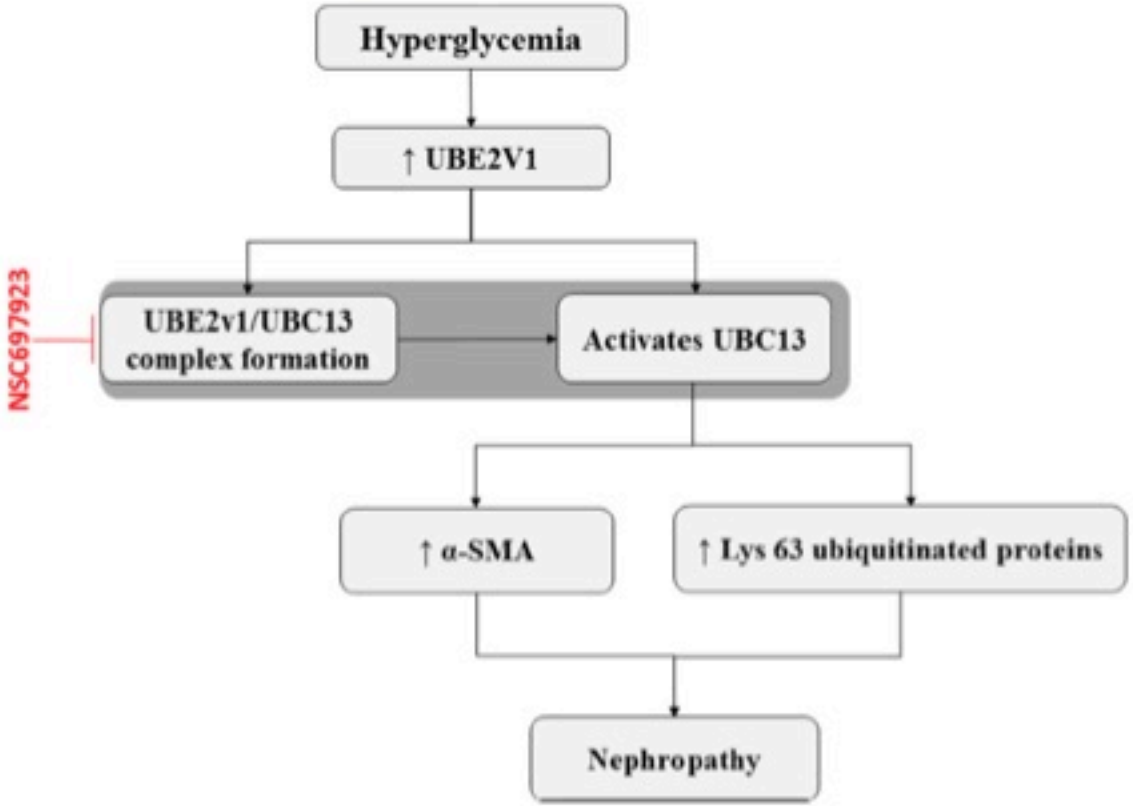


Fig. 2. E2 conjugating enzyme UBE2v1 promotes lysine 63 polyubiquitination and accelerates DN: Increased UBE2v1, an activator of E2 enzyme UBC13 increased the expression of lysine 63 polyubiquitination of various substartes and promotes DN.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Review

Hidden targets of ubiquitin proteasome system: To prevent diabetic nephropathy

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Disease drivers:

Global consortia aim to unpack genetics of diabetes and obesity

By Shraddha Chakradhar

Nature Medicine 22, (2016)

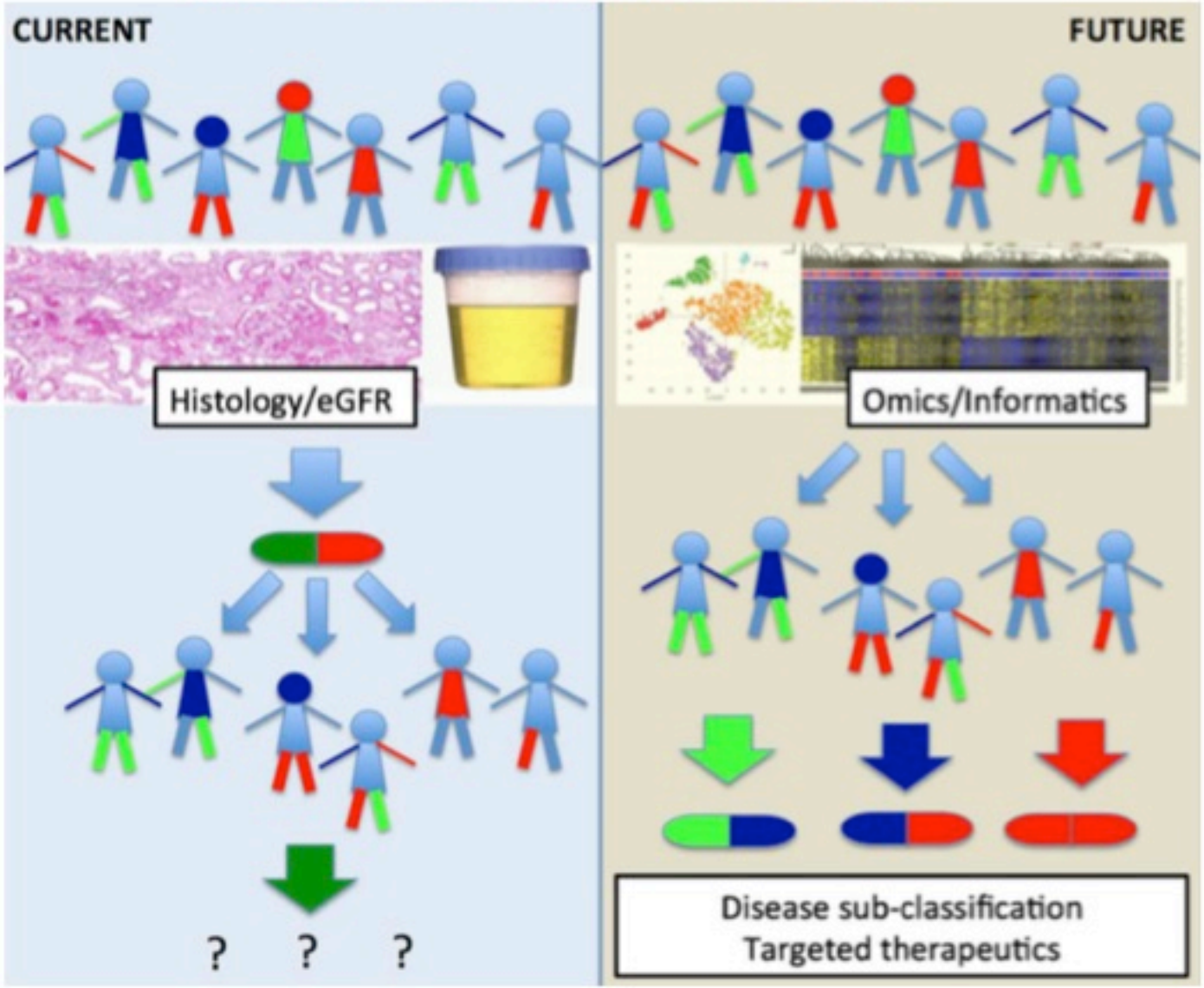
BEAT DKD

The **BEAt-DKD project** aims to deliver tools and knowledge that will facilitate the development of new, personalised treatments for DKD. Among other things, the project will identify and validate biological markers (biomarkers) to help researchers track whether a patient's condition has worsened, and whether a treatment is working for them. The project will also work to identify different sub-groups of patients that could respond differently to certain treatments. The results will therefore pave the way for the development of effective personalised treatments for DKD.

Funded by European Union
Erasmus+
Project Reference
2016-1-IT02-KA203-024318

remap
Renal Molecular Pathologist Network

Precision Medicine Approaches to Diabetic Kidney Disease



Gluck C. Curr Diab Rep. 2017

Conclusion I

Nephrol Dial Transplant (2015) 30: 155–157
doi: 10.1093/ndt/gfu372
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In Focus

Renal lesions in patients with type 2 diabetes: a puzzle waiting to be solved

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Renal biopsy might represent an important tool in diabetics, particularly for identifying subjects with NDRD who would benefit of personalized treatment for retarding ESKD. Future, well-planned studies on this issue are eagerly awaited for clarifying the exact role of this procedure in the clinical management of diabetics.

Conclusion II

There is an urgent need for specific, rapid, non-invasive and not expensive biomarkers that can discriminate NDRD from ND forms to help nephrologists in a safe and reliable diagnosis and set the most appropriate therapy.

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Thank you